



GSK-Chair of Infectious Diseases

(Chaire GSK de Maladies Infectieuses / GSK-Leerstool in Infectieziekten)

a joint academic activity of the

Université catholique de Louvain and the Katholieke Universiteit Leuven

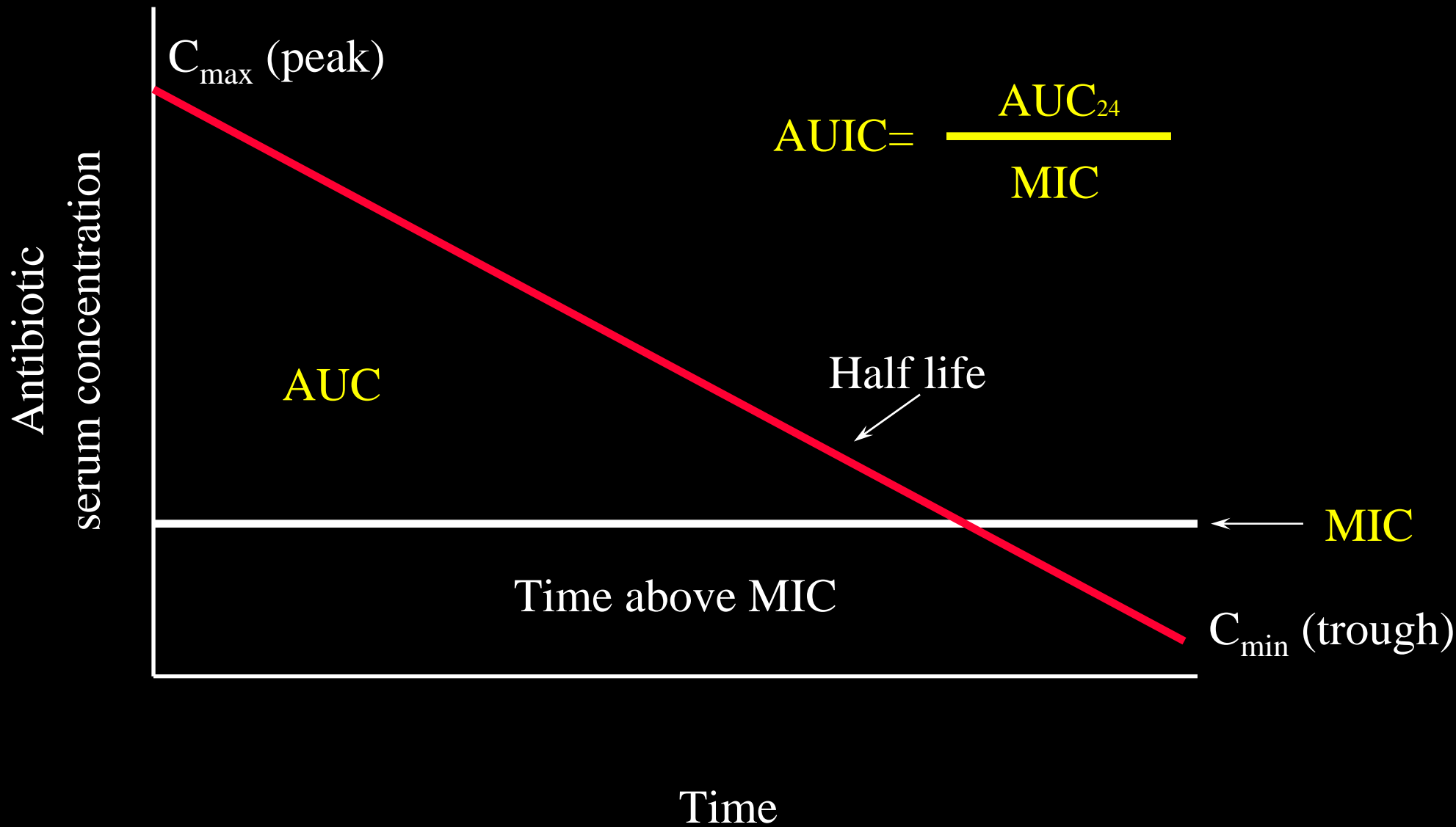
Clinical Pharmacy and Optimization of Antibiotic Usage: How to Use what you have Learned in Pharmacokinetics and Pharmacodynamics of Antibiotics

