CAT

Dosisaanpassing van antibiotica, toepasbaarheid van beschikbare calculators

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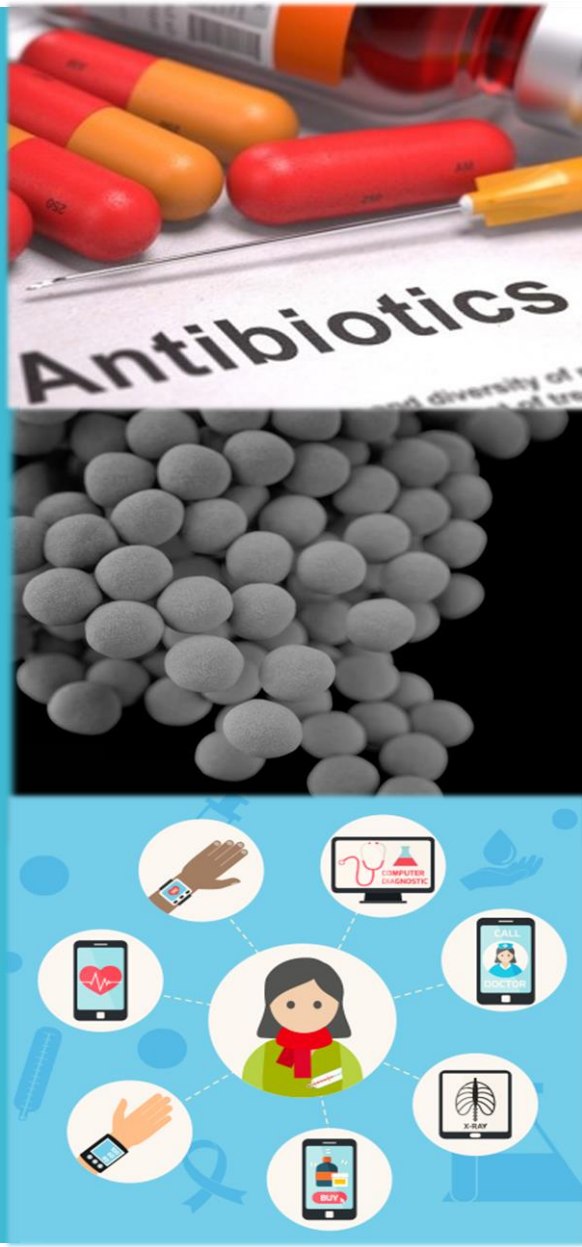
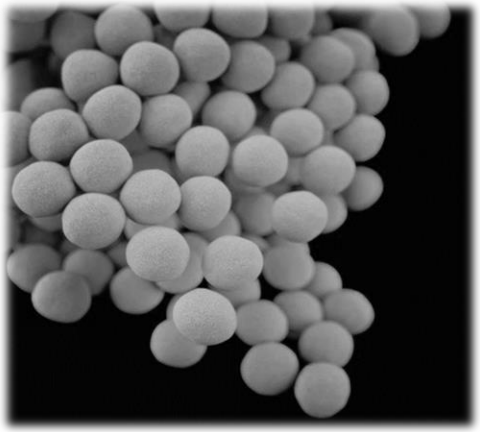


Questions

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

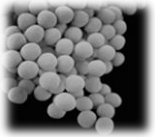
2. *Which methods are available for individualized vancomycin dosing? Can the use of pharmacokinetic software improve clinical outcome?*

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?*



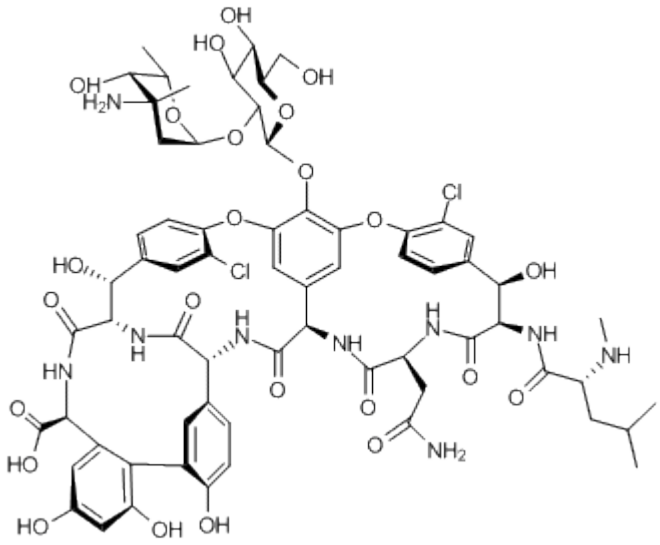
1.

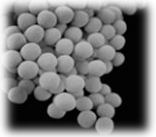
What are the current guidelines and recommendations on TDM for vancomycin therapy in S. aureus infections?



Vancomycin

- Cationic glycopeptide antibiotic
- Slowly bactericidal for Gram-positive bacteria
- Forms stable complex with peptidoglycan precursor lipids
- Ototoxicity and nephrotoxicity

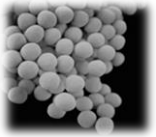




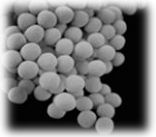
TDM

- Balancing resistance, efficacy, and toxicity !
- Warranted in the following patient groups
  - High doses or prolonged therapy (> 3 days),
  - Treatment with nephro- or ototoxic agents
  - Unstable renal function or renal replacement therapy
  - Hemodynamically unstable septic patients
- Primary pharmacodynamic parameter: AUC/MIC ≥ 400
  - Good correlation between AUC/MIC and through levels

Rybak et al. *Clin Infect Dis*. 2009



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



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2.

Which methods are available for individualized vancomycin dosing?

Can the use of pharmacokinetic software improve clinical outcome?

