Application of PK/PD in New Anti-Infective Drug Development:
Current Challenges and Future Perspectives

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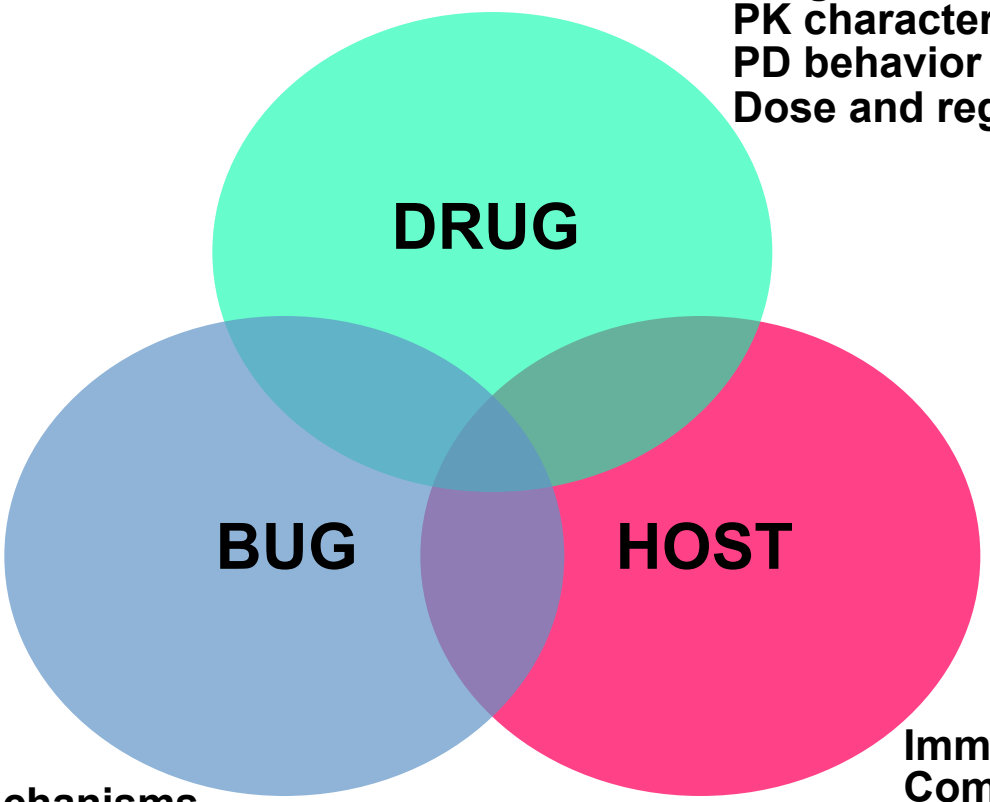
Outline

- Summarize PK/PD principles for anti-infective drugs: Current application
- Describe potential application of PK/PD in new anti-infective drug development
- Discuss current challenges and future perspectives

Why is PK/PD information important?

