

EMA Workshop

Estimating the Probability of Target Attainment

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Estimating the Probability of Target Attainment

- We all tend to think problems through to solutions at the mean or median value of factors that affect outcome
- Sick infected patients have substantial between-patient variability in factors such as GFR, hepatic blood flow, capillary leakiness which will influence the concentration-time profile of an antimicrobial at the infection site and hence, outcome
- “Superclearers” resident in a VABP patient population is a great example

Estimating the Probability of Target Attainment

- Not having “adequate” antimicrobial therapy early in the course of infection imposes a burden of significantly higher attributable mortality and also of septic shock and number of complications
- Therefore, in order to attain the goal of optimal patient outcome (maximal effect, minimal toxicity) dose choice for the empiric therapy situation needs to be chosen explicitly accounting for between-patient variability
- The use of Monte Carlo simulation as a way forward for dose selection and breakpoint determination was described by our laboratory in 1998

Estimating the Probability of Target Attainment

Use of Preclinical Data for Selection of a Phase II/III Dose for Evernimicin and Identification of a Preclinical MIC Breakpoint

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D. ANDES,³ O. VESGA,³ AND W. A. CRAIG³

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The original presentation of this approach was at an FDA Anti-Infective Drug Product Advisory Committee in 1998 – It was voted upon and approved

Transcript, meeting of the Anti-Infective Drugs Advisory Committee, 15 October 1998. Available at: <http://www.fda.gov/ohrms/dockets/ac/98tctm.htm> (accessed 1/3/03).

Estimating the Probability of Target Attainment

- So, what are some issues surrounding the use of this approach?
 1. What source of pharmacokinetic parameter values are being employed and used to make inferences about a specific population?
 2. What is the “correct” probability of target attainment and **What is the target?**
 3. How do we factor in the balance between exposure and outcome and exposure and toxicity for drugs with an exposure-driven toxicity? (Yes, I did read the guideline)

Estimating the Probability of Target Attainment – **What Population?**

- It is important to make final dose choices on the basis of pharmacokinetic parameter values that are drawn from the population about which decisions are being made
- Using PK parameters from young CF patients is decidedly not a good idea if you are making decisions about adult VABP patients
- **The process is an iterative one** – start with Phase I volunteer data; inflate the variance; as new, more appropriate data come in, repeat the process until the most appropriate data are available

Estimating the Probability of Target Attainment – What Population?

Table 2. Population pharmacokinetic parameter values for meropenem used in the Monte Carlo simulations.

Value	CL _T , L/h	V _C , L	CL _D , L/h	V _P , L
Mean	13.34	9.45	14.96	5.78
SD	4.59	3.07	15.86	2.41

NOTE. CL_D, distributional clearance; CL_T, total serum clearance; V_C, volume of the central compartment; V_P, volume of the peripheral compartment.

34.4% Coefficient of Variation

Volunteer Data. Clin Infect Dis 2003;36 (Suppl 1): S42-50.

**63.9% Coefficient of Variation (Mean) or
71.9% Coefficient of Variation (Median)**

VABP Data. AAC 2011;55:3406-3412.

TABLE 3. Parameter estimates from the population pharmacokinetic analysis from 39 patients with ventilator-associated pneumonia

Parameter ^a	V _c (liters)	CL (liters/h)	K ₁₂ (h ⁻¹)	K ₂₁ (h ⁻¹)	K ₁₃ (h ⁻¹)	K ₃₁ (h ⁻¹)	V _{ELF} (liters)
Mean	12.6	15.2	8.32	14.1	10.1	14.2	30.4
Median	6.68	13.5	3.15	11.2	8.02	15.4	24.2
SD	13.3	9.71	9.82	11.8	8.63	11.4	25.2

^a V_c, volume of the central compartment; CL, plasma clearance; K₁₂, K₂₁, K₁₃, K₃₁, first order intercompartmental transfer rate constants; V_{ELF}, volume of the ELF compartment.

Estimating the Probability of Target Attainment – **What is the “Correct” Target Attainment Probability?**

- As to “What is the target?”, Dr. Ambrose and I have explored this previously
- What is the “Correct” Target Attainment Probability?
- Well, we would all like to have 95-100% target attainment (at least for dear old Mom – my Mother-In-Law is a different story – 75% looks pretty good to me)

Estimating the Probability of Target Attainment

“While this approach allows rational consideration of breakpoints, it still requires an explicit judgment to be made. *At what probability of success do we consider an MIC to represent susceptibility.*

This is not a question that can be definitively solved by any mathematical technique. Rather, it is a judgment to be reached by consensus among clinicians and microbiologists. These types of simulations represent decision support rather than decisions themselves.”

