Antibiotics and Patients: what can and must do the Pharmacist ?

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Antibiotic Classes

- Aminoglycosides
- Beta Lactams
- Fluoroquinolones
- Macrolides
- Glycopeptides
- Streptogramins
- Oxazolidinones

Antibiotic Development

Year	Antimicrobial
1930s	Sulfonamides
1940s	Penicillin G
1950s	E-mycin, TCs, Chloramphenicol
1956-9	Vancomycin, Metronidazole
1961-4	Ampicillin, Methicillin, Nalidixic Acid
1968	Aminoglycosides, Cephalosporins
1970s	Carbenicillin, 2nd Gen Cephs
1982-5	3rd Gen Cephs, Imipenem, BL/BLIs
1987	Ciprofloxacin and the FQs
1999	Streptogramins
2000	Oxazolidinones

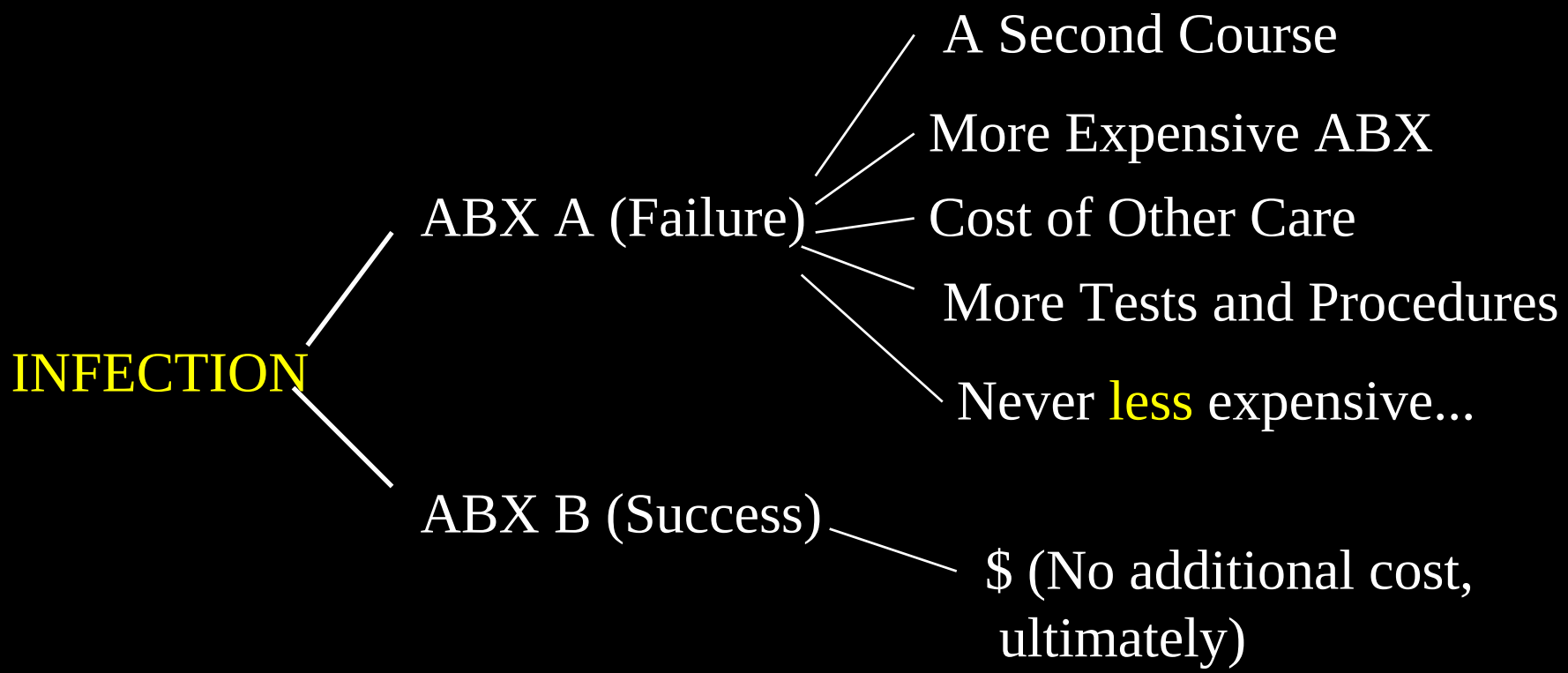
Clinical Use of Antimicrobials

- Prophylaxis
- Empirical Therapy
- Known Pathogen Therapy
- Switch Therapy/Streamlining
- Emphasis on Clinically useful information, from years of study

My Biases

- One dose for all, must yield to one dose for each. This is the emphasis on dosing to MICs and CCr
- One drug for all, must yield to one drug for each. This is the emphasis on selecting the most potent member of a therapeutic class for treatment of target pathogens.
- Cost of care is a much more important issue than cost of antibiotic, for reasons of efficacy, safety, and time of response vs drug dose and concentration.
- The most expensive regimen is the one that does not work the first time