Dosing methods

- Different algorithms have been already been developed for vancomycin monitoring
  - Population methods
  - Linear regression analysis
  - Bayesian estimation

Dosing methods

Population

- *A priori* dosing methods or nomograms
- Population estimates of pharmacokinetic parameters

Examples

- Kullar nomogram
  - Based on Cl_{CR} and total weight
  - Intermittent infusion
  - Adult patients with stable parameters
  - Target through: 15-20 mg/L

Weight (kg)	Creatinine Clearance (ml/minute)						
	40–49	50–59	60–69	70–79	80–89	90–99	≥ 100
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

Kullar et al. *Pharmacotherapy*. 2011

	Method	Study	Patients	Goal	Results
Clinical outcomes					
Kullar et al 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

Dosing methods

Population

- Advantages
  - Easy to interpret
  - No pharmacokinetic knowledge required
  - Limited use of resources
- Disadvantages
  - Parameters must remain stable
  - Rarely for critically ill patients
  - Rely on clinicians' experience for interpretation

Dosing methods

Linear regression

- *A posteriori* drug dosing methods
- 1-compartment pharmacokinetic model

Examples

- ## Sawchuk-Zaske formulas

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

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

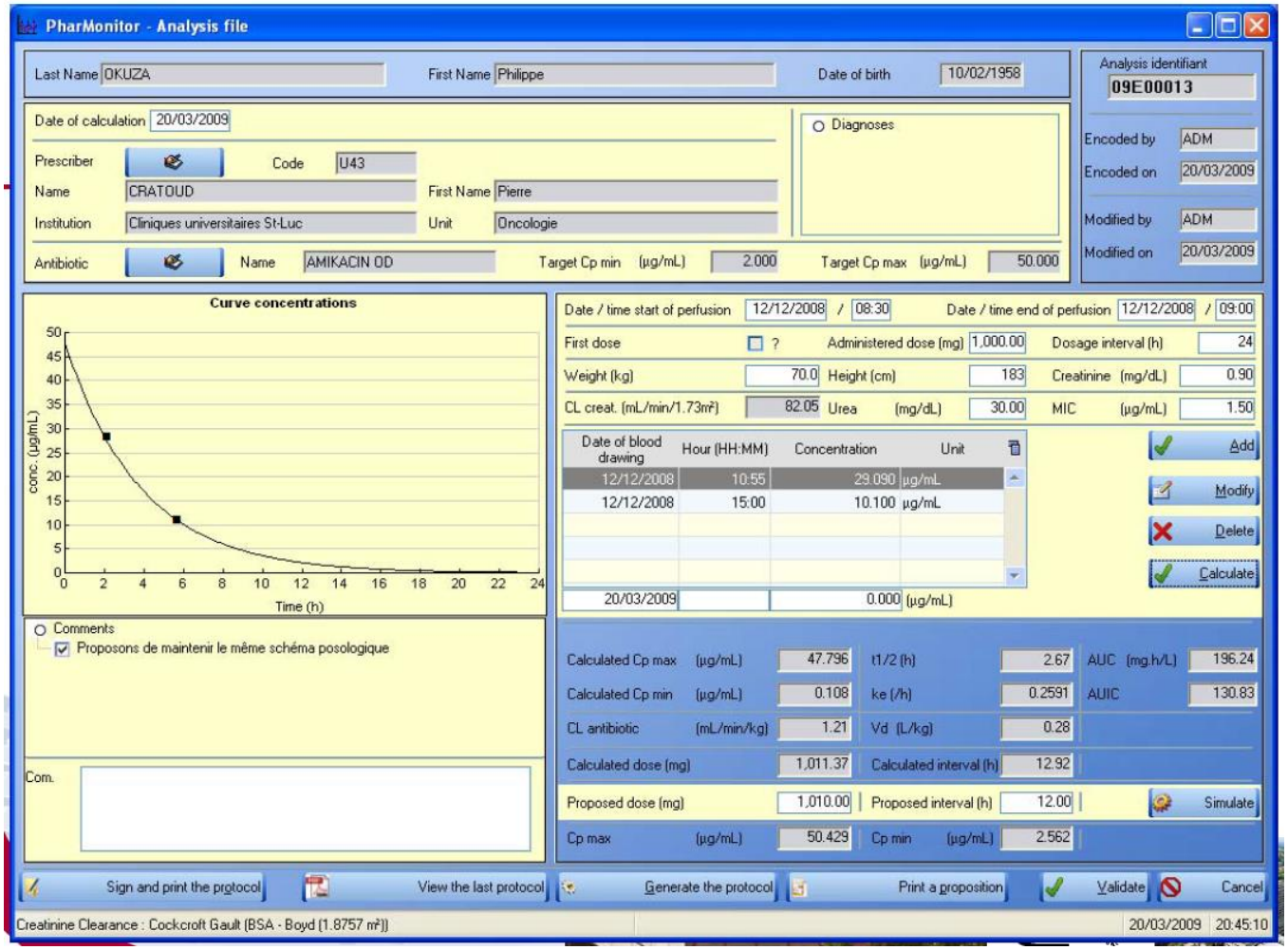
$$C_{min} = C_{max} \times e^{-k_e \times (\tau_{desired} - t_{inf})}$$

