Therapeutic Drug Monitoring
ECCMID Session ME14

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Practical issues in delivering TDM services

- Sampling strategies
  - Pre or post dose samples?
  - Short PK profile?
  - Limited sampling and Bayesian analysis?
- When to sample
  - Steady state?
  - Within 24h of starting?
  - Rapidly changing physiology?
- How to adjust dosing
  - Empirically?
  - Using specialist software?

From
Andrew Lovering

What's the point of TDM?

- To measure a surrogate variable (i.e. drug concentration) when the desired or undesired clinical effect is delayed or not easily measurable
- To use that data to optimize the dose and maximize chances of a successful therapeutic outcome

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

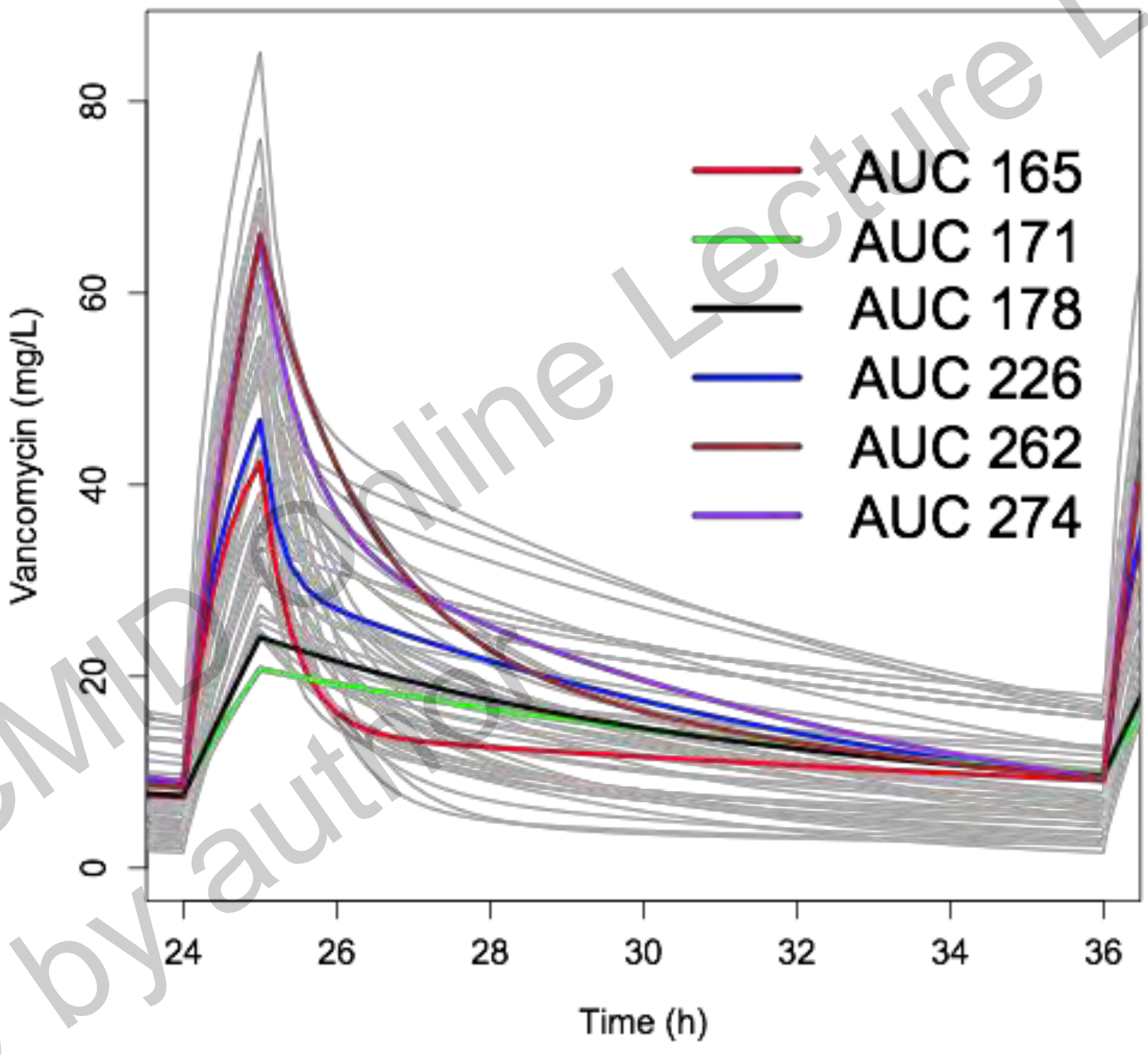
Michael J. Rybak,[1,2,3] Ben M. Lomaestro,[4] John C. Rotschafer,[5] Robert C. Moellering, Jr.,[6,7,8] William A. Craig,[9] Marianne Billeter,[10] Joseph R. Dalovisio,[11] and Donald P. Levine[12]

