

Experiences with MIC-based PK/PD indices in the dose selection of antimicrobial drugs

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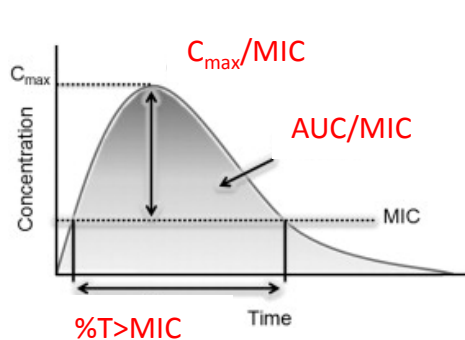
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Outline

- General workflow using MIC-based PK/PD indices
- Implications of MIC-based PK/PD indices
- Concerns and caveats
- Limitations of MIC-based PK/PD indices
 - Pharmacological Consideration
- Potential solutions
- Summary

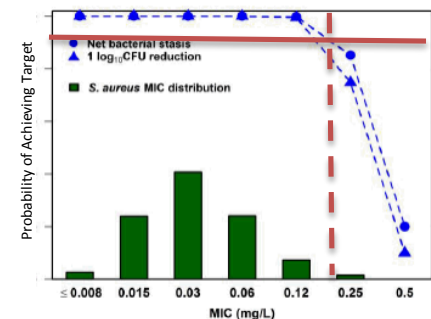
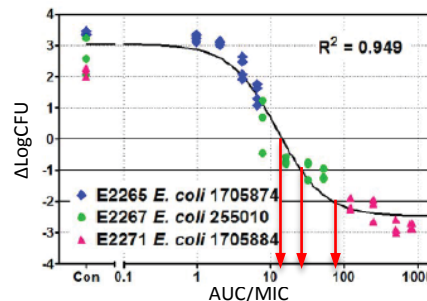
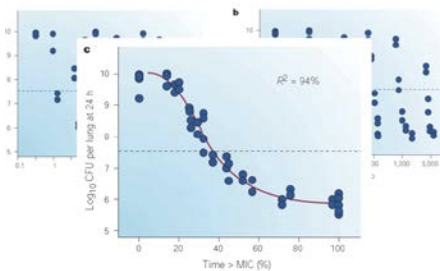
General Workflow Using MIC-based PK/PD Indices



Identify an appropriate PK/PD index in dose fractionation studies

Determine a PK/PD target value in animal infection models

PTA analysis, select a dose that can cover a target MIC



Implication of MIC-based PK/PD Indices

- Limited supportive evidence for clinical efficacy at high MICs in clinical trials

Drug name	Year Approved	Indication	Proposed Target MIC (mcg/mL) by PTA Prediction	Clinical Efficacy at the Proposed Target MIC, n/N (cure/total)
Meropenem and Vaborbactam	2017	cUTI	8	Enterobacteriaceae: 1/1*
Delaflaxacin	2017	ABSSSI	0.5	<i>S. aureus</i> , 2/4
Ceftazidime-Avibactam	2015	cIAI/cUTI	8	<i>Escherichia Coli</i> , 0
Dalbavancin	2014	ABSSSI	0.25	<i>S. aureus</i> , 2/2
Oritavancin	2014	ABSSSI	0.25	<i>S. aureus</i> , 13/17
Tedizolid	2014	ABSSSI	0.5	<i>S. aureus</i> , 54/55
Ceftolozane/Tazobactam	2014	cIAI/cUTI	8	<i>P. aeruginosa</i> : 3/4 Enterobacteriaceae: 16/29
Telavancin	2013	cSSSI, HABP/VABP	2	<i>S. aureus</i> , 0