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

Sawchuk et al. *J. Pharmacokinet. Biopharm*. 2011

Examples

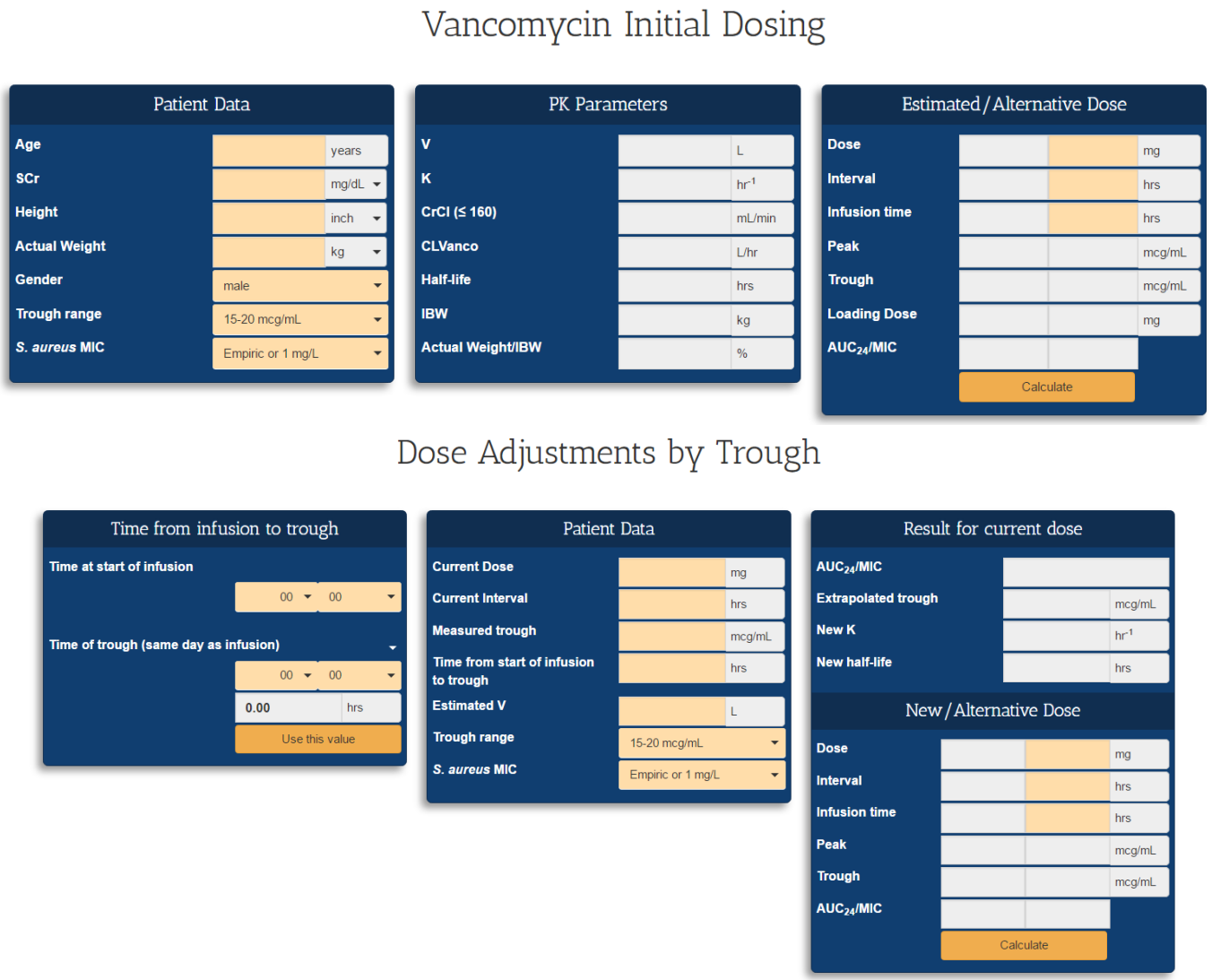
- Pharmonitor



Leal et al. *Clin Chem*. 1991
Delattre et al. *Acta Clinica Belgica.* 2010

Examples

- Vancomycin-calculator.com



Fewel et al. *J Clin Pharm Ther*. 2016

Dosing methods

Linear regression

- Advantages
  - Easy to interpret
  - Relatively simple calculations
- Disadvantages
  - Discard data outside of single dosing intervals
  - Cannot account for changing renal function
  - Accurate details of drug dosing are required

Dosing methods

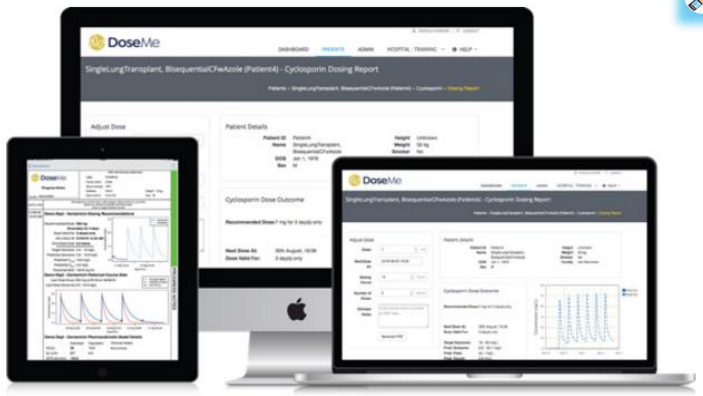
Bayesian estimation

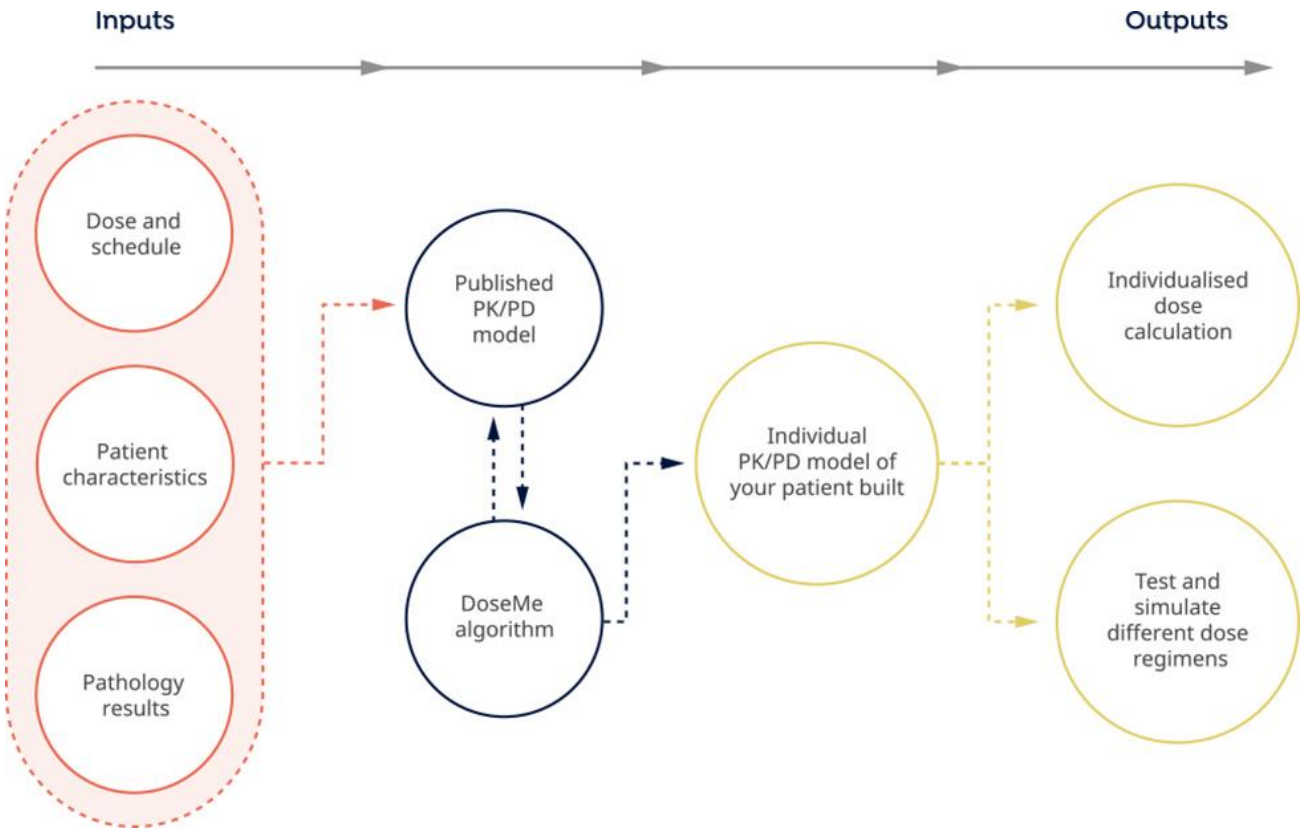
- Incorporates population + pharmacokinetic model (a *priori* with *a posteriori)*
- Based on 1 or 2 serum concentrations
- Includes analysis of sequential serum data, changes in pharmacokinetic parameters, and the experimental error

Examples

DoseMe

http://doseme.com.au





Dosing methods

Bayesian estimation

- Advantages
  - Incorporate all available patient data
  - Single-serum concentrations possible
  - Calculate appropriate starting dose
- Disadvantages
  - Requires pharmacokinetic knowledge
  - Patient parameters cumbersome to gather
  - Easy and accurate software under development

3.