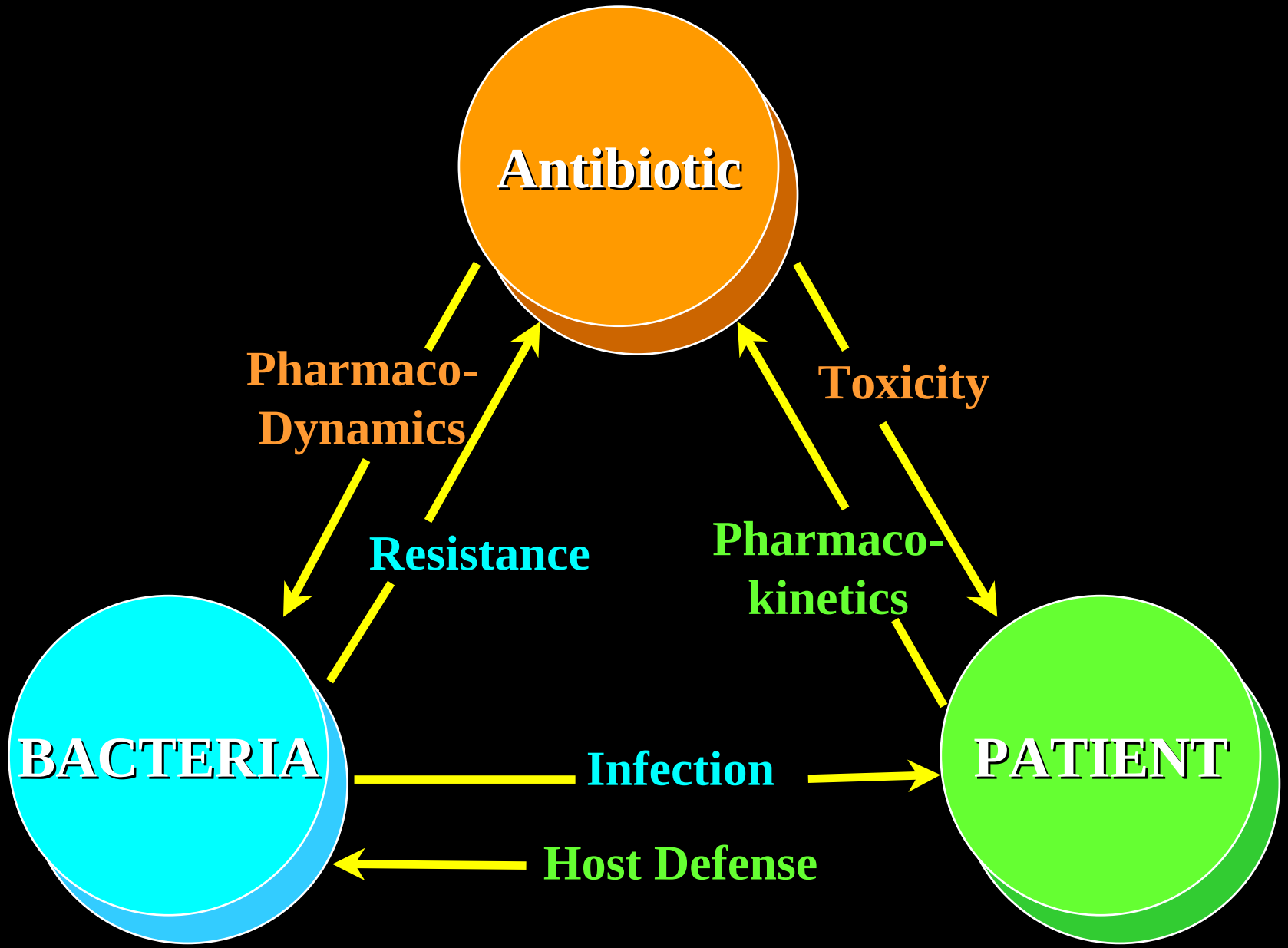
The one that doesn’t work....



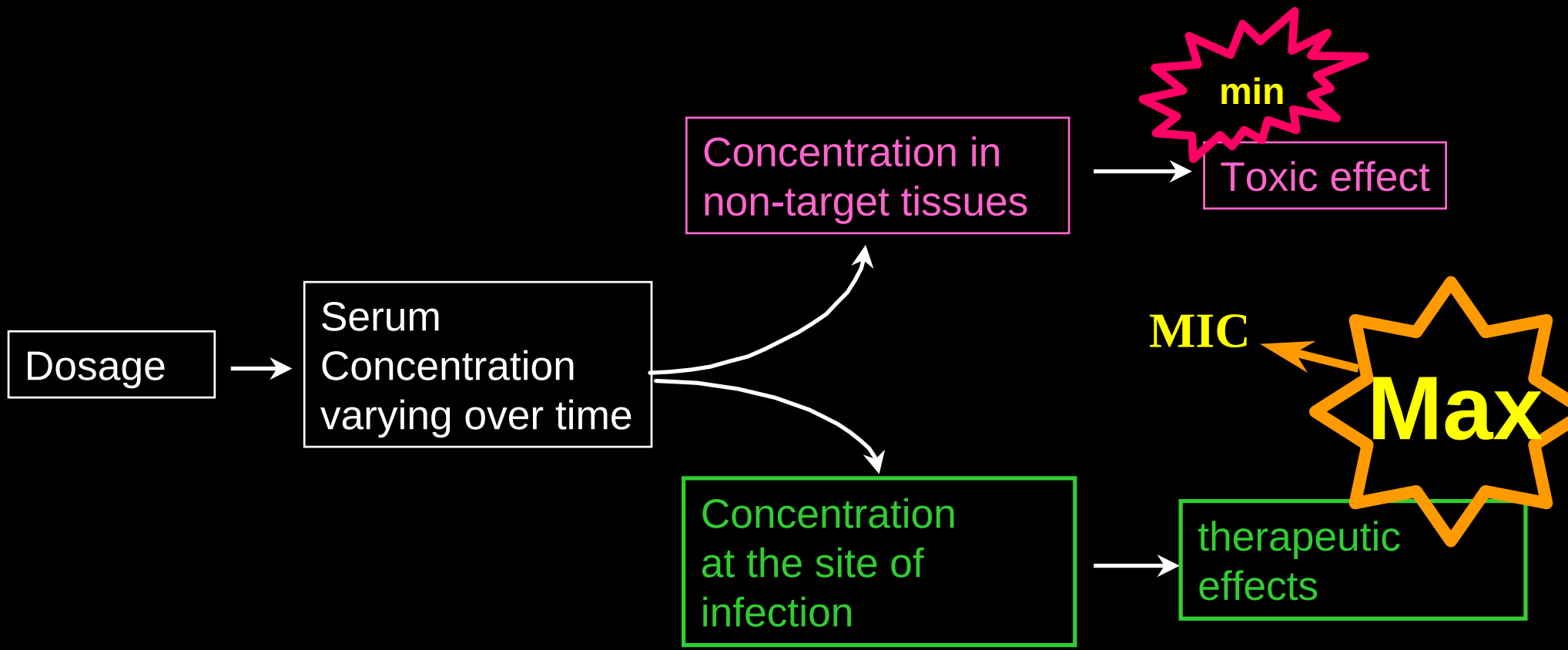
JA Paladino, 1997.

More of my Overall Biases...

- Tobramycin over Gentamicin, for Safety reasons.
- Ciprofloxacin among the FQs for situations that may encounter *Pseudomonas aeruginosa* (Resistance issues)
- 8-F or 8-Methoxy FQs for patients with *Streptococcus pneumoniae* (resistance issues)
- Less overall cephalosporin use, especially in settings of high risk of MRSA and/or VREF
- We need alternatives to Vancomycin, and we need them very quickly...