* Data from MIC=32 mcg/mL

Source: Drugs@FDA

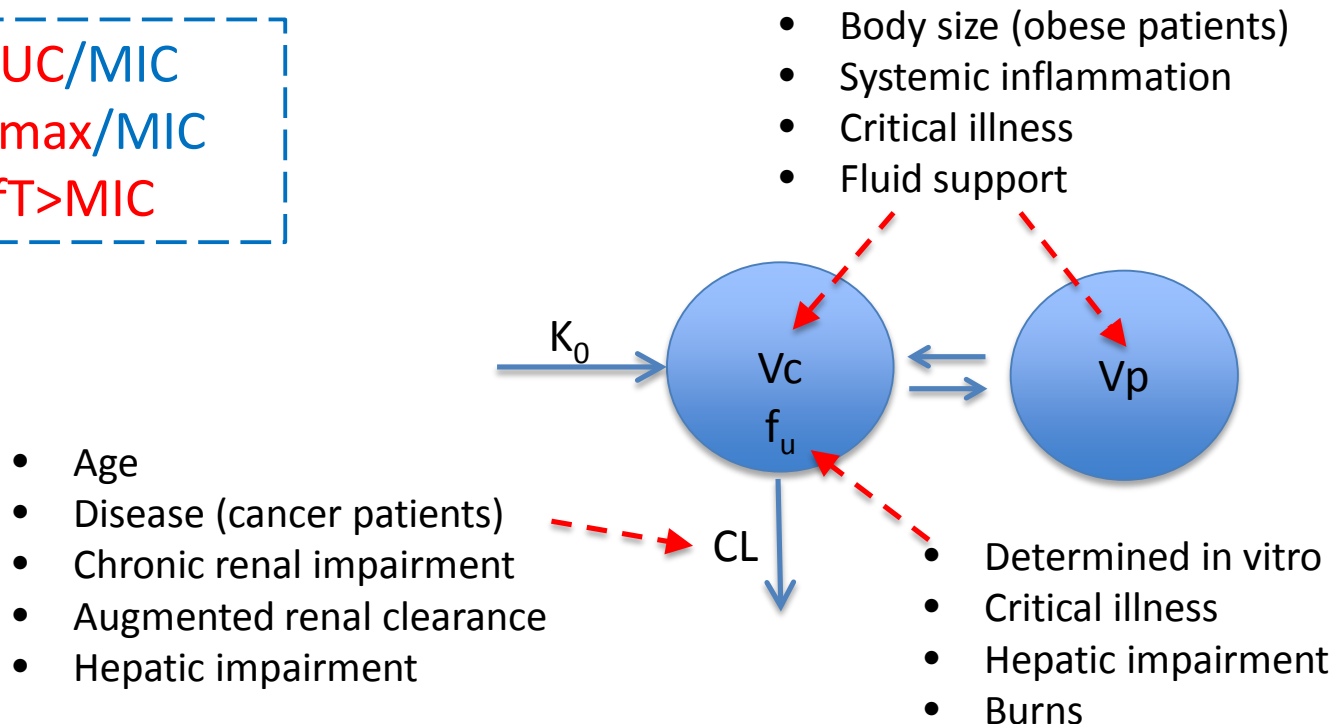
Concerns and Caveats

(current MIC-based PK/PD indices to support dose selection)

- PK components

- PK from healthy subjects, assuming similar PK;
- Literature PK values and/or inflated PK variation from the same drug class in the target patient population, e.g., cIAI, cUTI, HABP, VABP.

fAUC/MIC
fC_{max}/MIC
%fT>MIC



Concerns and Caveats

(current MIC-based PK/PD indices to support dose selection)

- “PD” component

- MIC, a categorical/ordinal variable

fAUC/MIC
fC_{max}/MIC
%fT>MIC

- MIC value has no correlation with infectious disease severity

- Variability of MIC assays

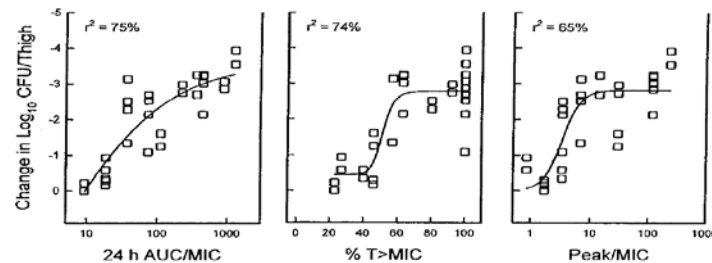
- 2-fold differences in a standard microbiological assay

- Uncertainty of MIC range that should be included in an animal study.

Concerns and Caveats

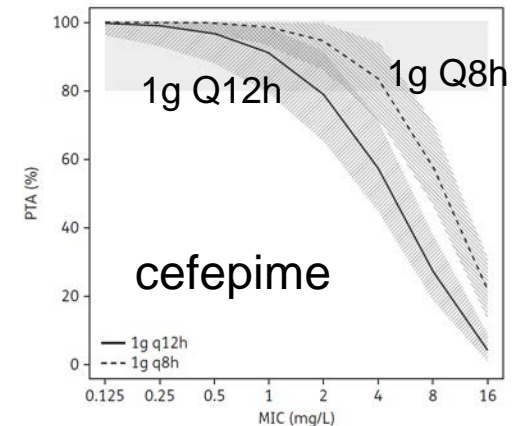
(current PK/PD approach to support dose selection)

- Identification of an appropriate PK/PD index is most important.



or others

- Bacterial killing,
 - Net stasis, 1-log reduction, or 2-log reduction
 - Relationship with clinical effectiveness is not clearly known.
- PTA analysis,
 - The PK/PD target value is a single number
 - Confident with median/mean?
 - Same target value for all indications?
 - Is confidence interval on PTA curve helpful for interpretation?