How are guidelines and recommendations on vancomycin TDM implemented in Leuven and Belgium?

Is there truly a need for software-driven approaches?

Leuven

Methods

- Retrospective study from 1 to 31 November 2016
- All patients started on vancomycin therapy with TDM
- Queries of the KWS and LWS electronic health systems
- No patients were excluded from the study

Leuven

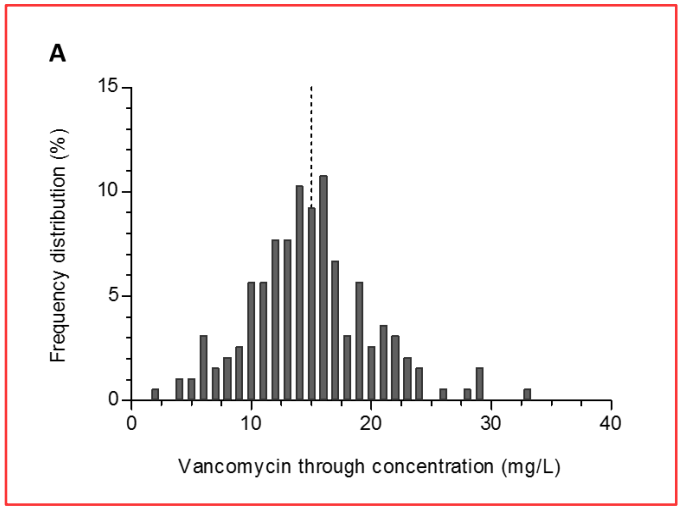
TDM

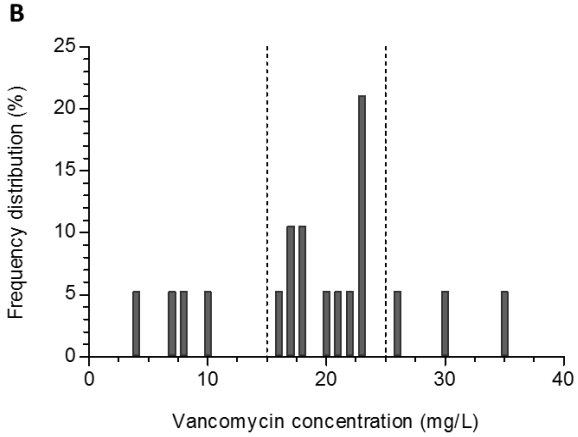
- ✓Adults with normal renal function: 2x1 g IV
- ✓Children: 4x40 mg/kg IV or 4x60 mg/kg IV (meningitis)
- ✓TDM sampling: Before administration of the 4th dose (steady-state).
- ✓TDM measurements on HITACHI/Roche COBAS c702

Leuven

Intermittent

- Reference: ± 15 mg/L through
- 195 patients with 989 serum samples
  - Median samples/patient = 3 (range 1-30)
  - Median (IQR) through = 14,60 (11,70-17,46) mg/L
- 15-20 mg/L was never reached in 38,97% of patients





Leuven

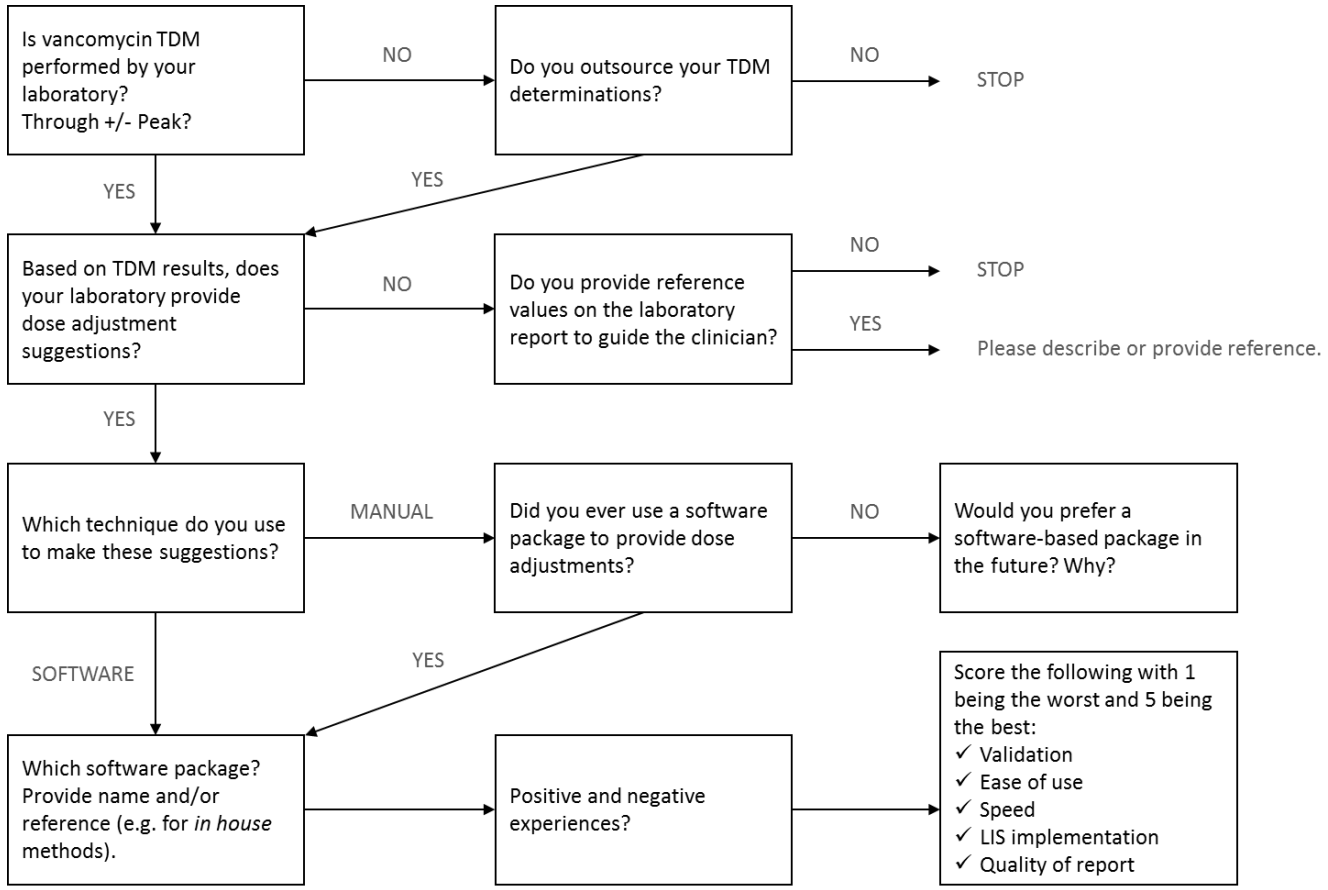
Dose suggestions

- Provided for 458/1046 (43.8%) TDM samples
- No specific calculators or software packages
- Dose adapted in next 48 hours?
  - Dose adjustments based on clinical judgment: 53.8%
  - Dose suggestion by laboratory followed: 32.6%
  - Vancomycin stopped after TDM: 13.6%