This also directly applies to **dose choice**

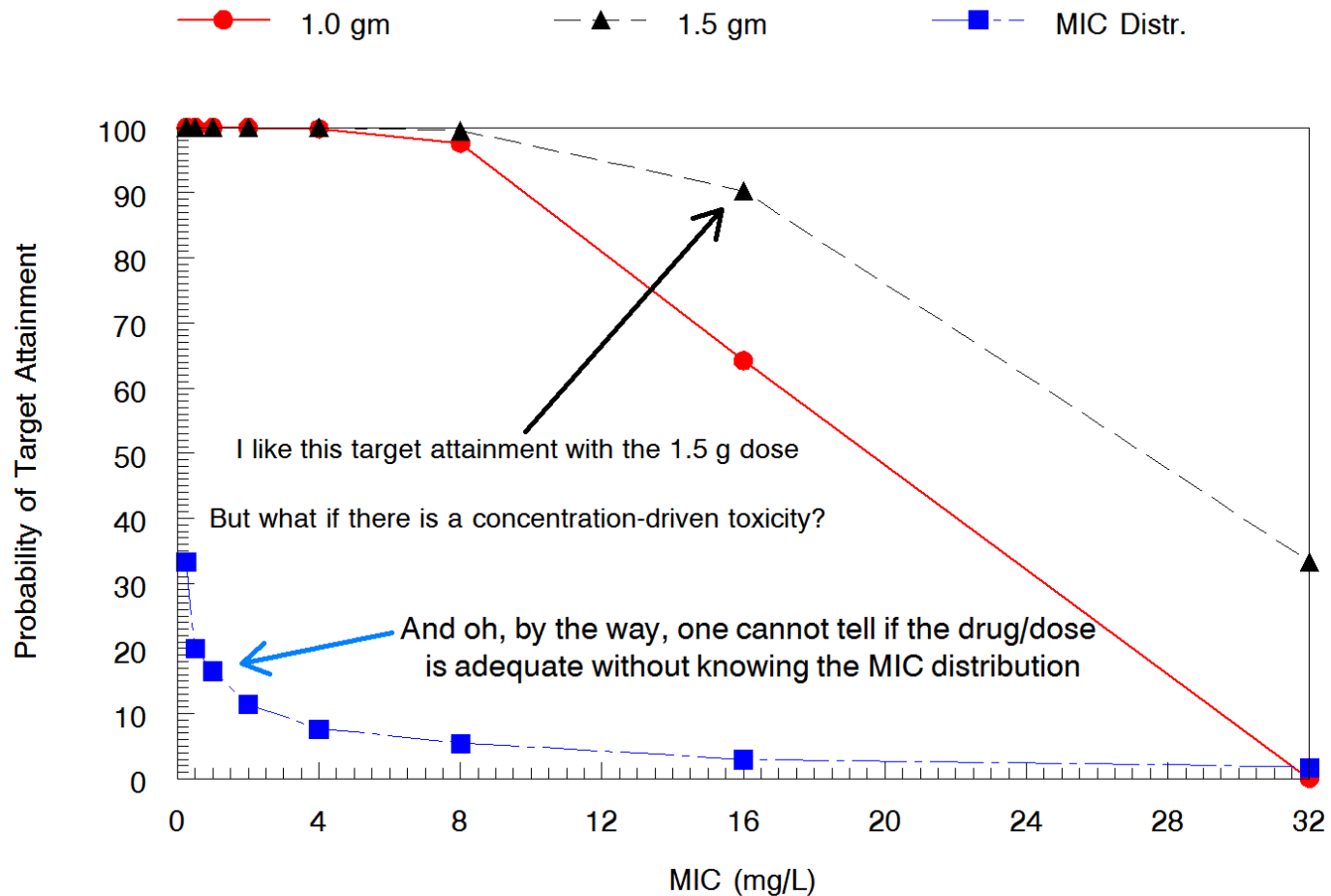
It is NOT an excuse to use an inadequate dose on the basis of something like cost of goods. If this is limiting, kill the drug!