Antibiotic
Pharmaco-
Dynamics
Resistance
Toxicity
Pharmaco-
kinetics
BACTERIA
Infection
PATIENT
Host Defense

Killing a bacteria with an antibiotic



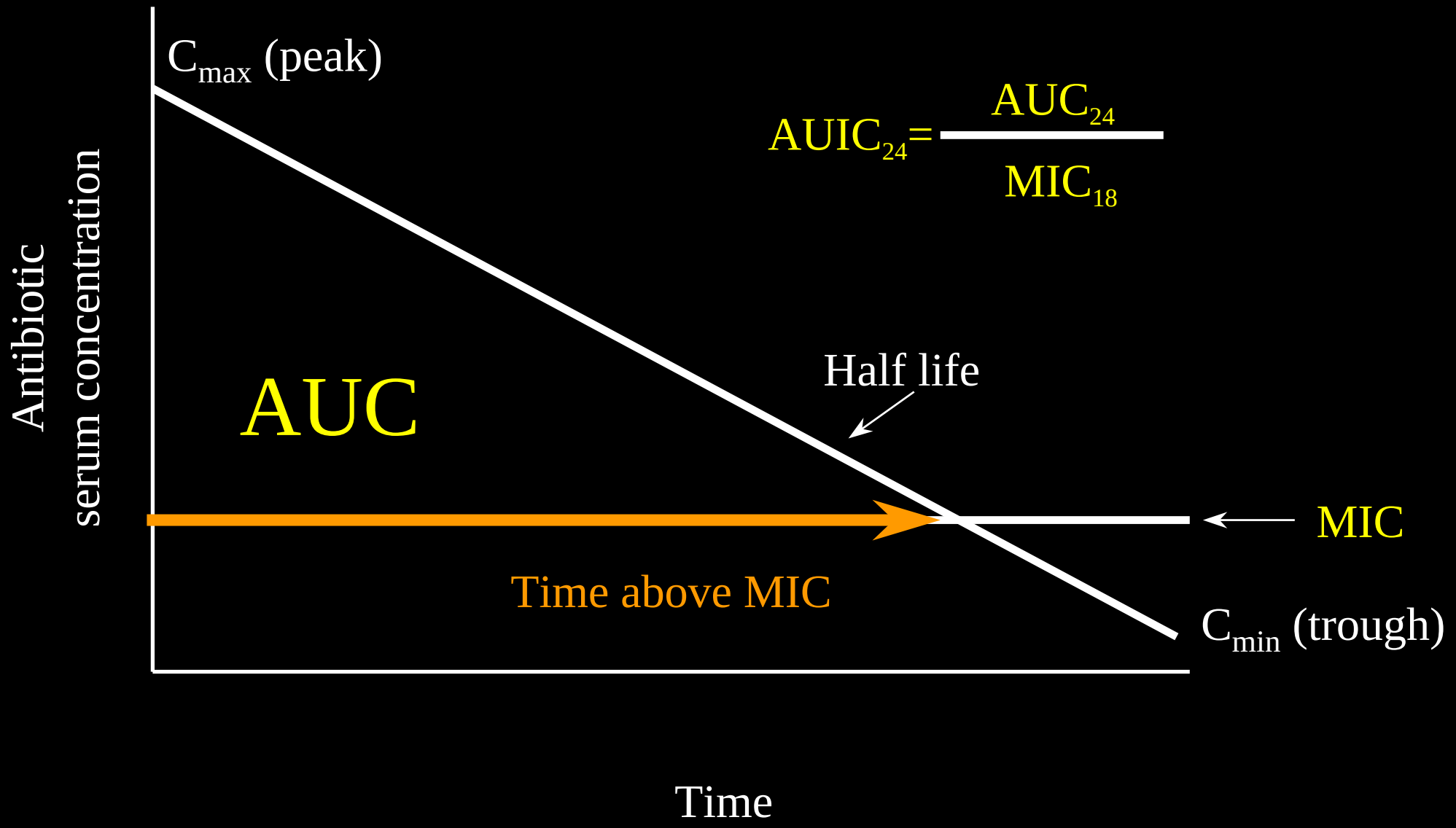
adapted from W.A. Craig...

Model Antibiotics for Human PK/PD trials:

- Ciprofloxacin
- Grepafloxacin
- Tobramycin
- Piperacillin
- Ceftazidime
- Azithromycin
- Linezolid
- Cefmenoxime
- Cefepime
- Vancomycin
- Aztreonam
- Synercid
- Imipenem
- Amikacin

Antibiotic Monitoring

- **Serum Concentration Target**
  - **assumes all pts with the same MIC, or at least a low MIC covered by usual doses.**
- **Antibiotic Effect Target**
  - **Microbial Killing measured with gram stain or serial cultures**
- **Both Targets, the Strengths of Each**

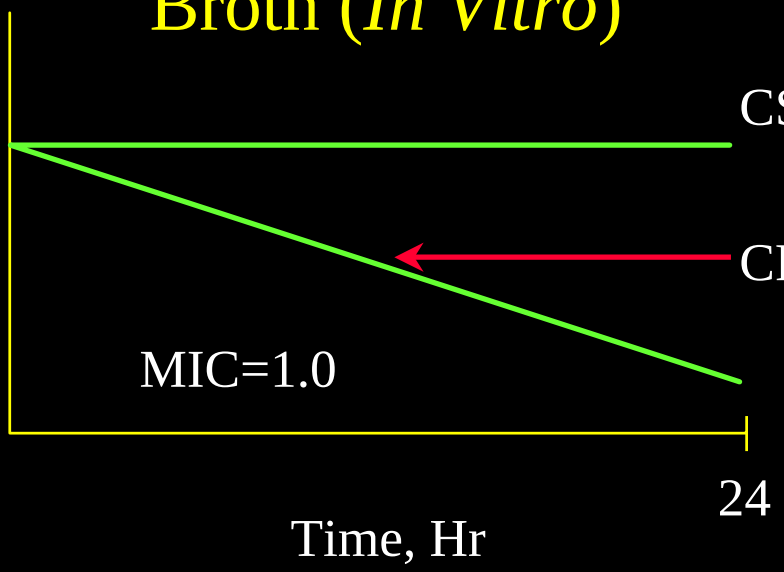

C_{max} (peak)
$AUIC_{24} = \frac{AUC_{24}}{MIC_{18}}$
Antibiotic serum concentration
AUC
Half life
MIC
Time above MIC
C_{min} (trough)
Time