Belgium

Methods

- Electronic Google Docs survey
- Send to 46 different Belgian laboratories
- Response rate: 30 participants from 30 laboratories (65%)



Belgium

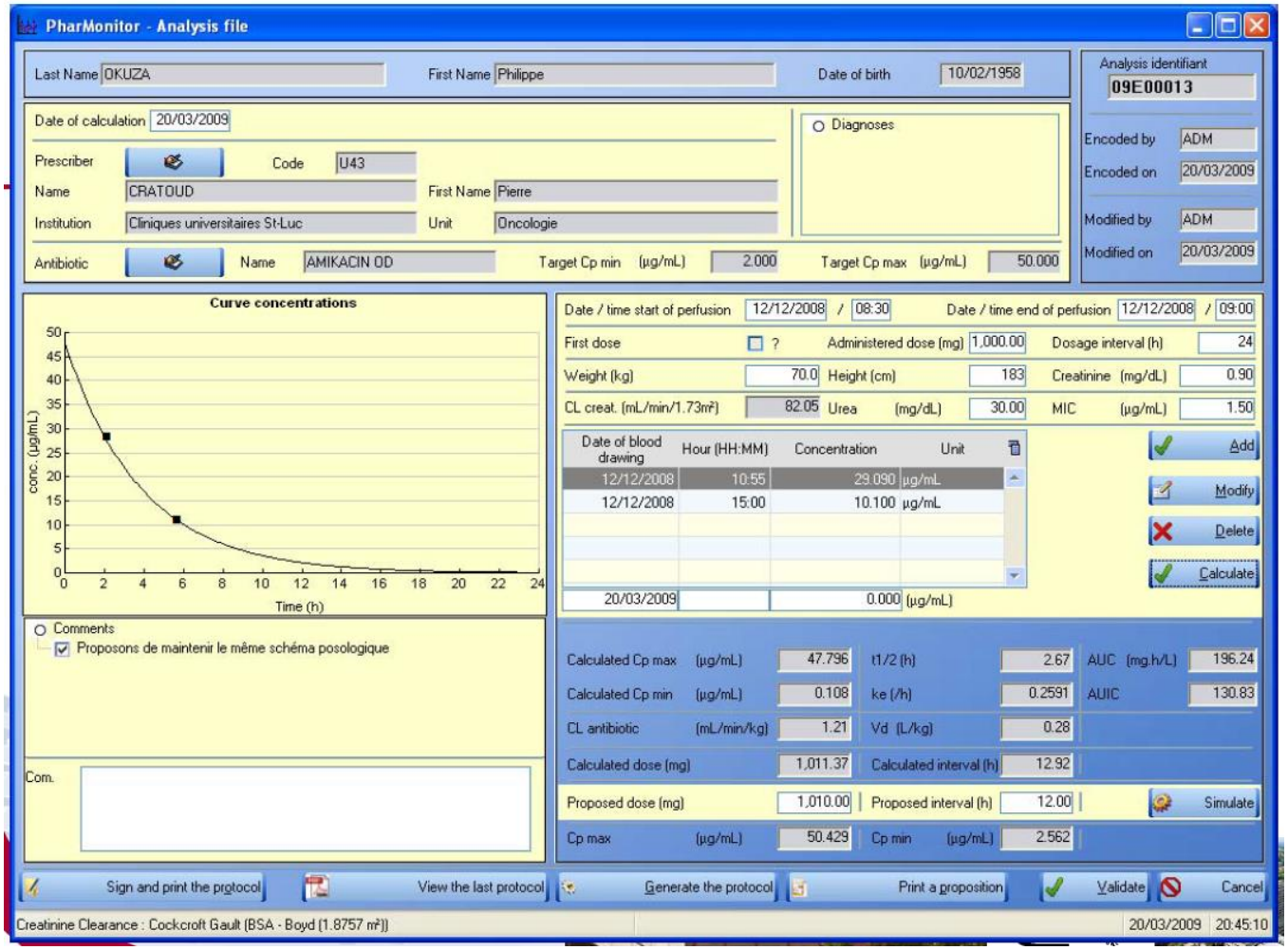
TDM

	Laboratories n = 30
TDM performed by laboratory	28
– Through only	11
– Peak and through	16
– Continuous infusion separately	8
Reference values	
– Through reference values	21
– Sanford edition 2010[5]	5
– Rybak et al. 2009[4]	11
– Peak reference values	9
– Continuous reference values	21
– Sanford edition 2010[5]	3
– 20-30 mg/L	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

Pharmonitor !

Examples

- Pharmonitor



Leal et al. *Clin Chem*. 1991
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Belgium

Software

- Three laboratories stopped using Pharmonitor?
  - Malfunctioning software (1x)
  - Switch from intermittent to continuous infusion (1x)
  - Switch to an Excel based formula (validated using Pharmonitor) (1x)
- Experiences with Pharmonitor (5 labs)
  - Advantages
    - Quality of reports
    - User-friendliness
    - Validation in literature
  - Disadvantages
    - Need 2 concentrations in the same dosing interval
    - Difficulties in LIS implementation
    - Performance is dependent on provided sample information

Belgium

Software

- Interest for future implementation (n = 16)?
  - Used in the past: 3 labs
  - No : 4 labs
  - Yes: 9 labs!
- Advantages?
  - Objectivity
  - Standardization
  - Time- and cost-benefit

Conclusion

Clinical bottom line

Conclusion

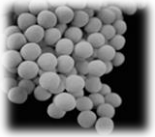
- Vancomycin TDM is recommended in selected patient groups
  - Higher rates of clinical efficacy and decreased nephrotoxicity
  - Pharmacokinetic dose calculators could be useful
- Enormous lack of prospective and cost-effectiveness studies
  - Bayesian methods have the largest potential
- Interest?
  - Leuven
    - Low adherence to laboratory dose suggestions
    - Significant percentage of patient never reaches 15 mg/L through
  - Belgium
    - 5/18 labs had (previous) experience with software tools
    - 9/16 participants: software packages could lead to a significant increase in objectivity, standardization, and time-efficiency.
- Urgent need for user-friendly, cost-effective, LIS-integrated, and validated software solutions !