2 mg/L. Vancomycin displays concentration-independent activity against *S. aureus*, with the area under the concentration curve (AUC) divided by the MIC as the primary predictive pharmacodynamic parameter for efficacy. On the basis of in vitro, animal, and limited human data, an AUC/MIC value of 400 has been established as the pharmacokinetic-pharmacodynamic target. To achieve this target, larger vancomycin doses

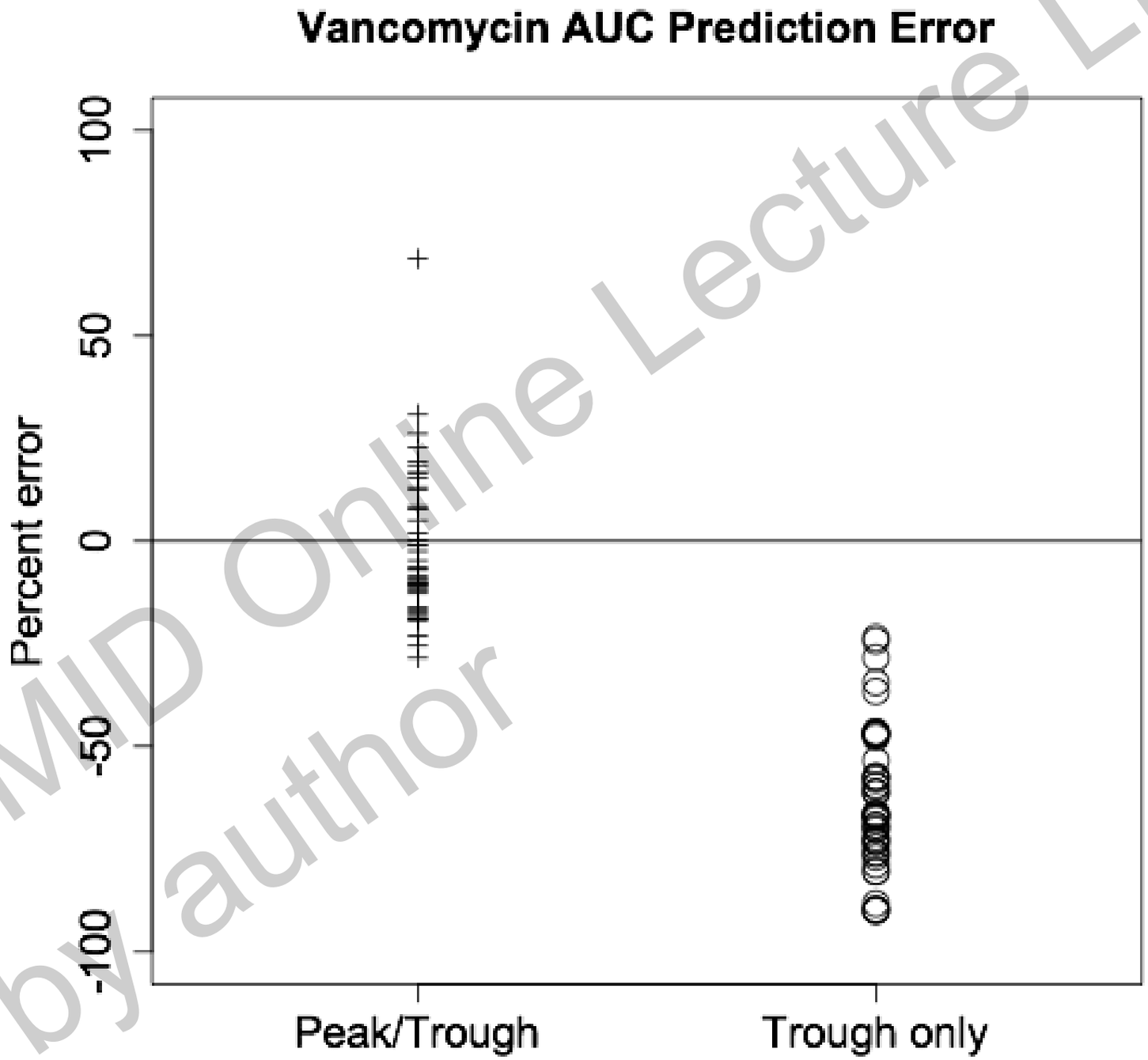
Peak versus trough concentrations. Trough serum vancomycin concentrations are the most accurate and practical method of monitoring the effectiveness of vancomycin. Trough serum concentrations should be obtained just before the fourth dose, at steady-state conditions. (Note that steady-state achievement is variable but occurs approximately just before the fourth dose.) (Level of evidence, II; grade of recommendation, B.)