Emphasis added for this presentation

Direct quotation from AAC original PTA Evernimicin paper

Estimating the Probability of Target Attainment

Probability of Target Attainment for Maximal Bacterial Cell Kill



Estimating the Probability of Target Attainment – Balancing Effect & Toxicity

- We sometimes are fortunate to have relationships both between exposure and response as well as exposure and toxicity
- Two examples are:
 1. Aminoglycosides
 2. Vancomycin
- Let us examine how the Monte Carlo simulation process allows rational decisions to be made. I will concentrate on vancomycin

Relationship between Initial Vancomycin Concentration-Time Profile and Nephrotoxicity among Hospitalized Patients

Thomas P. Lodise,^{1,2} Nimish Patel,¹ Ben M. Lomaestro,³ Keith A. Rodvold,⁴ and George L. Drusano²

¹Albany College of Pharmacy and Health Sciences, ²Ordway Research Institute, and ³Albany Medical Center Hospital, Albany, New York; and ⁴Colleges of Pharmacy and Medicine, University of Illinois at Chicago, Chicago

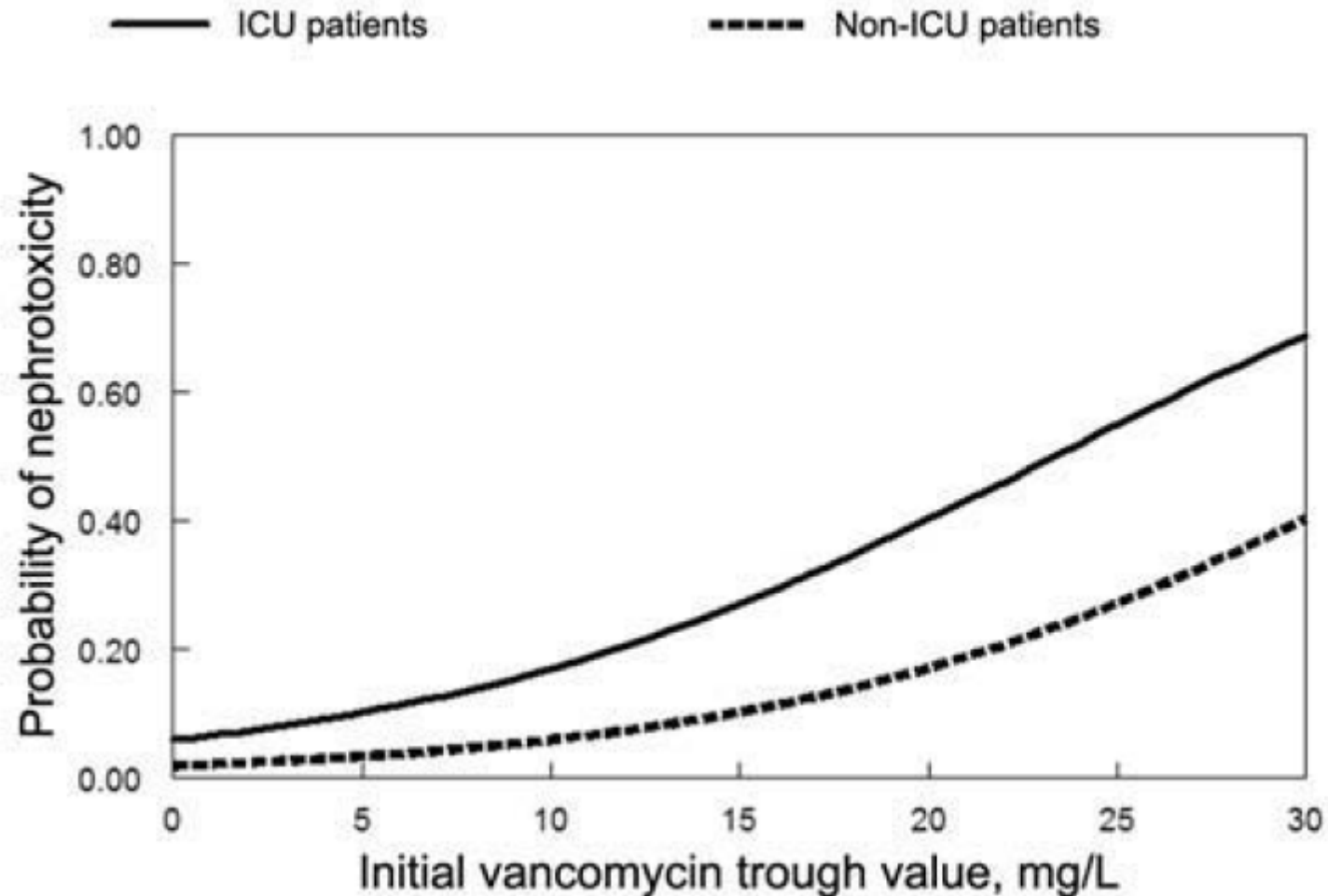
MAJOR ARTICLE

Vancomycin Exposure in Patients With Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infections: How Much Is Enough?