To Do

- Discuss results of dose suggestion adherence with the UZ Leuven clinicians
- Investigate possible confounding factors in reaching steady-state through levels
- Discuss whether implementation of a software tool is advised at UZ Leuven

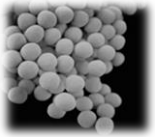
Questions?

Thank you!



Vancomycin

- Pharmacokinetics
  - A. Oral absorption is very limited.
    IV administration with infusion time ≥ 1h.
  - D. Poor tissue distribution (V_D = 0,4 – 1 L/kg)
    Protein binding ranges from 10-50%.
  - M. No significant hepatic metabolism
  - E. Mostly by glomerular filtration (> 80-90% unchanged).
    Half-life of 6-12 hours with normal renal function.



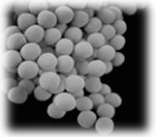
Dosing

- Initial intermittent doses: ABW and renal function

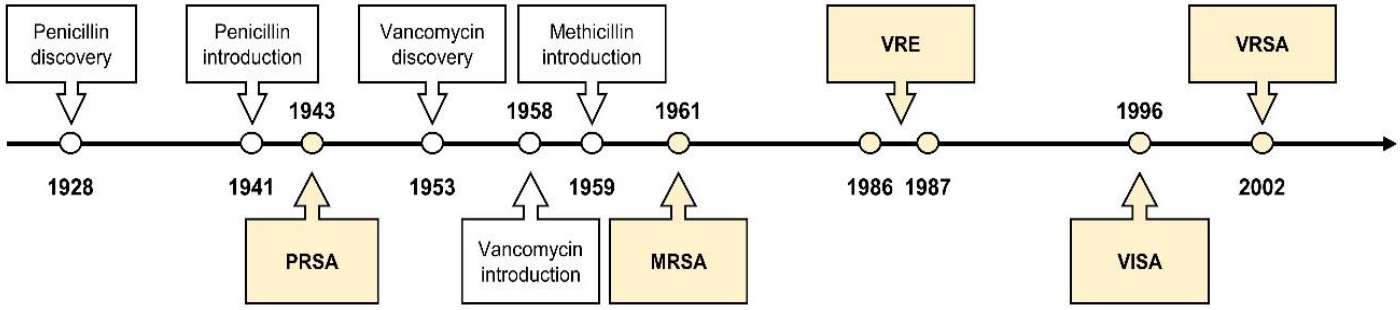
Regimen	≥ 90	89 - 60	59 - 30	29 -15	< 15	CRRT	CAPD
CI	30 mg/kg 24h	30 mg/kg 24h	20 mg/kg 24h	15 mg/kg 24h	15 mg/kg 48h	20 mg/kg 24h	15 mg/kg 48h
II	15 mg/kg q12h	15 mg/kg q12h	15 mg/kg q12-24h	15 mg/kg q24-48h	15 mg/kg q48-72h	15 mg/kg q12-24h	15 mg/kg q48-72h

- Adjustments based on vancomycin serum concentrations
- Loading dose of 25-30 mg/kg for critically ill patients
- Lower incidence of nephrotoxicity in patients receiving continuous infusion.
  - Loading dose: 20 mg/kg (1-2 hours)
  - Subsequent doses: 30 mg/kg/day

Sanford Guide. 23rd edition. 2012-2013
Hao et al. *Int J Antimicrob Agents*. 2016



Resistance

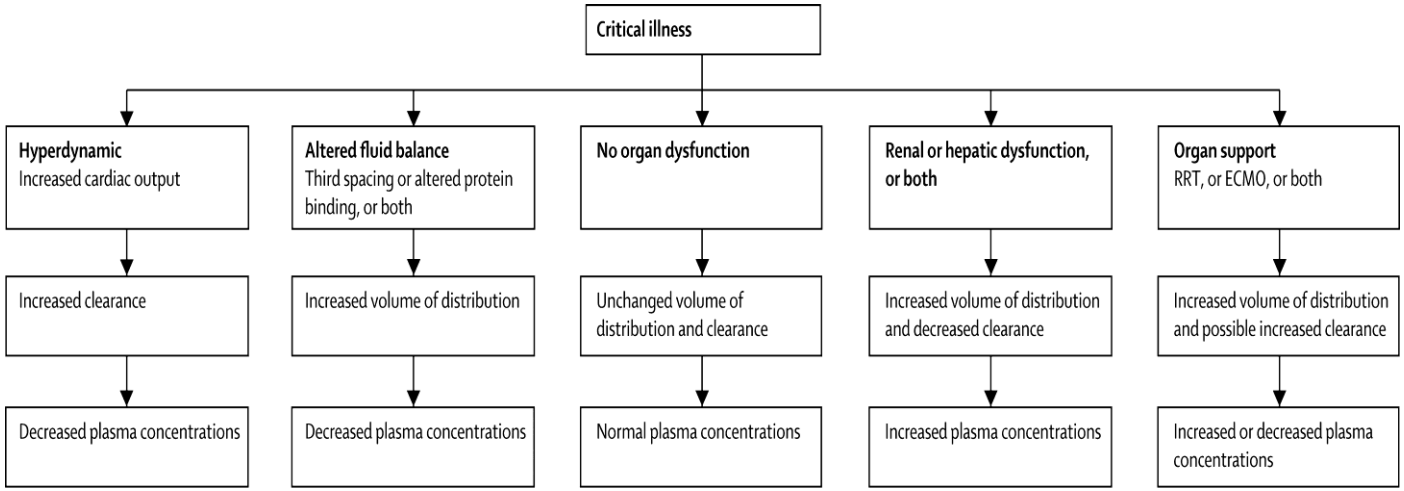


- Significant increase in vancomycin use since MRSA°
- Vancomycin-intermediate *S. aureus* (VISA)
  - MIC = 4-8 mg/L
  - Heteroresistance (hVISA): MIC ≤ 1 mg/L
  - Thickened cell walls, reduced autolysis, reduced virulence
  - Suboptimal, prolonged, or repeated vancomycin therapy
- Vancomycin-resistant *S. aureus* (VRSA)
  - MIC ≥ 16 mg/L
  - Transfer of *vanA* transposon from VRE strains
  - No significant spread - high fitness cost

Hu et al. *Front Microbiol*. 2016

Rationale

- Is TDM combined with clinical dosing software useful?
  - Changes in pharmacokinetic function during critical illness
  - In specific patient populations (e.g. pediatric, obesity)