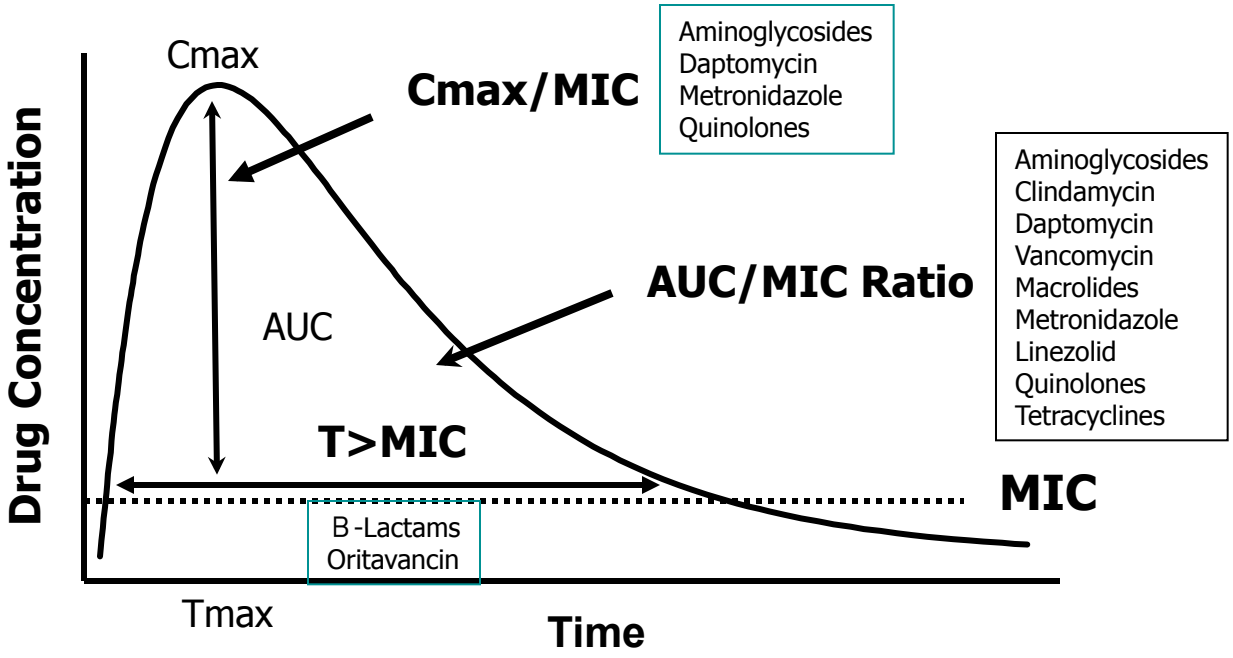


Drug class/MOA
PK characteristics
PD behavior
Dose and regimen

Susceptibility
Resistance mechanisms
MIC

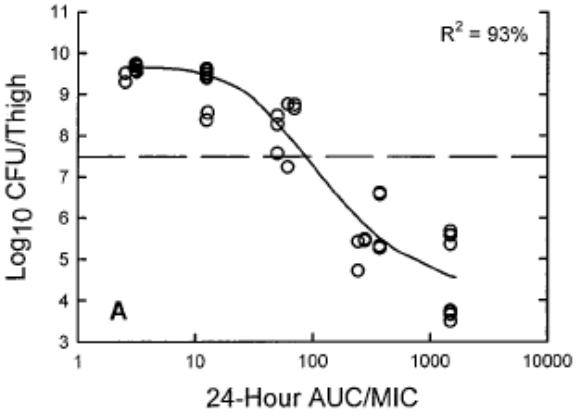
Immunocompetence
Comorbidities
Previous treatment
Colonization

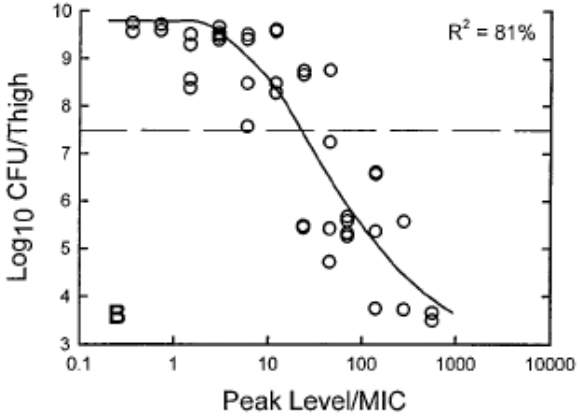
PK/PD index: Determinant of drug response