Vancomycin dosages of 15–20 mg/kg (based on actual body weight) given every 8–12 h are required for most patients with normal renal function to achieve the suggested trough serum concentrations when the MIC is ≤1 mg/L. It should be noted that currently available nomograms were not developed to achieve these targeted end points. Individual pharmacokinetic adjustments and verification of achievement of target serum concentrations are recommended. When individual doses ex-

Trough Information



Trough Information



What is “Clinical Pharmacometrics”?

- Pharmacometrics - A multidisciplinary practice incorporating clinical, biomedical, biological, engineering, statistical and mathematical concepts and techniques to guide all aspects of human therapeutic drug science, from basic research, through pre-clinical and clinical development, to rational and optimal use in patients.[1]
- Clinical pharmacometrics - The application of pharmacometric skills to optimize dosing in an individual patient by achieving target concentrations with maximal precision and accuracy.[2]

1. Pfister M and D’Argenio D. The emerging scientific discipline of pharmacometrics. J Clin Pharmacol 2010;50(Supp 1):6S
2. Neely M and Jelliffe R. Practical, individualized dosing: 21st century therapeutics and the clinical pharmacometrician. J Clin Pharmacol 2010;50(7):842-7

Pharmacometric lingo

- PK - pharmacokinetics
- PD - pharmacodynamics
- Models - equations to summarize a biologic system, e.g. the time-concentration relationship of a drug in the body
- Parameters - Variables in a model, values of which are generally to be estimated, e.g. clearance or volume of distribution
- Population modeling - Models which summarize biologic systems in groups of individuals, estimating sources of variability
- Simulation - Using a population model and its estimated parameter values to generate new data, and compare these predictions with observations

More lingo

- Bayesian statistics - In contrast to traditional frequentist statistics, Bayesian statistics formally incorporate prior experience into current analyses
- Bayesian priors and posteriors

When is TDM potentially useful?

1. Variable inter-individual pharmacokinetics
2. Drug for which efficacy (and/or toxicity) target concentration has been established
3. Drug assay available
4. It is more cost-effective to employ concentration-control strategies than to dose “traditionally”
5. Drug with a “narrow” therapeutic index
6. High drug cost

Gentamicin

- Non-randomized, sequential cohort, multi-center
- Adult immunocompetent patients without severe renal insufficiency and with suspected or documented Gram neg infection
- First cohort: standard gentamicin dosing (tid)
- Second cohort: individualized dosing

- Lent-Evers et al. Impact of goal-oriented and model-based clinical pharmacokinetic dosing of aminoglycosides on clinical outcome: a cost-effectiveness analysis. Ther Drug Monit. 1999 Feb;21(1):63-73.