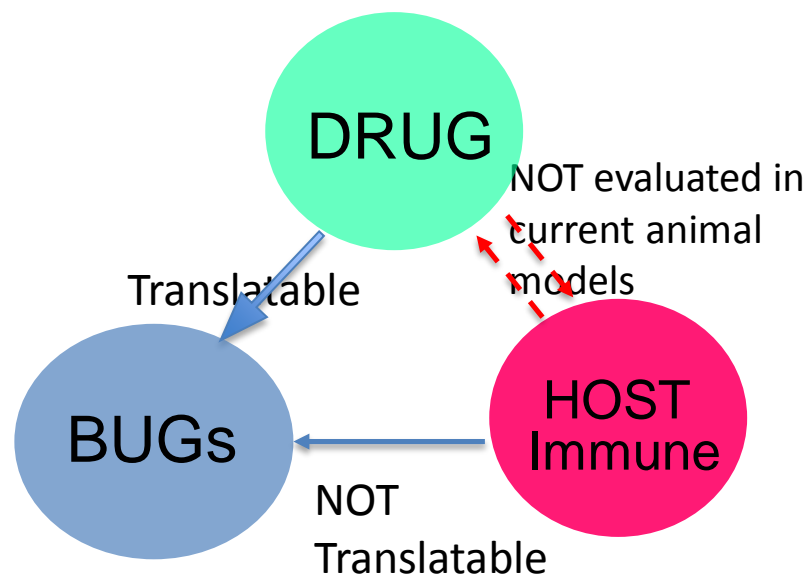
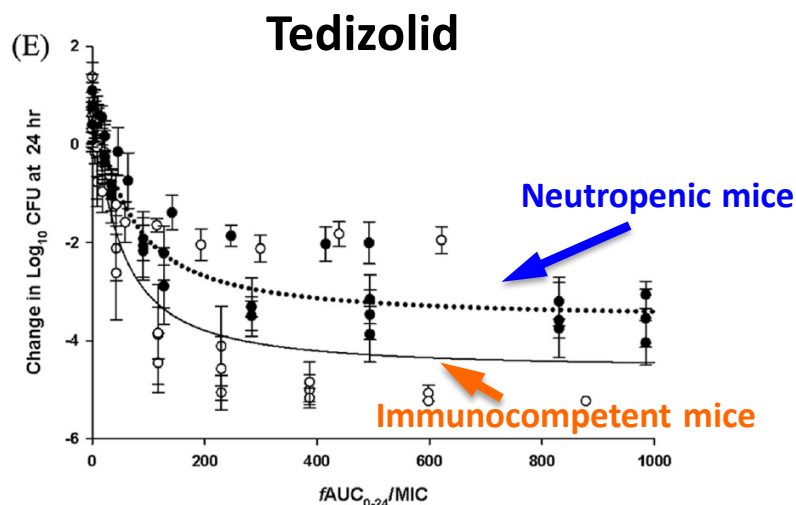


Limitations of MIC-based PK/PD Indices

(Pharmacological Consideration- Case 1)



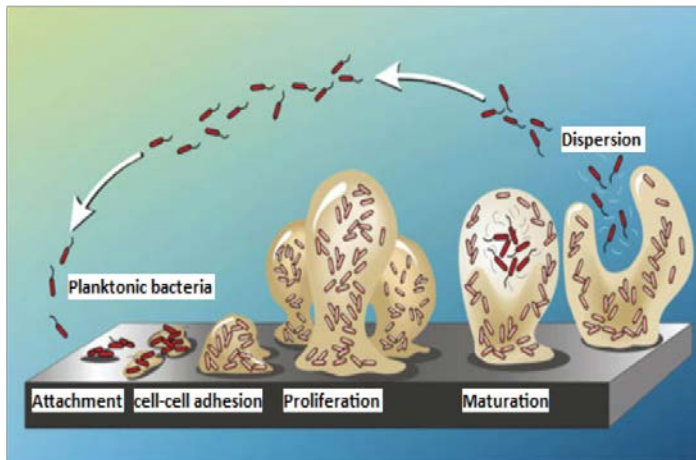
- Bacterial killing in humans is a combination of drug effect and host immunologic reaction
 - Drug effect and immune response may be additive.
 - Drug action may require the presence of neutrophils.