Thomas P. Lodise,¹ George L. Drusano,² Evan Zasowski,¹ Amanda Dihmess,¹ Victoria Lazariu,³ Leon Cosler,¹ and Louise-Anne McNutt³

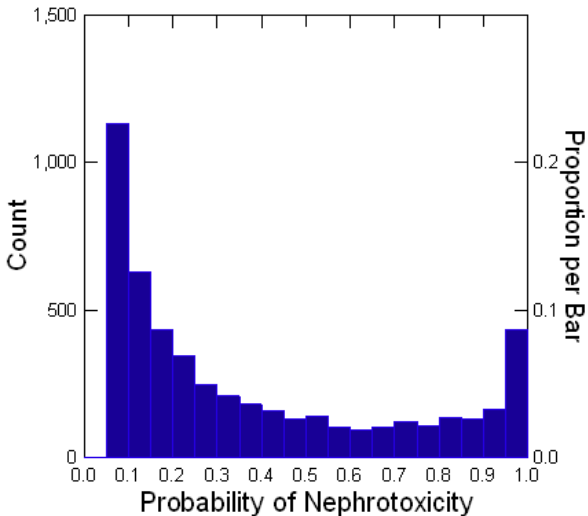
¹Albany College of Pharmacy and Health Sciences, New York; ²Institute for Therapeutic Innovation, College of Medicine, University of Florida, Lake Nona; and ³University at Albany, State University of New York