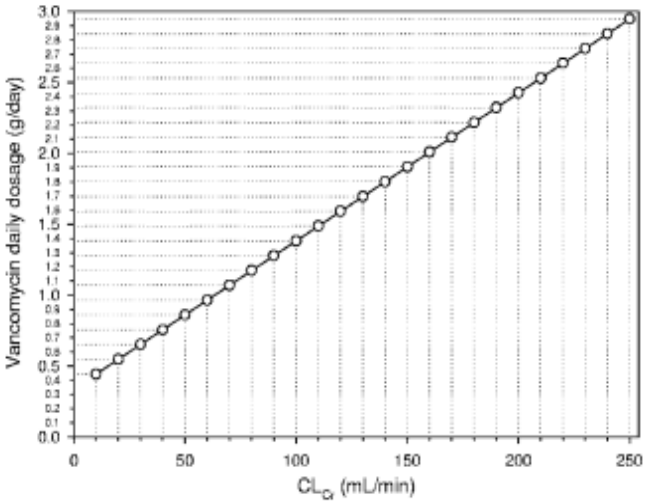


Roberts et al. *Lancet Infect Dis*. 2014

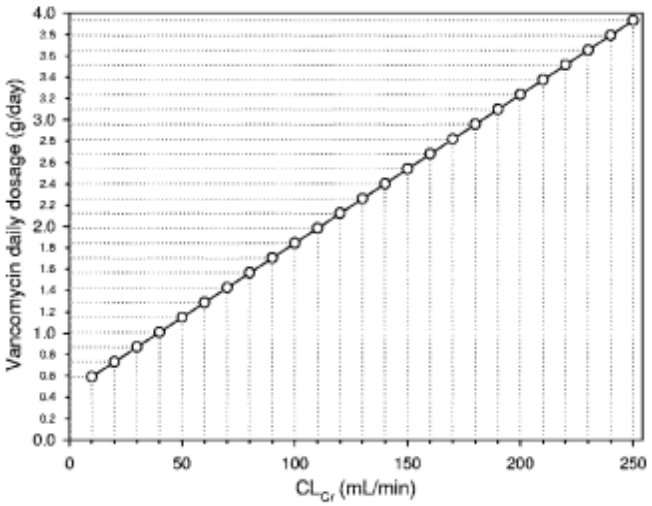
Examples

- Pea nomogram
  - Based on Cl_{CR} estimates
  - Continuous infusion
  - Critically ill adult patients
  - Target through: 15 mg/L or 20 mg/L

15 mg/L



20 mg/L



Pea et al. *Antimicrob Agents Chemother*. 2009

Benchmark

- Most recent software benchmark in 2013
- Literature search: 12 software tools
- All programs were scored on a standardized grid
  - Pharmacokinetic relevance
  - User friendliness
  - Computing aspects
  - Interfacing
  - Storage
- Weighing factor for relative importance of each criterion

Fuchs et al. *Clin Pharmacokinet*. 2013

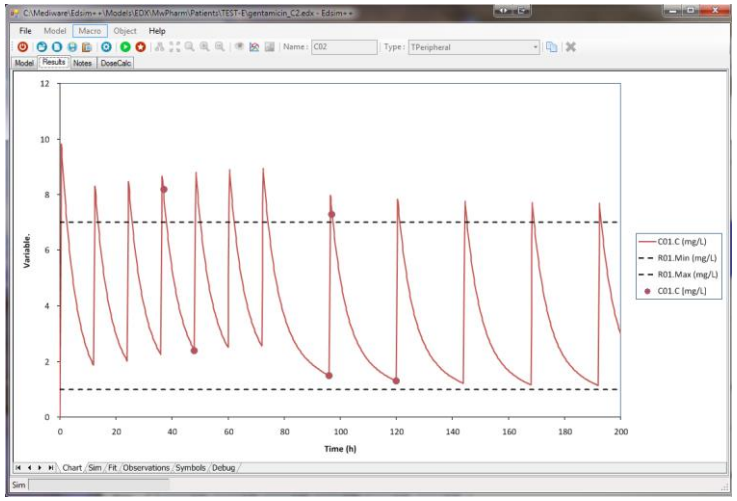
	MM-USCPack	Mw-Pharm	TCIworks	JKPD	TDM for R	Antibiotic Kinetics	APK	Kinetics	Kinetidex	TDMS 2000	Data Kinetics	RAD kinetics
General characteristics												
User interface	10	4	7	6	11	3	**1**	2	5	9	8	12
Interfacing	5	**1**	5	5	5	2	2	2	5	5	5	5
Storage	7	**1**	8	10	10	10	2	2	5	6	4	9
Report	10	**1**	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

Benchmark

- Best two programs: MwPharm and TCIWorks
- Others: Less sophisticated or user friendly
- Programs vary in complexity and might not fit in all healthcare settings
- Most software not available or supported anymore !

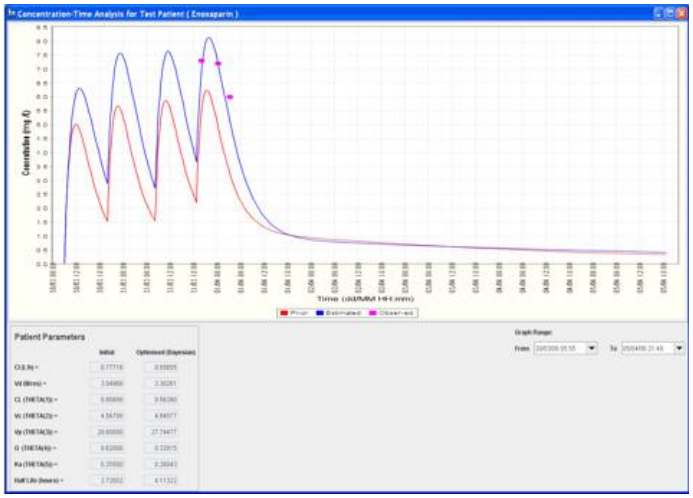
MW PHARM

http://www.mediware.cz



TCIWorks

http://www.tciworks.info



Predictive performance

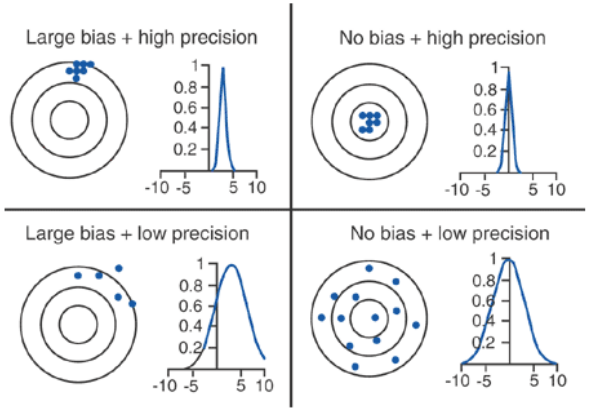
ME, MAE and RMSE

(reported by Sheiner and Beal)

$$ME = 1/n \sum_{i=1}^{n} (C_{pred} - C_{meas})$$

$$MAE = 1/n \sum_{i=1}^{n} |C_{pred} - C_{meas})|$$

$$RMSE = \sqrt{1/n \sum_{i=1}^{n} (C_{pred} - C_{meas})^2}$$



- Prediction of serum concentrations (n = 8 studies)
  - Correlation observed and predicted through: r > 0.80
  - The mean prediction error (ME)
    - Measure of bias
    - ME = 0 mg/L in 2/3 studies that provided 95% CI intervals
    - ME < 1.0 mg/L in all other studies reporting ME values
    - ME values mostly <0 mg/L