AUIC is a ratio, it does not have units[1]

- Mathematical derivation from integrated inverse ‘cidal titers measured over time (Barriere et al, J Antimicrob Chemother 16: 49-59, 1985)
  - The connection to measured ‘cidal activity in vivo led Forrest et al to use SIT^{-1} in the 1993 paper discussing Ciprofloxacin (AAC 37: 1073-1081, 1993)
- AUIC is the Ratio of 24hr:
  - AUC: mcg x hr/ml (conc x time) to
  - MIC: mcg/ml x 18-24 hr incubation: mcg x hr/ml
- Therefore, use the 24hr mcg x hr/ml units for MIC as well as AUC, and units cancel out in AUIC calculations

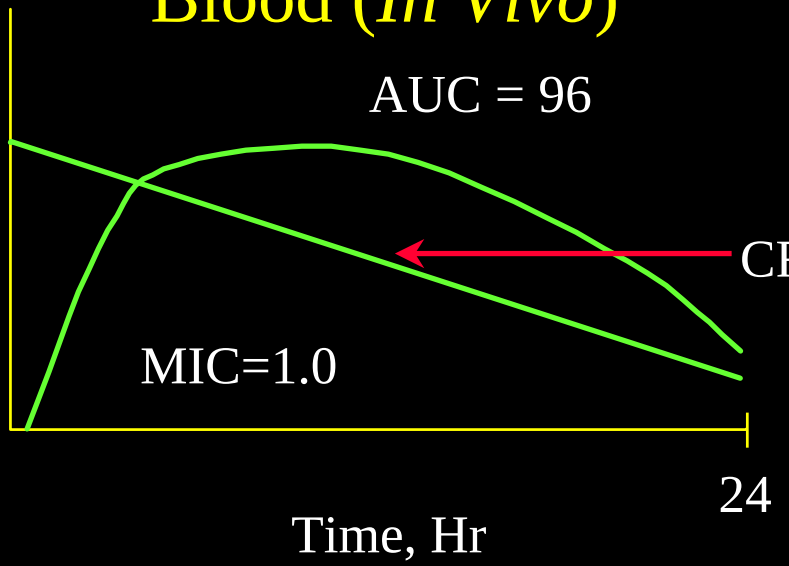
1. Mouton J., et al. Intl J Antimicrob Agents 19: 355-388, 2002

Broth (*In Vitro*)



AUC = 4x24 = 96
24 hr AUIC = 96÷1=96

Blood (*In Vivo*)



Hyatt et al, Clinical Pharmacokinetics 28: 143-160, 1995

CSS = AUC ÷ 24 HR = 4.0
24 hr AUIC = 96÷1=96

Pharmacokinetic/Pharmacodynamic Correlates of Cure for Different Classes of Antibiotics

	Correlates of Successful Outcome		
Drug Class	In-Vitro	Animals	Humans
Aminoglycosides	C_{max}:MIC	AUC:MIC	C_{max}:MIC, AUIC
ß-lactams	T>MIC	T>MIC	T>MIC, AUIC
Quinolones	C_{max}:MIC	AUC:MIC	C_{max}:MIC, AUC:MIC, AUIC
Glycopeptides	T>MIC	T>MIC, AUC/MIC	MIC<1.0, T>MIC, AUIC

Antibiotics for Study in Human LRTI

- **Concentration Dependent Actions**
  - **Fluoroquinolones**
  - **Aminoglycosides**
  - **Carbapenems**
- **Concentration Independent Actions**
  - **Beta Lactams**
  - **Vancomycin**
  - **Macrolides**
  - **Linezolid**

AUIC breakpoints in Mice and Man

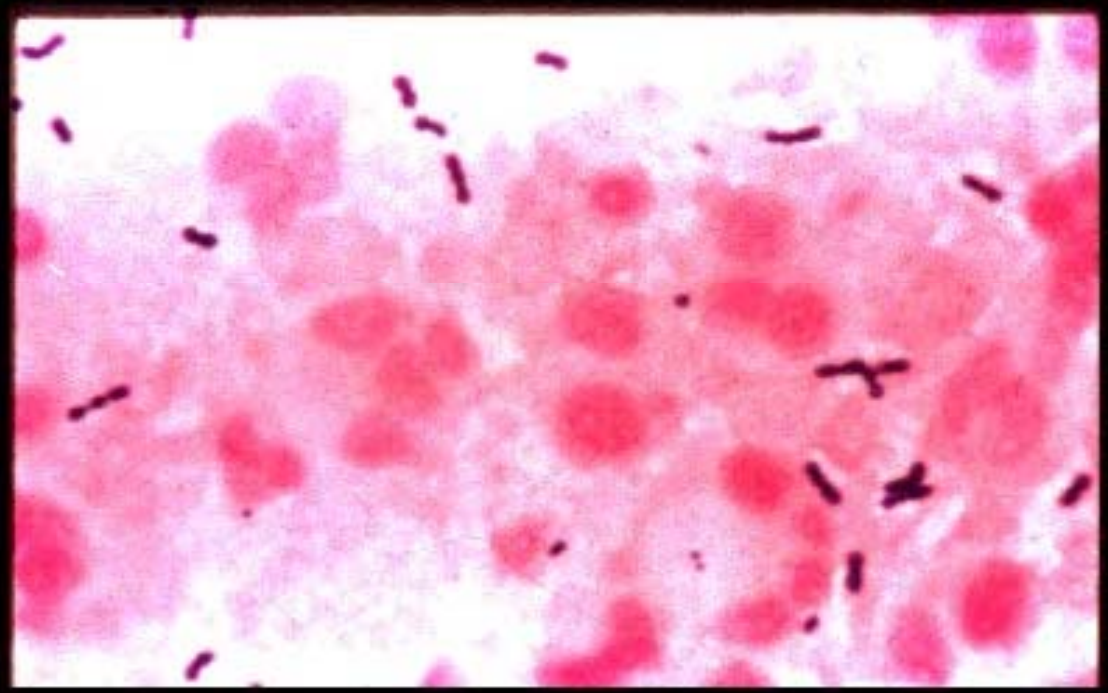
AUIC	*Discussion*
25-40	PD_{50} in animals; Some evidence for activity in mild infections in outpatients with normal host defenses; peak:MIC ~ 3:1
125	Separates cure and failure in compromised patients; At 125, the AUC is 80% above MIC, and the peak:MIC ratio ~5:1; The threshold for avoiding resistance is an AUIC of 100
250	Maximal killing rate for concentration dependent ABX; peak:MIC ~ 10:1