Estimating the Probability of Target Attainment – Balancing Effect & Toxicity

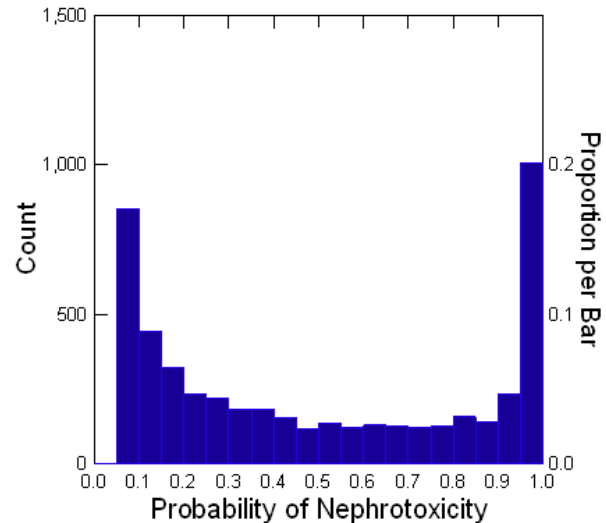


Estimating the Probability of Target Attainment – Balancing Effect & Toxicity

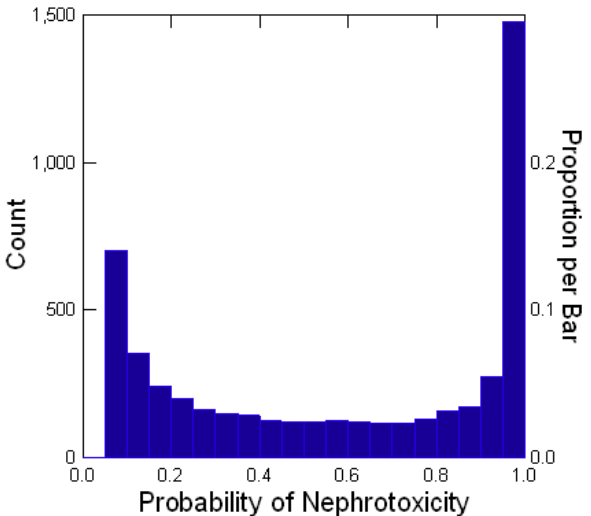
Vancomycin 1 g IV Every 12 h



Vancomycin 1.5 g IV Every 12 h



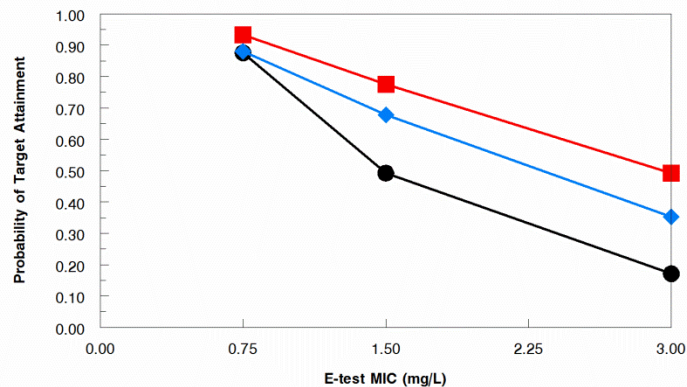
Vancomycin 2 g Every 12 h



Probability of Vancomycin Effect

Patients with MRSA Blood Stream Infections

● 1 g IV Every 12 h ◆ 1.5 g IV Every 12 h ■ 2 g IV Every 12 h

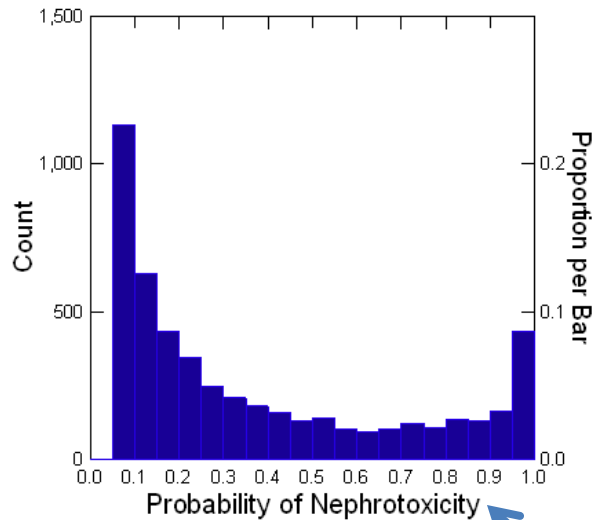


Probability of nephrotoxicity was derived from the Logistic Regression analysis in Clin Infect Dis 2009;49:507-514.

Probability of vancomycin effect in patients with MRSA bloodstream infections was derived using an E-test AUC/MIC target of 320 in Clin Infect Dis 2014;59:666-675.

Estimating the Probability of Target Attainment – Balancing Effect & Toxicity

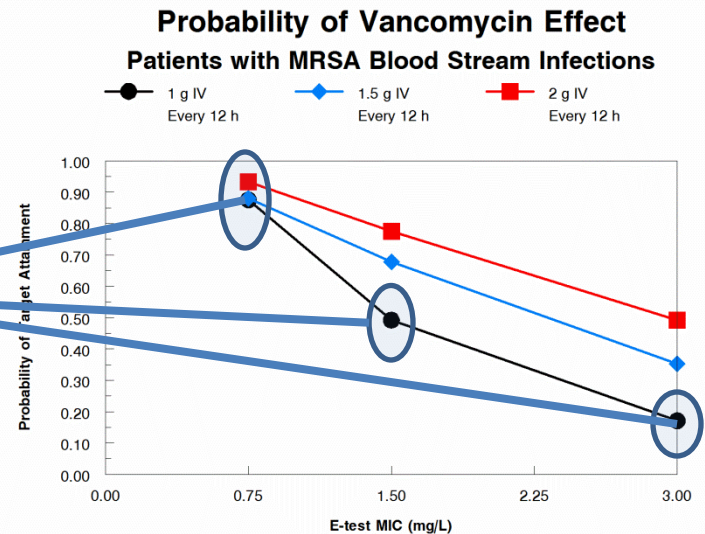
Vancomycin 1 g IV Every 12 h



**Amortized Probability of
Vancomycin Nephrotoxicity is
24.3%**

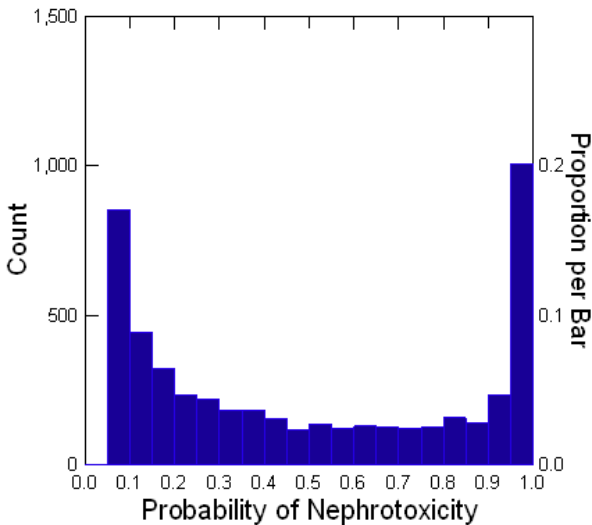
These were drawn from a population of MRSA bacteremia patients

Nephrotoxic probability stays the same irrespective of MIC. Target attainment falls to unacceptable levels with an E-test MIC > 0.75 mg/L.