Methods

- Main outcome variables
  - Costs – hospitalization, TDM service
  - Effects – survival, days of hospitalization (if a survivor), length of therapy, days in ICU, incidence of nephrotoxicity and ototoxicity

Results

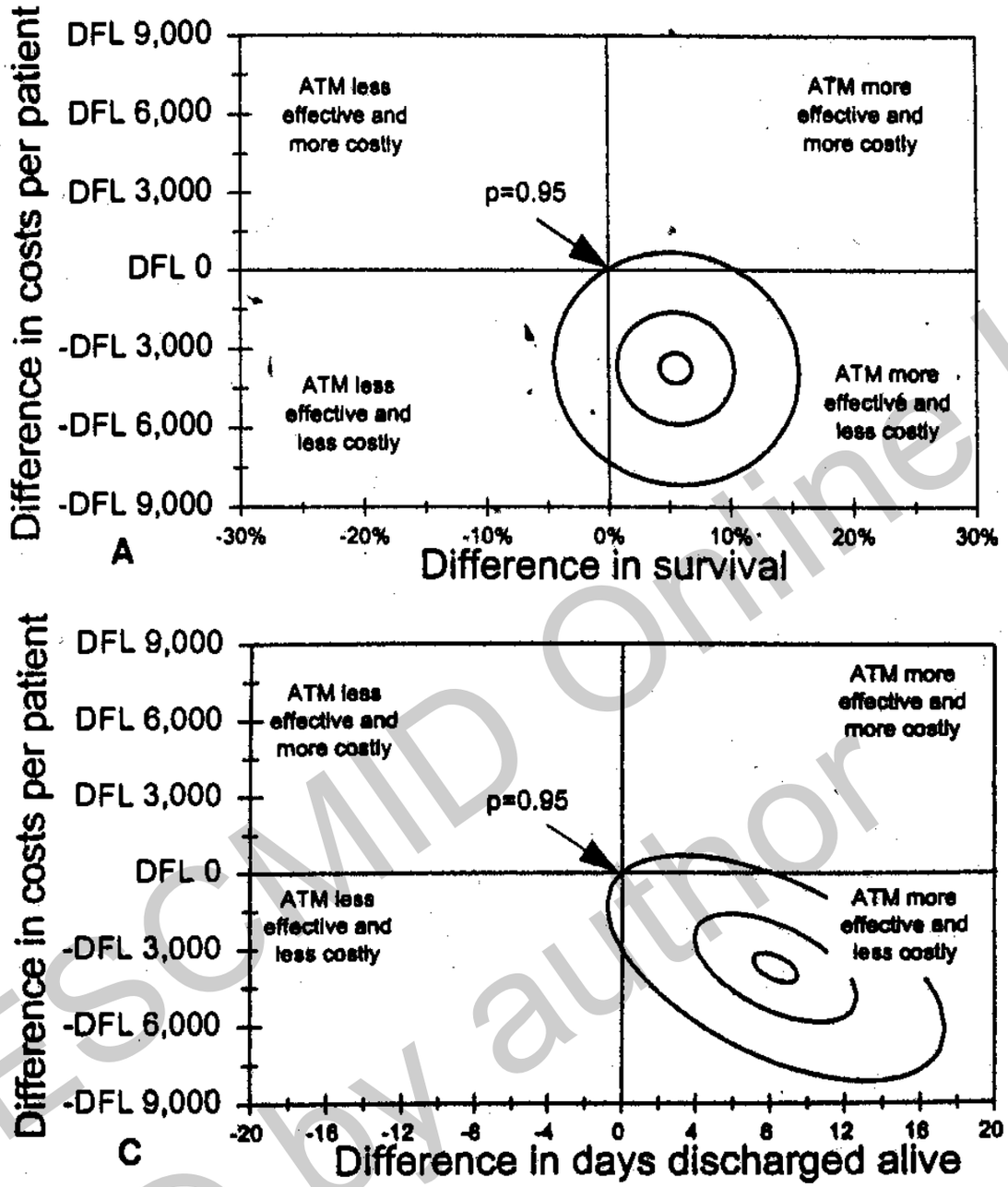
	Adaptive TDM	Standard TDM
Patients	105	127
Proven infection	48 (46%)	62 (49%)
Peak conc	10.6±2.9 ug/ml	7.6±2.2 ug/ml*
Trough conc	0.7±0.6 ug/ml	1.4±1.3 ug/ml*
Mortality	9 (9%)	18 (14%)
with infection	1 (2%)	9 (15%)*