Nosocomial Pneumonia, a Human Model for Studies of antibiotic PK/PD

- Precedent from Animal Models
- Infection site concentration is equal to the blood concentration, limiting the confusion over tissue penetration.
- low cure rate, rapid learning curve.
- Easy access to tracheal organisms, allowing time-killing studies in vivo

Advantages of Antibiotics

- You can isolate and study the bacterial “receptor” directly for conc/effect relationships
- Because testing of the individual sensitivity is easy, the correlation of *in vitro* Pharmacokinetics with *in vivo* Pharmacodynamics becomes feasible
- Gram stains, done serially, can tell you if you are eradicating the organism, or at least that you are reducing their numbers....



BACTERICIDAL ACTIVITY

- Concentration-dependent killing
  - the higher the drug concentration, the greater the rate and extent of activity
  - aminoglycosides, quinolones, metronidazole
- Minimal concentration-dependent killing
  - saturation of killing rate occurs at low multiples of the MIC - usually 4-5X the MIC
  - extent of killing dependent on time of exposure
  - β-lactams, vancomycin, clindamycin and macrolides

PHARMACOLOGY OF ANTIBIOTICS

- PHARMACOKINETICS
  - serum concentration profile
  - penetration to site of infection
- PHARMACODYNAMICS
  - relationship between serum concentration and the pharmacological and toxicological effects
- Both determine the time course of activity and the clinical outcome of the patient

Applying AUICs to Empiric Therapy

- **Measure or Calculate PK parameters (AUC)**
- **Measure or default MICs**
  - **Defaults in settings of breakpoints**
  - **Exact Values when available, and for streamlining**
- **Measure Antibiotic Endpoint as Bacterial Killing**
  - **Gram Stain pre vs post (i.e., Serial)**
    - The only true 10 minute determination of the correct dose
  - **Culture**
    - Use culture positivity as an index of Low AUIC
    - Use early negative cultures to shorten duration of therapy

Case 03

- **A 47 year old female with MS, was admitted from a nursing home in Respiratory distress with a temp of 104 ºF; Intubated in ER. Her CXR was positive for a LLL infiltrate.**
- **Urine was packed with WBCs and bacteria.**
- **Blood cultures have gram negative rods x2**
- **Ht was 5'6", weight 135 lbs, Cr was 1.0 mg/dl**
- **She had multiple courses of TMP/SMX in the nursing home, for frequent UTIs over 2 years.**
- **What is the most likely pathogen in this case, and what should be chosen for therapy?**

The A.U.I.C. Program for Antimicrobial Dosing

ANTIBIOTIC UTILIZATION INFORMATION AND CONSULTATION
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Version 1.0.0a

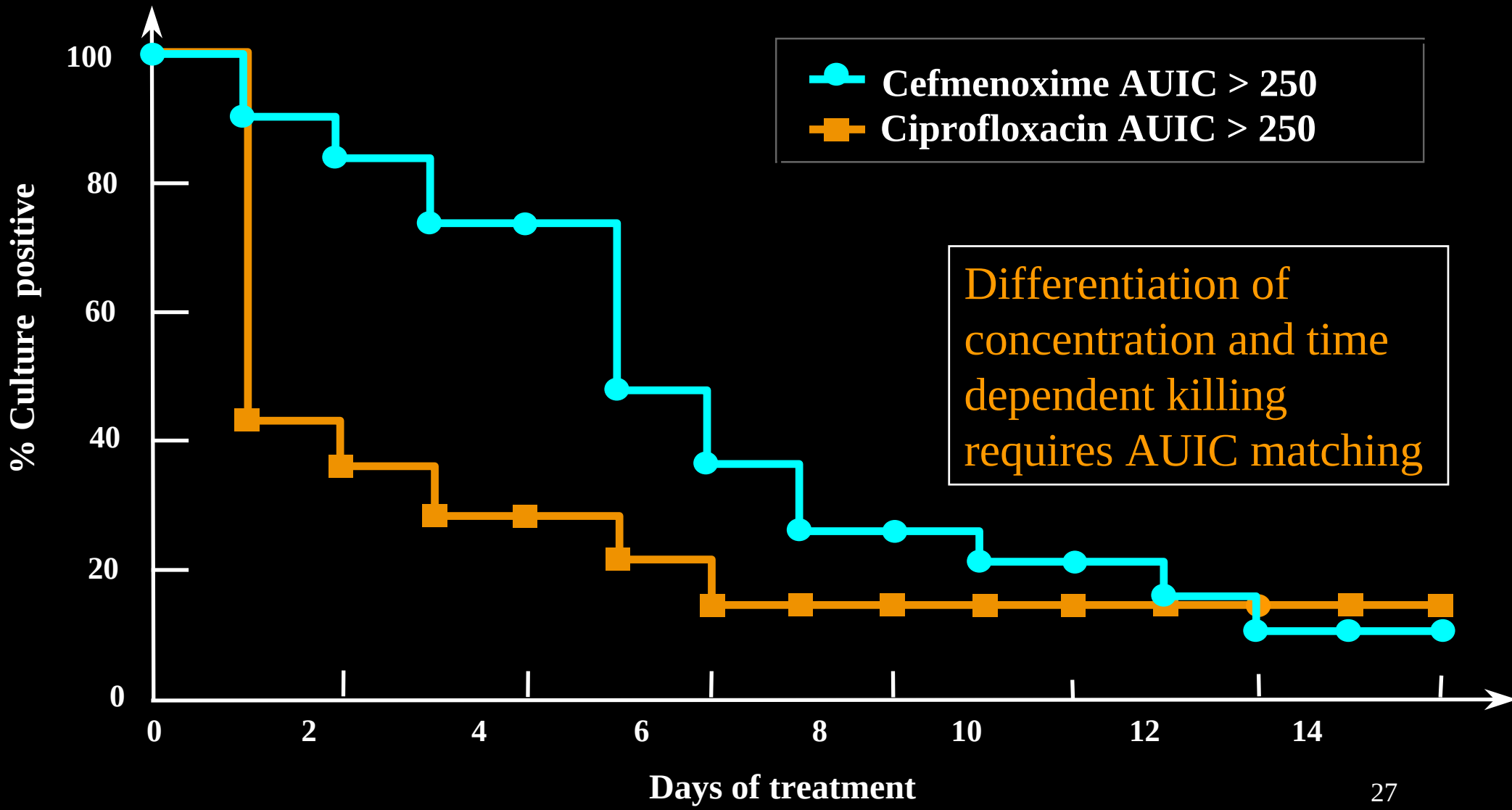
Developed by: Martin Adelman, PhD
and Jerome J Schentag, PharmD