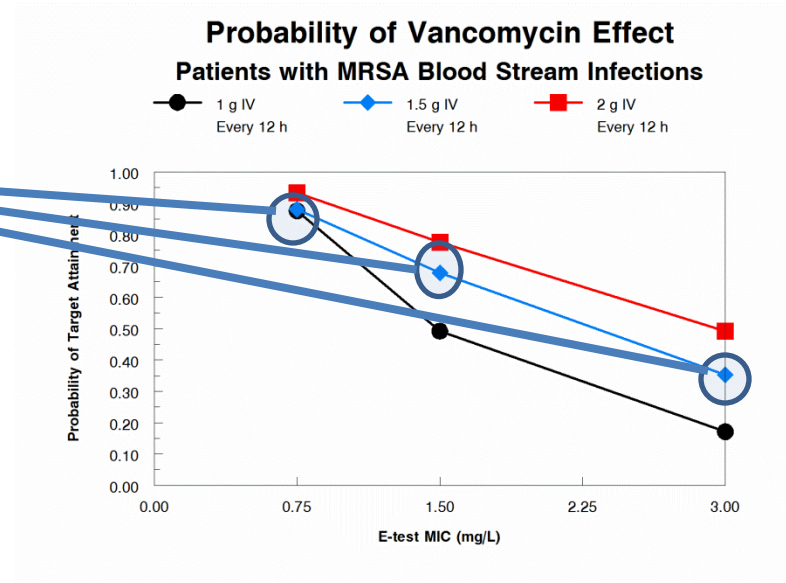
Estimating the Probability of Target Attainment – Balancing Effect & Toxicity

Vancomycin 1.5 g IV Every 12 h



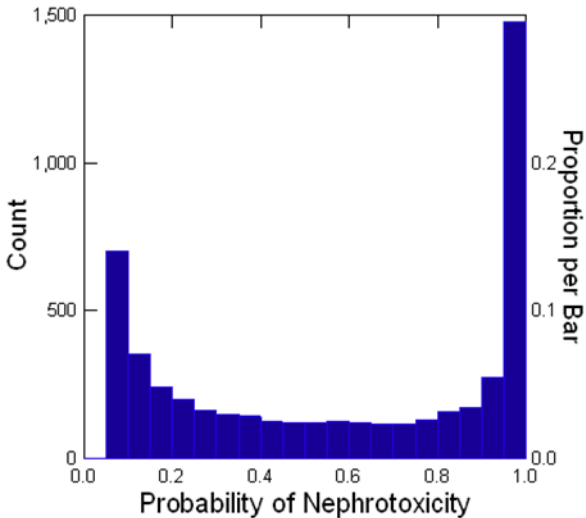
Amortized Probability of Vancomycin Nephrotoxicity is 42.2%

Nephrotoxic probability stays the same irrespective of MIC but increases due to dose. Target attainment falls to 68% levels with an E-test MIC of 1.5 mg/L.



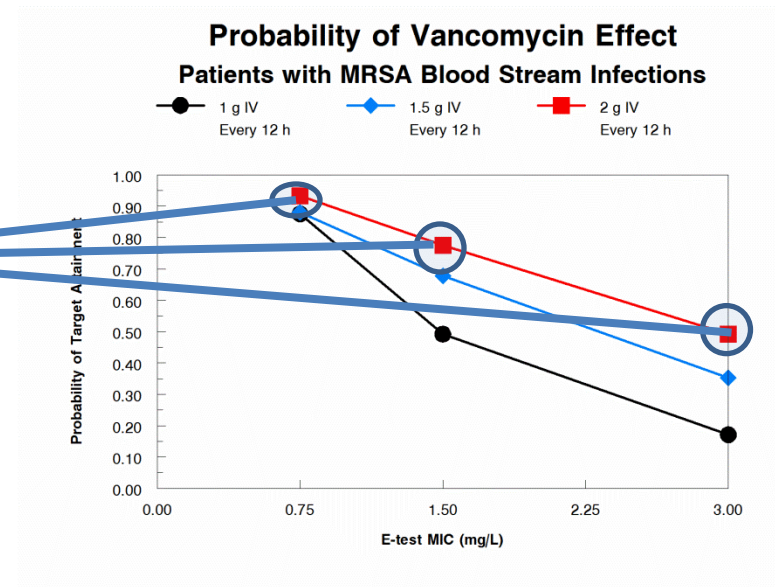
Estimating the Probability of Target Attainment – Balancing Effect & Toxicity

Vancomycin 2 g Every 12 h



Amortized Probability of Vancomycin Nephrotoxicity is 62.4%

Nephrotoxic probability stays the same irrespective of MIC but increases due to dose. Target attainment falls to 77.5% with an E-test MIC of 1.5 mg/L and 49.2% at 3.0 mg/L.