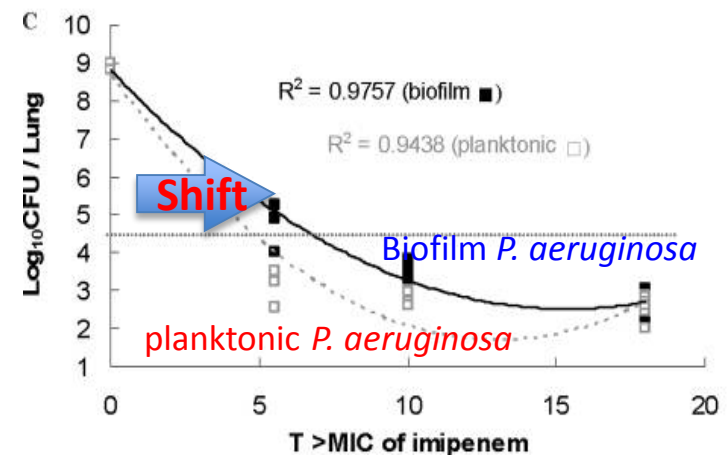
Limitations of MIC-based PK/PD Indices

(Pharmacological Consideration- Case 2)

- Biofilm formation in chronic infections (e.g., cystic fibrosis, chronic wound infections)



<https://microbewiki.kenyon.edu>



Antimicrob Agents Chemother 2012 May; 56(5): 2683–2690

Potential Solutions

(Robust PK/PD studies in vitro or in animals)

- Dose fractionation and animal efficacy studies
 - Choose appropriate animal infection models
 - Include a sufficient number of isolates, with some around MIC90
- PTA analysis
 - Identification of PK/PD index
 - If both AUC/MIC and T>MIC are relevant, use both to support each other.
 - Don't limit evaluation to the traditional indices; try something different/innovative (e.g., AUC/MIC/tau, AUMC/MIC).
 - The PK/PD target value
 - Median (mean), 75th percentile, 95th percentile, from multiple isolates of EACH pathogen.

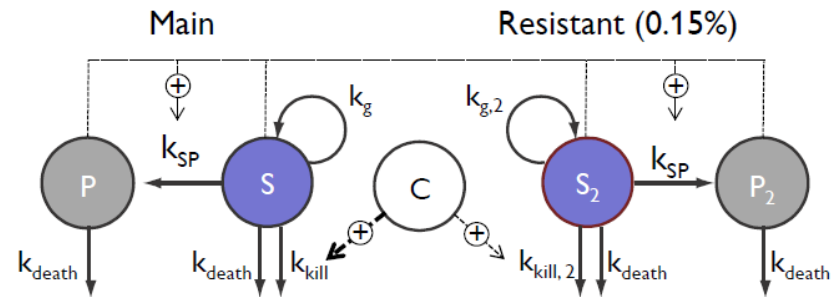
Potential Solutions

(if PK/PD indices do not work)

- Explore some other PK-PD modeling approaches

- Mechanism-based PK-PD modeling

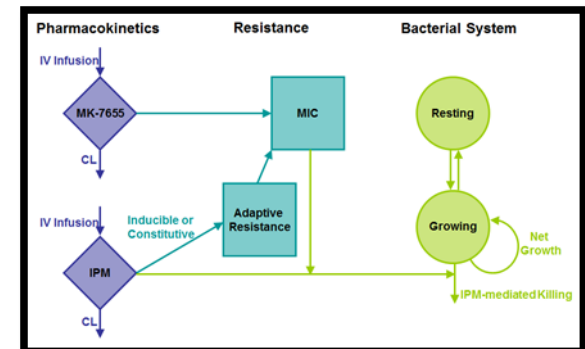
- Meropenem
on *Pseudomonas aeruginosa*



J Antimicrob Chemother. 2016;71(5):1279-1290.

- Semi-mechanistic PK-PD modeling

- Imipenem/Relebactam
on *Pseudomonas aeruginosa*



Rizk, et al. ICAAC (2012)

Sailing with PTA



Knowledge to distinguish the fins of sharks and dolphins would save you.



**MORE UNDERSTANDING
OF YOUR DRUG COULD
SAVE YOU.**

A- "Let's just agree they are dolphins, not sharks..."

B- "I will not jump...."

THE GOAL

Always keep in mind:

What you are looking for is the robust evidence to support your dose selection, no matter what PK-PD approach is being used.

Summary

- Value of PK/PD indices has been well recognized in many successful drug development programs.
- In some cases, traditional MIC-based PK/PD indices are not very informative.
- Concerns and caveats should be considered, when PK/PD indices are used.
- ANY reasonable PK-PD modeling approach to support drug development is encouraged.

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