Measures of Antimicrobial Action

- On the patient
  - Clinical Cure (contains no time sensitive information)
  - Rate of improvement in signs and symptoms
  - Daily symptom scoring and quantitative indices of antimicrobial effects
- Clinical Cure endpoint is not sensitive to:
  - Rate of improvement over time
  - combination antibiotic effects vs single agents

Time to Eradication vs AUIC

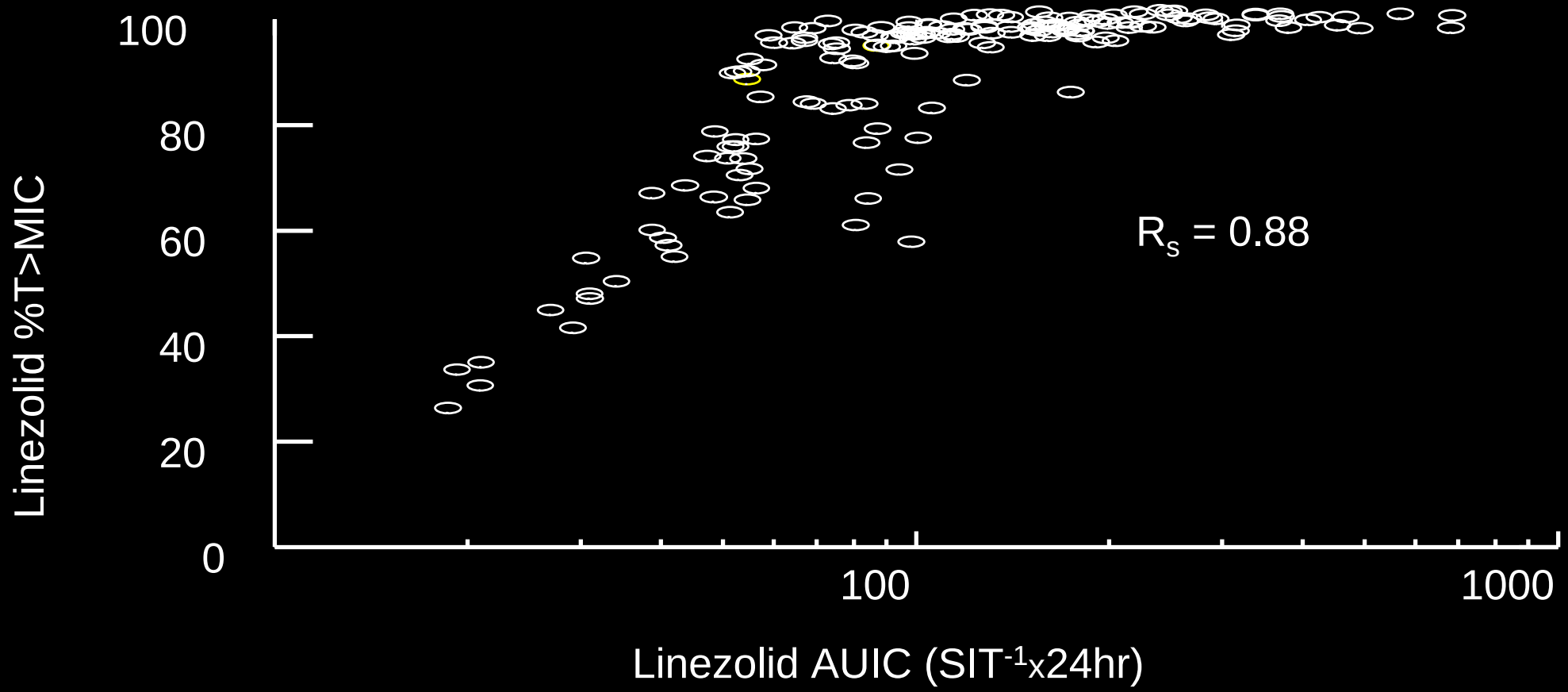
Goss T et al. Ann Pharmacother 28: 863-868, 1994



Differentiation of concentration and time dependent killing requires AUIC matching

Trial Outcomes

- At similar AUIC, the antibiotic regimens tested performed similarly at EOT
- Most patients with AUICs above 125 were cured by the regimen that produced these values
- Daily scoring of these patients, to examine differences in speed of response vs antibiotic concentration in relation to MIC



Rayner et al. Clinical Pharmacokinetics 42: 1411-1423, 2003

Challenges in Antibiotic Monitoring

- AUIC values provide a precise means of expressing PK/PD changes in Exposure.
- Bacterial Eradication can be precisely monitored by serial cultures.
- We need an equally precise means of expressing and quantitating changes in the patients' condition
  - This is the weak link in monitoring antibiotic therapy at the moment.

Why standardize Antibiotic Activity Indices ?