Estimating the Probability of Target Attainment – Balancing Effect & Toxicity

- Yes, I know vancomycin is “cheap” – How much does an engendered nephrotoxic event cost?
- And at the standard dose, where toxicity is (sort of) tolerable, target attainment is unacceptable at the MIC value where most of the organisms are (at least in the US).
- Time for another MRSA drug

Estimating the Probability of Target Attainment - Conclusions

- Monte Carlo simulation is a valuable technique to drive the dose to the right place and to warn you when “You cannot get there from here”
- Pay attention to the population used for simulation!
- What is the “correct” target attainment? – whatever reasonable people say it is – I am OK with 70% target attainment if more goes to unbearable toxicity and no other drug is available (colistin sound familiar for multi-resistant Gm-’s?)

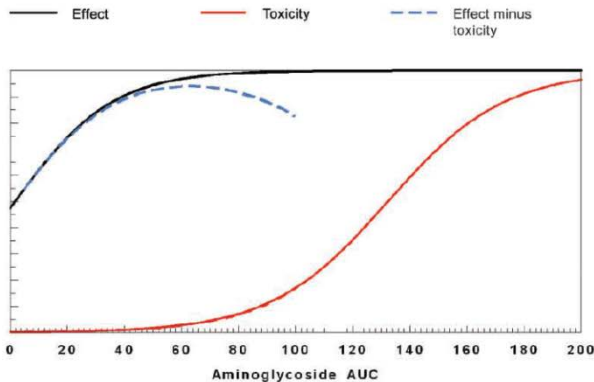
Estimating the Probability of Target Attainment - Conclusions

- What is the “correct” target? Dr. Ambrose and I have discussed this
- The aim of antimicrobial chemotherapy is to achieve maximal effect while minimizing concentration-driven toxicities
- So, please, if there are two exposure relationships available please use them
- Our patients deserve no less

Thank You for Your
Attention!

Estimating the Probability of Target Attainment – Balancing Effect & Toxicity

A.



INVITED ARTICLE

ANTIMICROBIAL RESISTANCE

George M. Eliopoulos, Section Editor

Back to the Future: Using Aminoglycosides Again and How to Dose Them Optimally

George L. Drusano, Paul G. Ambrose, Sujata M. Bhavnani, Joseph S. Bertino, Ann N. Nafziger, and Arnold Louie
Ordway Research Institute, Albany, New York

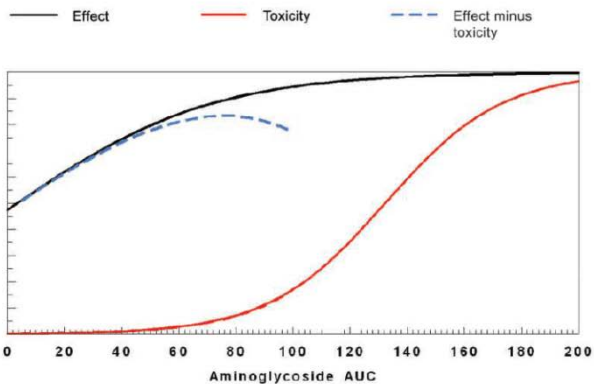
Clinical Infectious Diseases 2007;45:753–60

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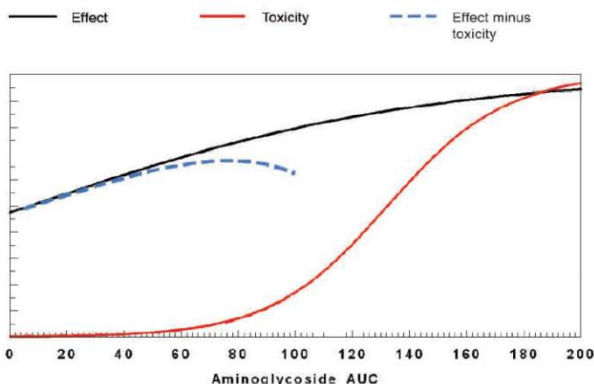
1058-4838/2007/4506-0013\$15.00

DOI: 10.1086/520991

B.



C.



The blue dotted line is the difference between the probability of response and the probability of nephrotoxicity.

This is deterministic. There is another approach using Monte Carlo simulation.