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Presented at UCL on Thursday February 28th

Systems Approach to Antibiotics

- **Value: Making sure every patient receives excellent care, every time..**
- **The Theoretical studies provide the means to do this**
- **We will talk about both theories and about putting them to work**

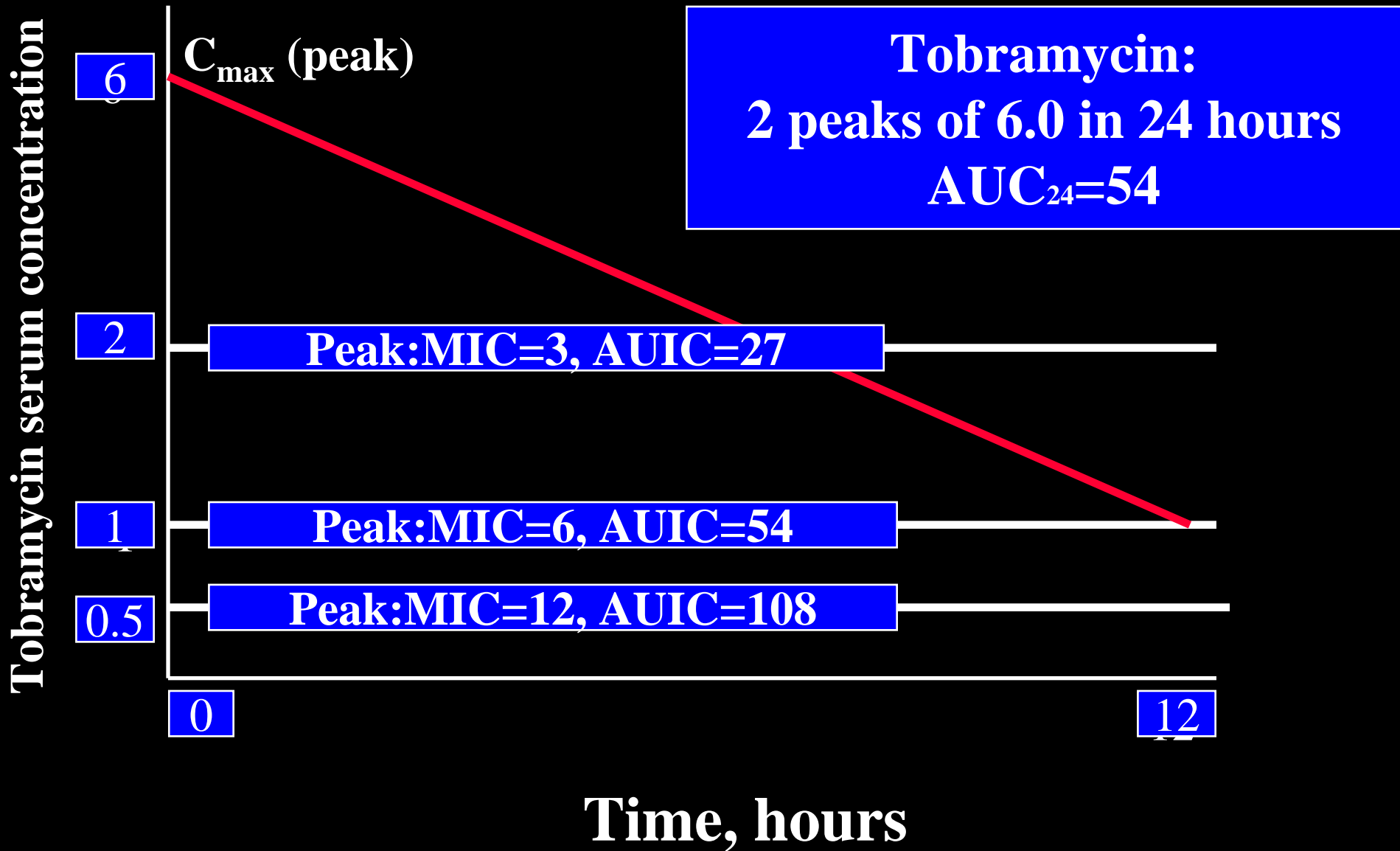


Antibiotic PK and PD attributes

- **For antimicrobial effect:**
 - C_{\max}/MIC ratio should be > 8 to 10
 - **AUIC should be > 125**
(For rapid killing AUIC > 250)
- **To minimize resistance development:**
 - **AUIC should be >100**