- Endpoints for clinical trials
- Hypothesis testing in development of new antibiotics
- Development of drug monitoring strategies
- Facilitates computerization and automation, so it becomes the core of a dosing strategy to maximize efficacy and minimize resistance

Antibiotic Combinations

- Antibiotics are nearly always given in combination in the treatment of hospitalized patients
- Combinations broaden empiric spectrum and are felt to lower resistance. Some cases of Synergy are observed, although the normal effect appears to be additivity.
- Monotherapy is typical in outpatients, but the recent development of community resistance in S. pneumoniae, E. coli, and S. aureus suggests this is about to change
- A rational combination method is urgently needed both for the hospital and the community

Antibiotic Combinations

Compound	AUC_{24}	MIC P.aerug	AUC/MIC
Ciprofloxacin	64	1.0	64
Pip-Tazo	1544	8.0	193
Total(Cipro+Pip-Tazo)			257

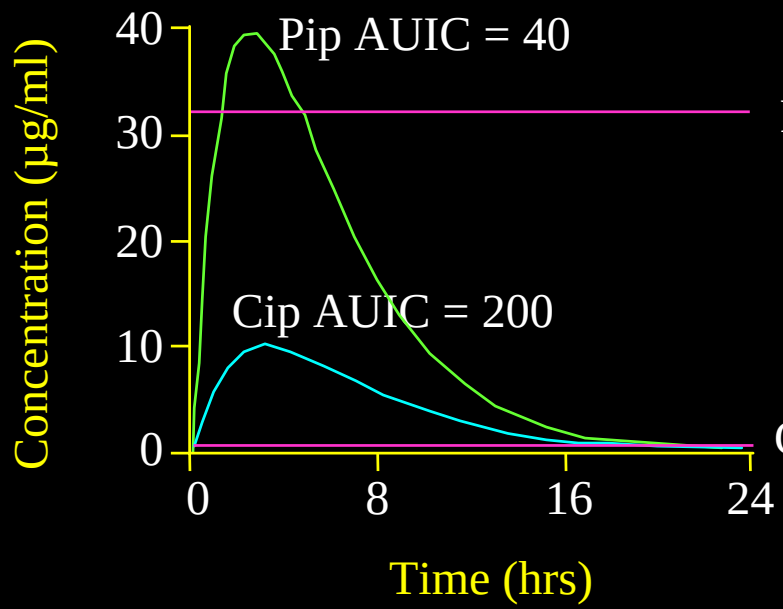
Synergy or Additivity between FQ and β-Ls?

- Additive in vitro, in most cases
  - in spite of different intra-cellular targets
  - in spite of different mechanisms of action
- First assessment is the action of each antibiotic alone vs the specific pathogen
  - Killing should appear conc dependent when most of the total activity comes from the FQ
  - Killing should appear conc Independent when most of the activity comes from the β-L

Ciprofloxacin with Pip/Tazo

- Depends on the absolute sensitivity of the organism to each antibiotic alone
- Best case is highly sensitive to ciprofloxacin, since that increases the speed of bacterial killing in vivo....

Pseudomonas aeruginosa, #1

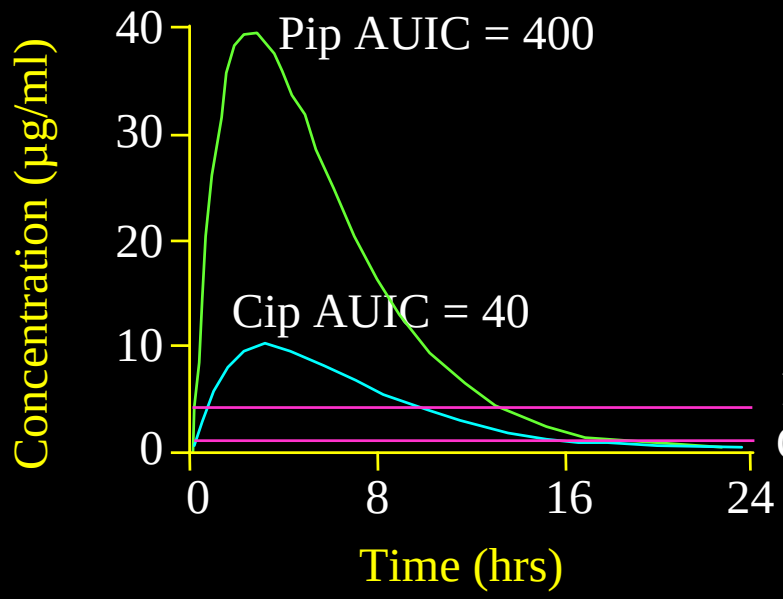


Pip MIC = 32 µg/ml

AUIC Total = 240
DTE = 1 (Additive)
DTE = 6 (Antagonism)

Cip MIC = 0.25 µg/ml

Pseudomonas aeruginosa, #2



AUIC Total = 440
DTE = 6 (Additive)
DTE = 2 (Synergy)

Pip MIC = 4 µg/ml
Cip MIC = 1 µg/ml

Ciprofloxacin plus Piperacillin Synergy or Additivity?

			Days to Eradication (DTE)		
Organism	MIC Cipro	MIC Pip	Predicted DTE, Cip	**Predicted DTE, Pip**	DTE (Actual)
P.aeruginosa	1.0	4.0	>32	7	6
P.aeruginosa	0.25	32.0	1	7	2
E.cloacae	0.125	1.0	1	6	1
S.aureus	0.4	>256	5	>32	4

Ciprofloxacin with Pip-Tazo

- Piperacillin at maximal rate of bacterial killing will sterilize cultures in 4-6 days
- Ciprofloxacin at maximal rate of killing will sterilize cultures in 1 day
- Find pathogens where the predicted rate of sterilization is in excess of 7 days for either antibiotic alone, then optimize the other.