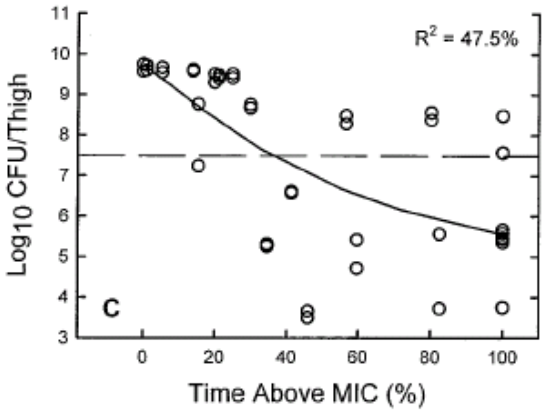


Identifying the PK/PD index that best correlates with efficacy

- In vitro hollow-fiber system
- Animal model of infection

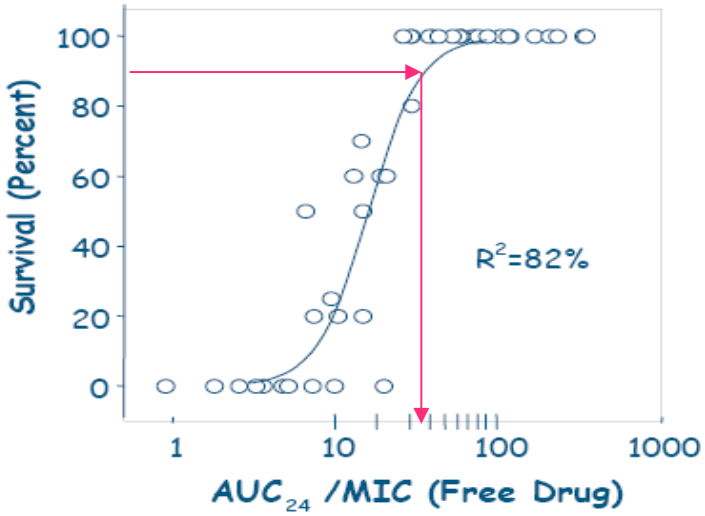


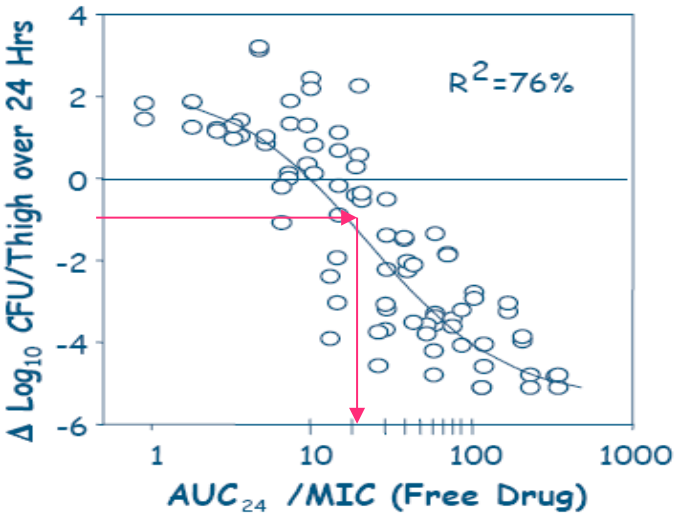




Determination of PK/PD Target

PK/PD target: The magnitude of PK/PD index required for desired efficacy in animal models of infection