Sheiner et Beal. *J Pharmacokinet Biopharm*. 1981

	Method	Study	Patients	Goal	Results
Predictive performance					
Pea et al 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 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 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 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 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 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 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 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

	Method	Study	Patients	Goal	Results	
Clinical outcomes						
Kullar et al 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 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%

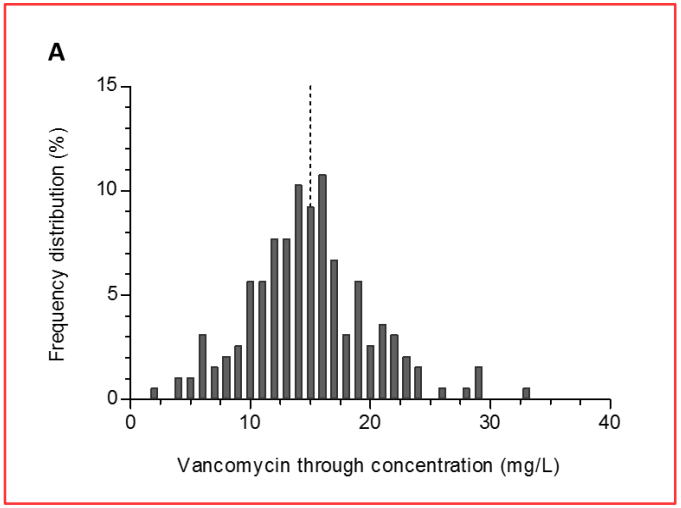
Leuven

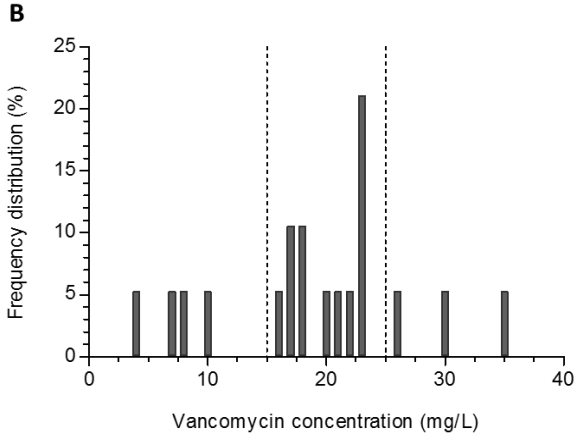
Intermittent

- Reference: ± 15 mg/L through
- 195 patients with 989 serum samples
  - Median samples/patient = 3 (range 1-30)
  - Median (IQR) through = 14,60 (11,70-17,46) mg/L
- Frequency distribution
  - 13-17 mg/L = 44,62%
  - 15-20 mg/L = 37.95%

Rybak et al. *Clin Infect Dis*. 2009

- 15-20 mg/L was never reached in 38,97% of patients

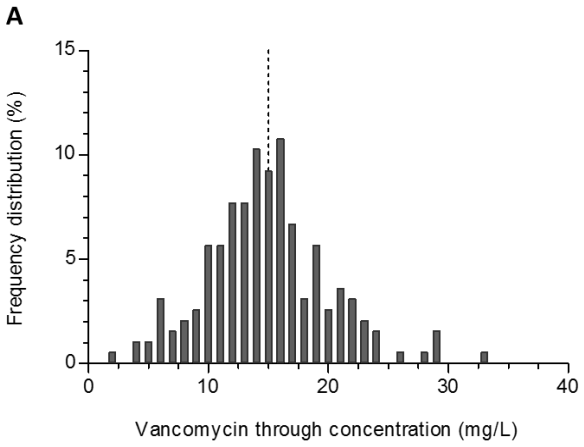


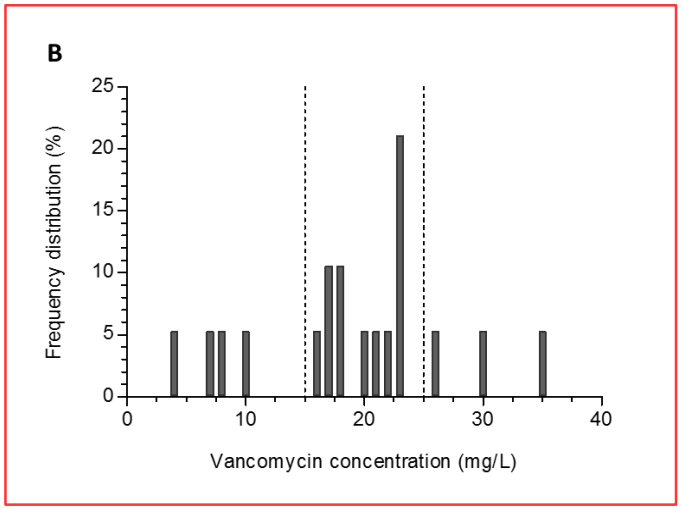


Leuven

Continuous

- Reference = 15-25 mg/L
- 19 patients with 57 serum samples
  - Median: 2 (range 1-17 samples/patient)
  - Median (IQR): 19,8 (15,6-23,4) mg/L
  - Erroneous test requests could not be excluded!
- Frequency distribution
  - 15-25 mg/L = 63.16%
  - 13-27 mg/L = 68.42%
- 15-25 mg/L was never reached in 31,75% patients





Belgium

TDM

	Laboratories n = 30
TDM performed by laboratory	28
– Through only	11
– Peak and through	16
– Continuous infusion separately	8
Reference values	
– Through reference values	21
– Sanford edition 2010[5]	5
– Rybak et al. 2009[4]	11
– Peak reference values	9
– Continuous reference values	21
– Sanford edition 2010[5]	3
– 20-30 mg/L	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

15-25 mg/L uncomplicated
25-35 mg/L complicated

10-15 mg/L uncomplicated
15-20 mg/L complicated

Belgium

TDM

	Laboratories n = 30
TDM performed by laboratory	28
– Through only	11
– Peak and through	16
– Continuous infusion separately	8
Reference values	
– Through reference values	21
– Sanford edition 2010[5]	5
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– In collaboration with other departments (e.g. hospital pharmacy)	5

20-25 mg/L uncomplicated
25-35 mg/L complicated