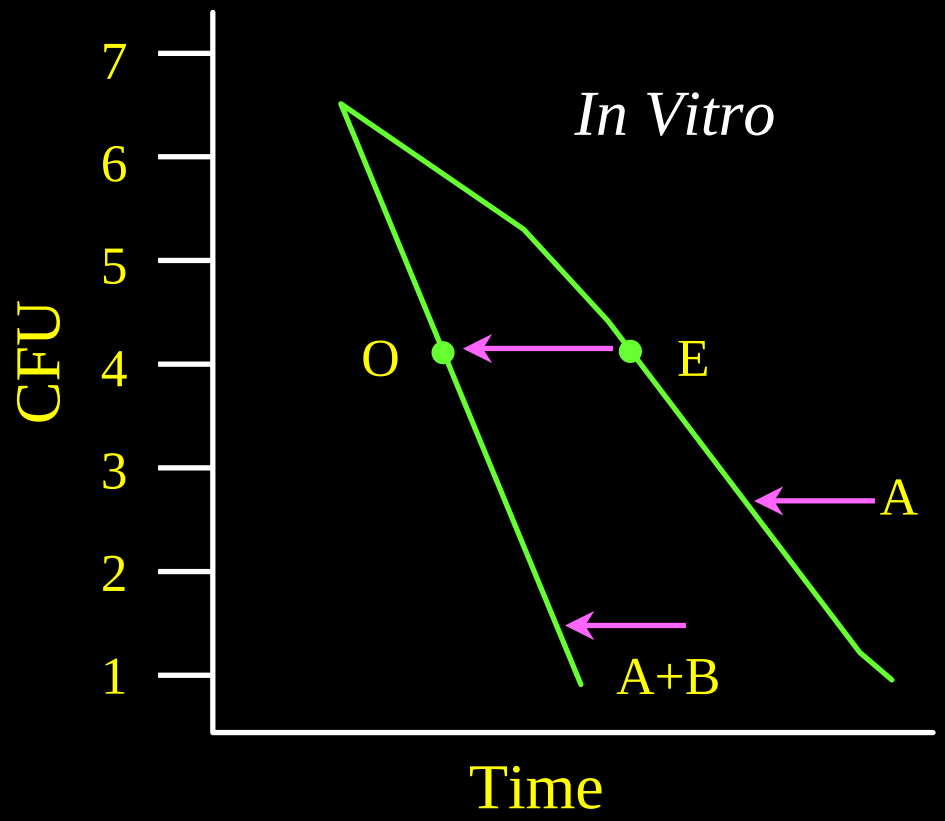
Ciprofloxacin with Pip-Tazo

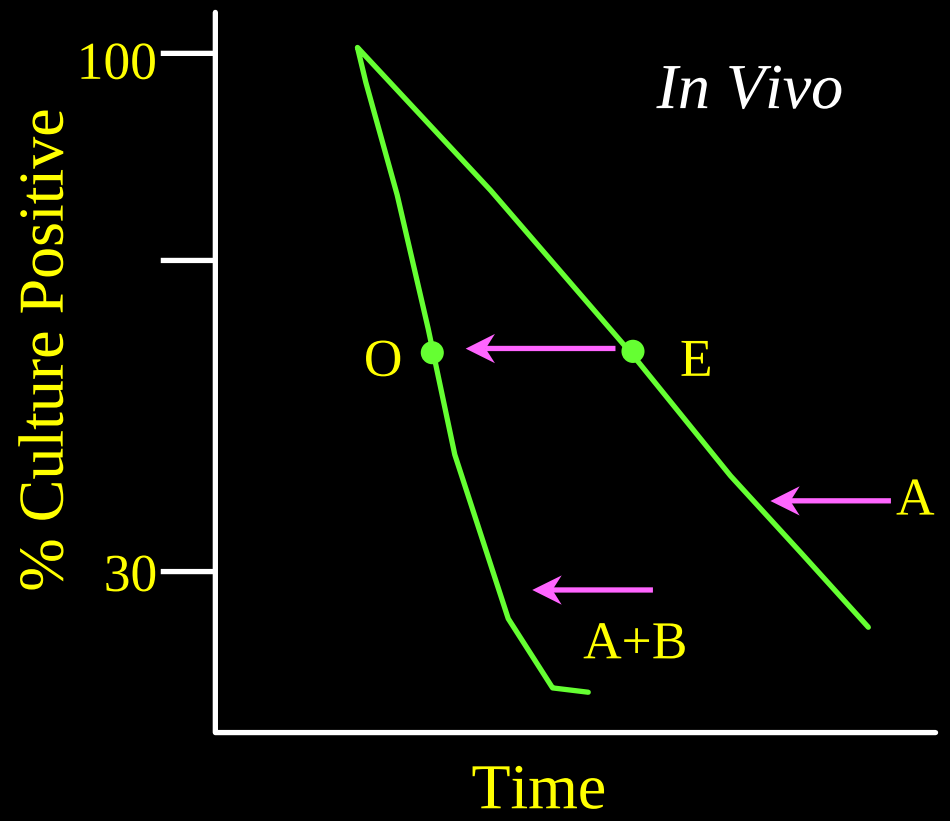
- Depends on the absolute sensitivity of the organism to each antibiotic alone
- Best case is highly sensitive to ciprofloxacin, since that increases the speed of bacterial killing in vivo
- Must therefore optimize the dose of ciprofloxacin first, and then optimize the dose of piperacillin. Each of these can be done as AUICs for the pathogen in question

Antibiotic Combination effect in patient care

- Additivity is the usual situation in vivo
- AUIC values are additive
- In vivo endpoint is more rapid bacterial killing than expected by additive AUIC values alone.

Killing Curves Detect Synergy As More Rapid Sterilization





Antibiotic Synergy

- Partly a matter of perspective
- From the viewpoint of a β-lactam, synergy is always possible, since they kill rather slowly on their own.
- Best partner antibiotic has concentration dependent killing
  - quinolones
  - aminoglycosides

Antibiotic Additions or Synergies

- Nosocomial Pneumonia is the best model for detecting the effects of synergy, as daily cultures can easily be performed.
- Once a bacteria is isolated, trach aspirate and BAL give the same information on the eradication of the pathogen, even though the original inoculum may be different
- Multiple organisms can be followed simultaneously

Impact of two drug regimens as calculated by A.U.I.C.

- $AUIC_{24}$ values for each drug can be added to yield a total $AUIC_{24}$ for the regimen
- True synergy would always speed organism eradication beyond the day predicted by the $AUIC_{24}$ from additivity
- True synergy by this definition appears to be uncommon. Most interactions where the bacterial killing is measured are suggesting additive interaction

Principles of Combination Therapy

- Potentially synergistic combinations:
  - Tobramycin-Ceftazidime
  - Ciprofloxacin-Piperacillin
- Synergy can only be visualized when the MIC to both components is high, and therefore, the killing of the pathogen by either is rather slow

Strengths of these models

- Clinical data on bacterial killing rate are supportive of the findings in animal models
- Supportive of in vitro mechanisms and findings
- Relevent to extracellular and probably also intracellular pathogens
- Relatively easy to use, since AUIC has a common target for most clinical settings

CONCLUSIONS

- Utilizing pharmacokinetic and pharmacodynamic principles to optimize antibiotic dosing regimens will improve clinical outcomes and potentially decrease the development of resistance.
- Subsequent Presentations will demonstrate this premise for each of the major classes of antibiotics.
- AUIC plays a unique role in the implementation of antimicrobial pharmacodynamics at the bedside