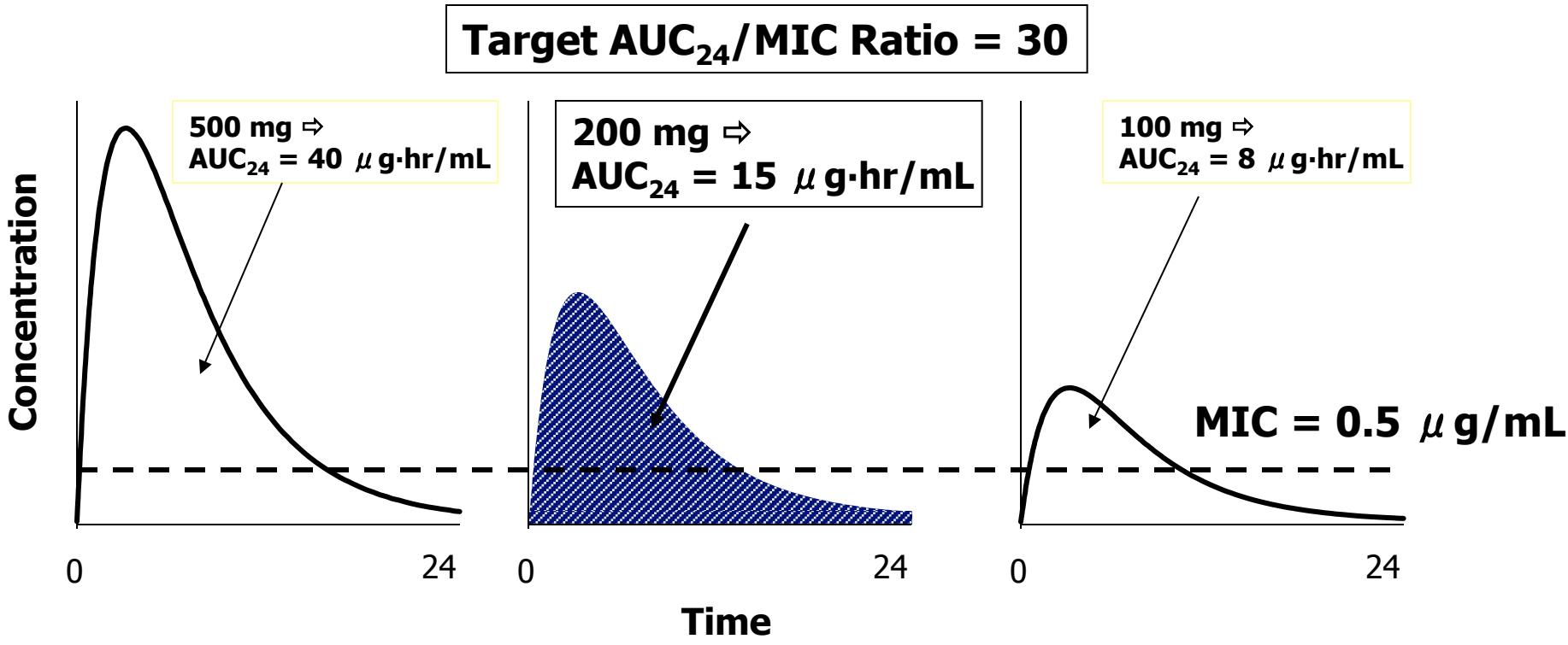




⇨ PK/PD target determined from animal models is used as the target for humans.

Current Utility of PK/PD target

Dose selection for clinical studies:



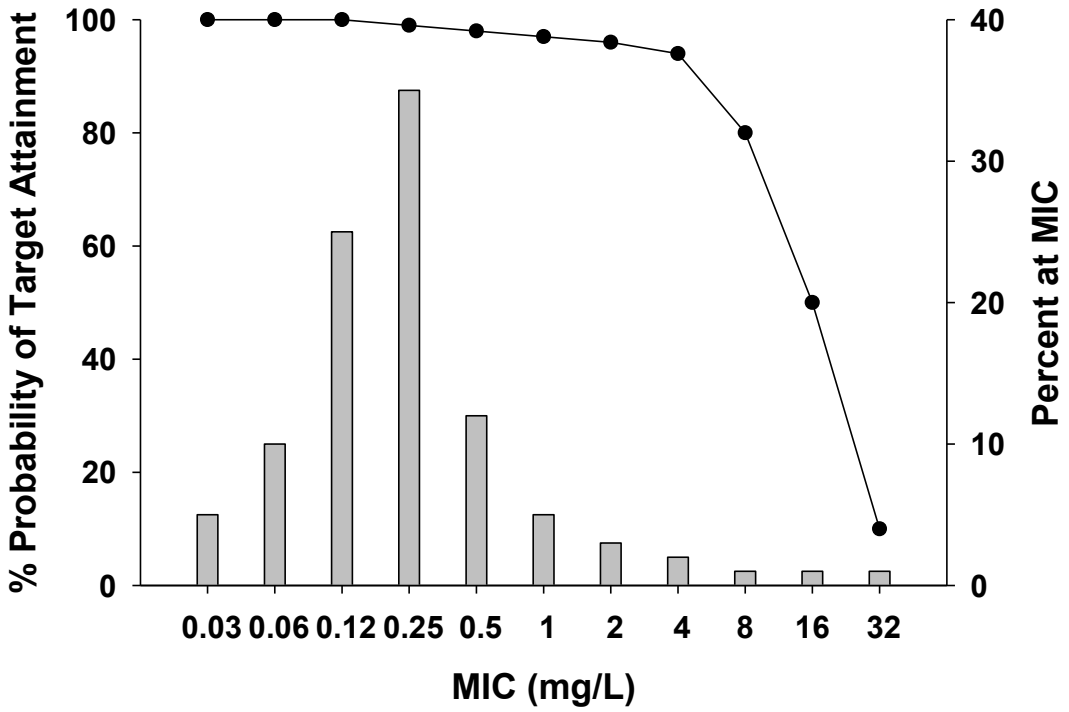
Current Utility of PK/PD target: Probability of Target Attainment (PTA)

PK/PD target & Human (Patients) PK

Target AUC_{24}/MIC Ratio = 5 Dose: 100 mg QD

AUC (n=1000)	AUC/MIC (n=1000)			
	MIC=1	MIC=2	MIC=4	MIC=8
10 (P1)….	10	5	2.5	1.25
20 (P10)….	20	10	5	2.5
30 (P25)….	30	15	7.5	3.75
40 (P40)….	40	20	10	5
…..	…..	……	…….	…….
200 (P100)	200	100	50	25
% PTA	**~100%**	**99%**	**90%**	**60%**

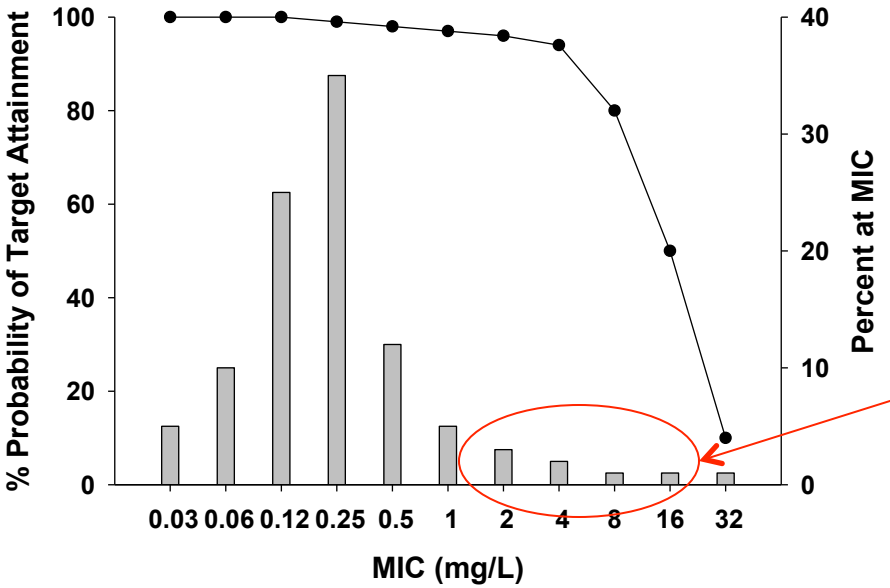
Probability of Target Attainment



- To determine susceptibility criteria
- To evaluate the clinical dose proposed

Potential Application of PTA as an Evidence of Drug Efficacy

When a clinical efficacy trial is not feasible or is limited for infections or pathogens of low occurrence,



too rare to evaluate clinical efficacy

Quality of data for **PK/PD target** and **human PK simulation** are critical.