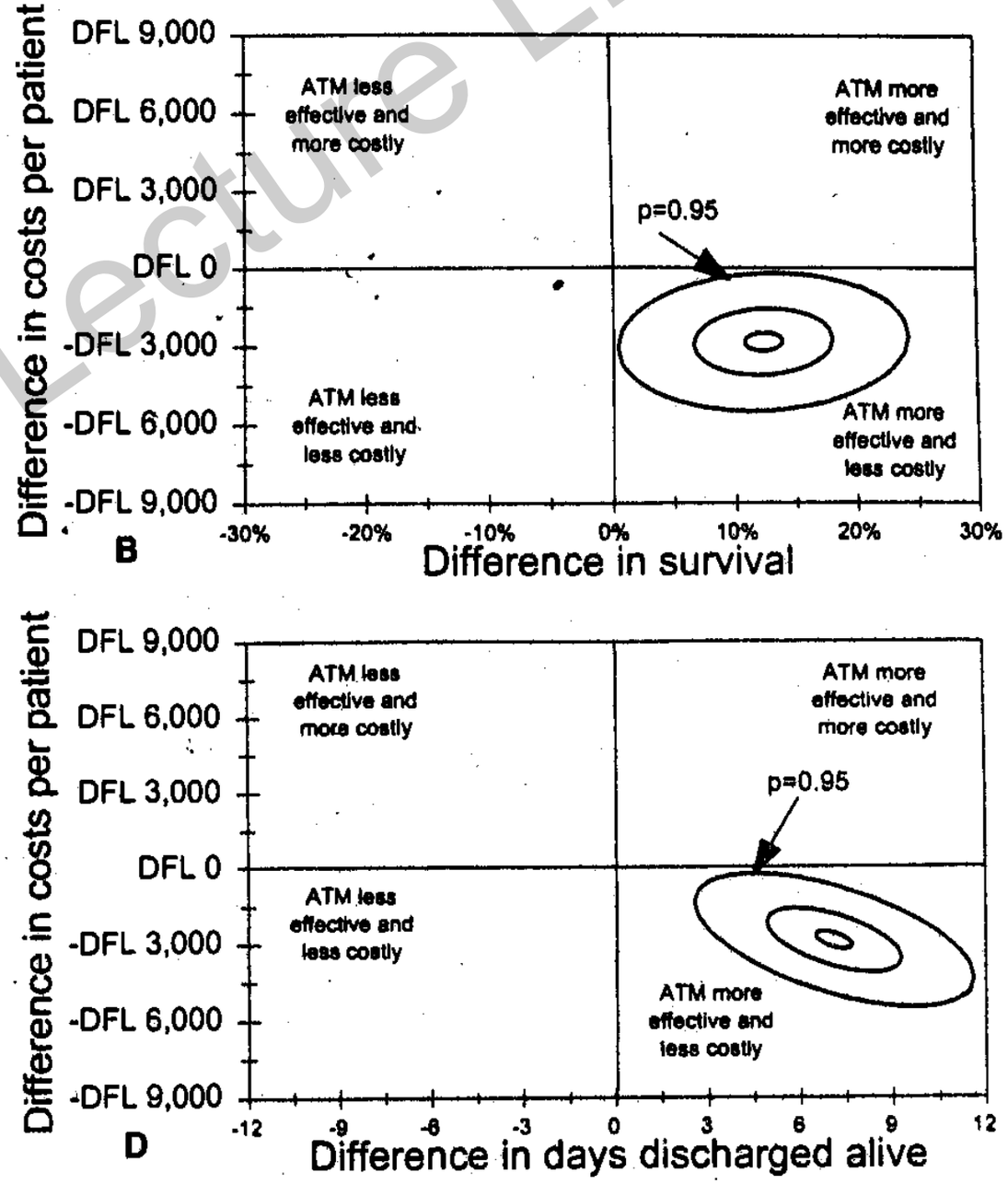
* P≤0.05

Results

All patients

Documented infection





NCA (Cmax, AUC, T>MIC

Exposure response

Safety model / relationship

(Population) PK model

(Population) PD model

Simulation of drug concentrations

Predict effect and safety for *in vitro* and animal models, and ultimately **patients**

estimation tools

BestDose
ID-ODS
DoseMe
TCI Works
MWPharm
First-dose
CADDy
WinAUIC

Optimal dosing

Optimal trial design → PK/PD model

Individual patient

Patient population

Robust Clinical Trial design

BUT ..!