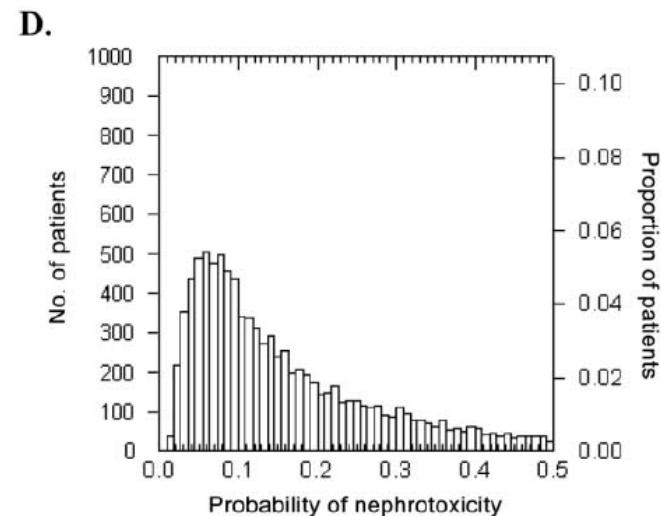
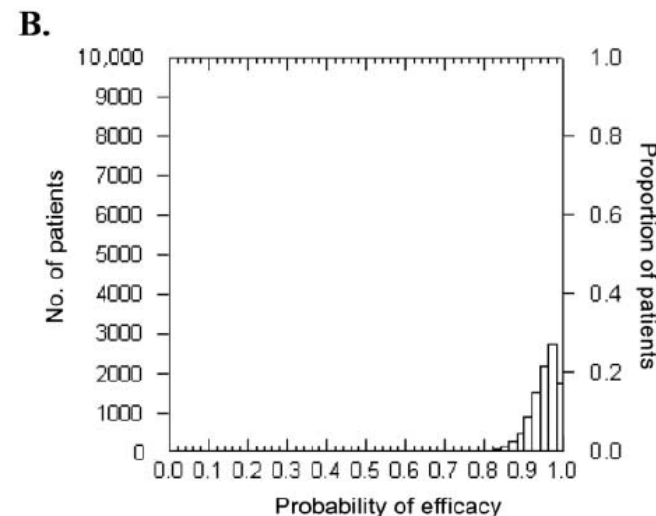
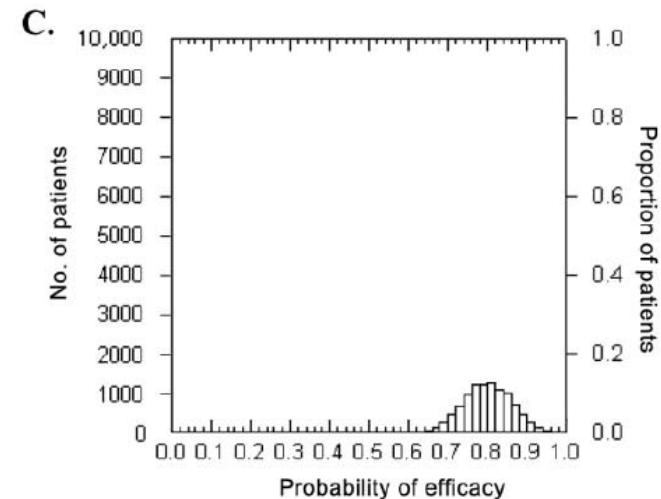
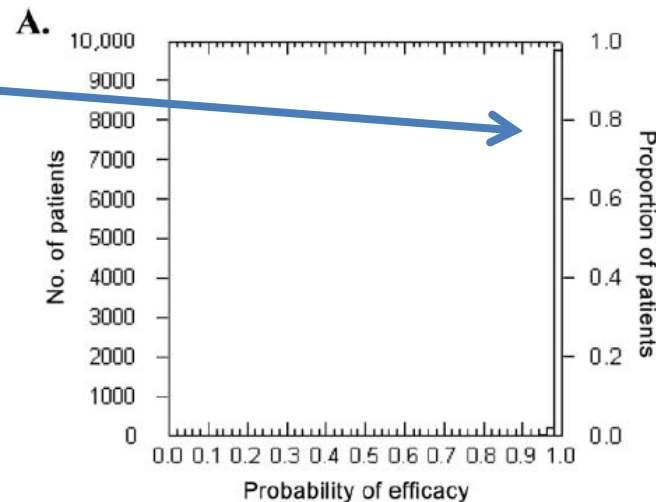
Estimating the Probability of Target Attainment – Balancing Effect & Toxicity

All the probability of response = 1.0

A: MIC=0.25 mg/L
B: MIC=0.5 mg/L
C: MIC=1.0 mg/L
D: Prob Nephrotox

The simulations are for 2.5 mg/kg of gentamicin every 12 hours.

The effect/toxicity distributions are derived from the logistic regression functions on the previous slide



Estimating the Probability of Target Attainment – Balancing Effect & Toxicity

- Even at the modest 5 mg/kg/day dose (administered 12 hourly), one runs out of room quickly to achieve effect with only a modest degree of toxicity
- This would look MUCH better had the aminoglycoside been administered daily
- The approach, however is the issue and can be applied when we have both relationships
- Let us look at my least favorite drug – vancomycin!