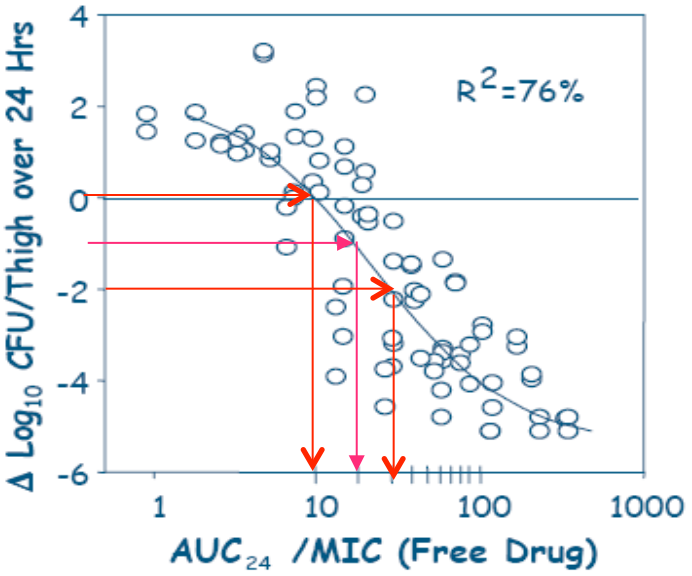
PTA as an Evidence of Drug Efficacy: Limitations and Challenges

PK/PD target determined in animal model

- PD endpoints *vs.* Clinical Response:
  stasis, 1-log kill, 2-log kill, or survival in animals

- Role of immune system:
  Immunocompromised animals

- Concentrations in infection sites
  Animals ≤ Human



PTA as an Evidence of Drug Efficacy: Limitations and Challenges

Human PK simulations

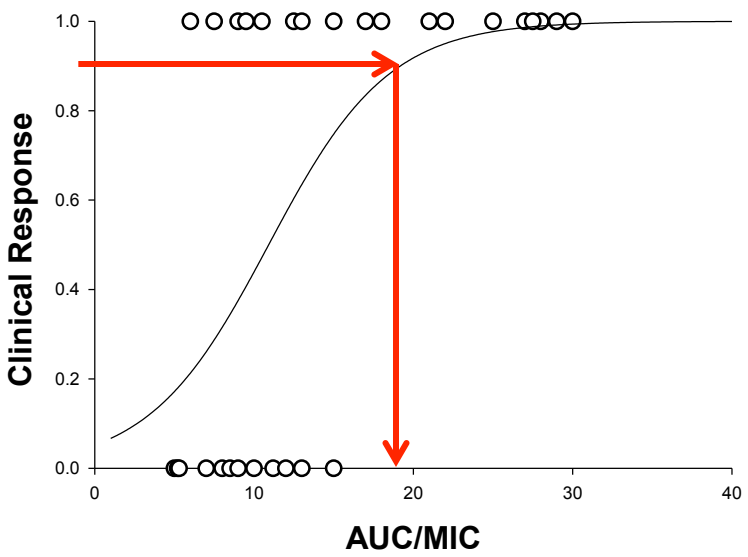
- Monte Carlo Simulation: Observed PK variability
- Different variability b/w healthy subjects vs. patients with infection

  35±8.5 (HS) *vs.* 33±23 (Pts)

- Covariates of Pop. PK:
  Comorbidities, Infection itself, and etc

PTA as an Evidence of Drug Efficacy: Future Perspective

- Intensive animal studies with better animal models
- PK/PD target using clinical exposure-response data
- PK, MIC, and clinical outcomes from Phase 2 dose-ranging studies
- PK, MIC, and clinical outcomes from Phase 3 studies:
  To apply to other infection sites



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