Patient

- male
- 33 years
- necrotizing fasciitis extended from right leg to the chest
- creatinine clearance 30 ml / min (CVVH)
- infecting strain: MRSA (dapto MIC 0,5)
- Treatment: daptomycin 6 mg/kg

Dose adjustments in patients with renal impairment by indication and creatinine clearance

Indication for use	Creatinine clearance	Dose recommendation
cSSTI without *S. aureus* bacteraemia	≥ 30 ml/min	4 mg/kg once daily
	< 30 ml/min	4 mg/kg every 48 hours
RIE or cSSTI associated with *S. aureus* bacteraemia	≥ 30 ml/min	6 mg/kg once daily
	< 30 ml/min	6 mg/kg every 48 hours

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000637/WC500036049.pdf

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2004, p. 2799–2807

Population Pharmacokinetics of Daptomycin

Barry Dvorchik,[1]* Robert D. Arbeit,[1]† Julia Chung,[2] Susan Liu,[2] William Knebel,[2] and Helen Kastrissios[2]

Pharmacokinetic parameter	Value for phase 1 subjects in CL_{CR} group			
	≥80 ml/min (n = 79)	<80 to >40 ml/min (n = 48)	≤40 ml/min (n = 8)	On dialysis (n = 18)
$AUC_{(0-\infty)}$ (μg · h/ml)[a]				
Median	443.79	453.18	987.02	1,310.05
Minimum	247.12	206.12	477.08	772.29
Maximum	802.04	1,181.00	1,677.00	1,906.00

The currently suggested ranges for daptomycin TDM may be

Cmin of 10–24.3 mg/L

30 min post-dosing peak level (C_{max}) of 66–112 mg/L,

with the intent of achieving an AUC24) of 465–761 mg*h/L

Chaves RL, et al.. J Antimicrob Chemother 2014; 69 (1):200–210.
Pea F, et al. Ann Pharmacother 2011; 45 (7–8): e37.
5

TDM

	Day 1 6 mg/kg	Day 2 8 mg kg	Day 3 10 mg7kg	Day 4 12 mg/kg
C min mg/L	2,3	4,6	7,3	14,7
Cmax	-	38,7	56,8	72,7

In a patient with 30 ml/min of Clr !!!

Barriers to effective TDM

- <u>Factors Related to the Individual Patient</u>
  - Predefined sample times, e.g. troughs, may not occur when the patient is in clinic.
  - The exact times of the doses preceding the blood sample are not known, introducing a large element of uncertainty in the interpretation of a single drug concentration.
  - Between-patient or within-patient (inter-occasion) pharmacokinetic variability, e.g. in bioavailability, confounds interpretation of drug concentrations.

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Barriers to effective TDM

- <u>Factors Related to the Therapeutic Process</u>
  - Drug concentrations may not be readily available
  - Concentration targets may be poorly defined
  - Turn around time for results may be excessive
  - Lack of staff expertise

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BArriers to effective TDM

- <u>Factors Related to the Therapeutic Process (cont'd)</u>
  - Pharmacokinetic data that are nonexistent or unusable for dose optimization
  - Paucity of tools such as user-friendly dose optimization software
  - Poor reimbursement by medical payors

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Barriers to effective TDM

- <u>Factors Related to the Scientific-Medical Culture</u>
  - Drug development process geared toward a “one-size-fits-all” dose and not target-oriented therapy
  - Limited commitment or mechanism to update dosing guidelines as post-market evidence emerges
  - Limited or no physician training in basic or applied pharmacology

Barriers to effective TDM

- Factors Related to the Scientific-Medical Culture (cont'd)
  - Insufficient partnership between physicians and clinical pharmacists to dose complex or atypical patients

Thank you