Antibiotics for Study in LRTI

- **Concentration Dependent Actions**
 - **Fluoroquinolones**
 - **Aminoglycosides**
- **Concentration Independent Actions**
 - **Beta Lactams**
 - **Vancomycin**

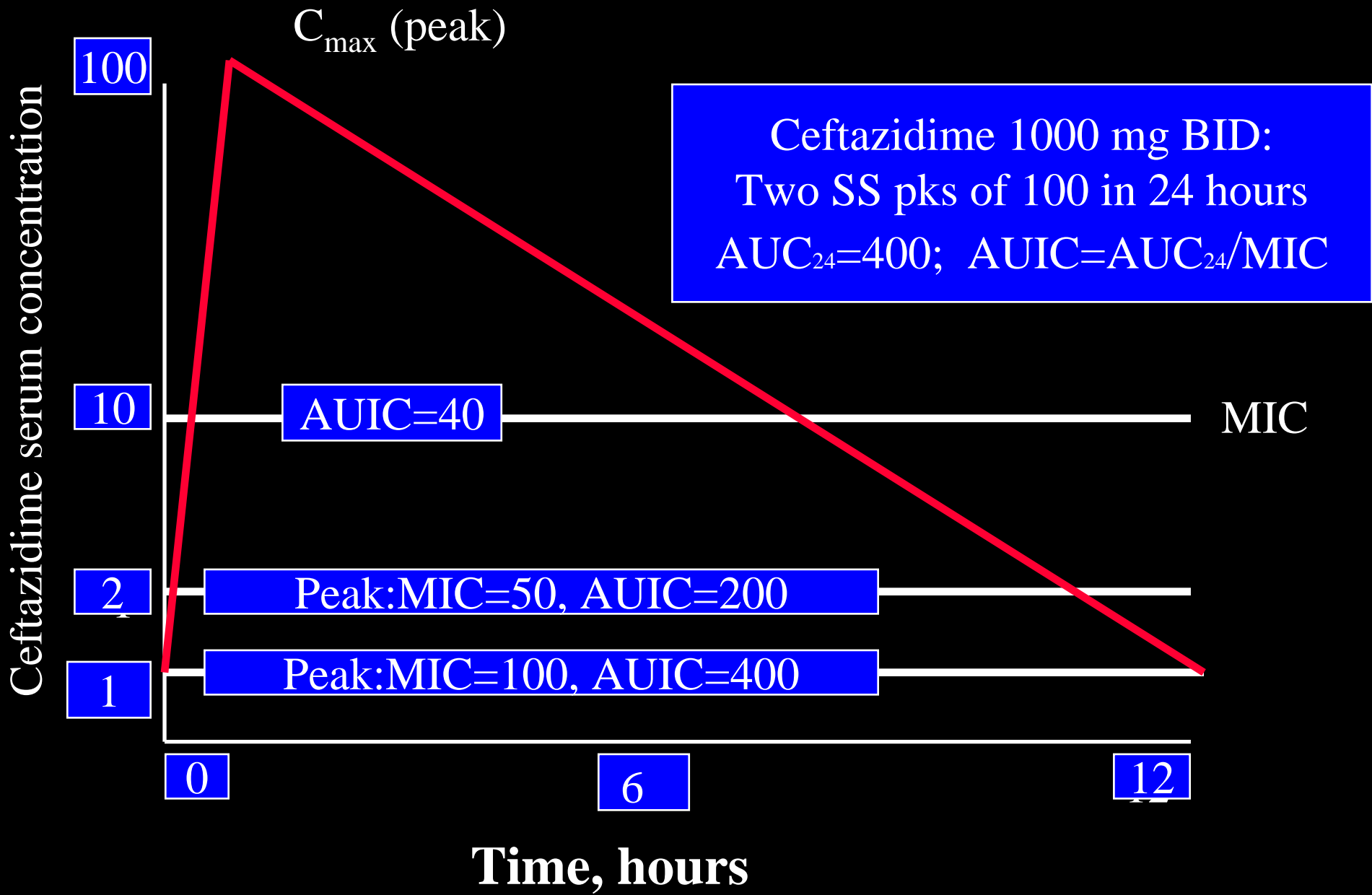


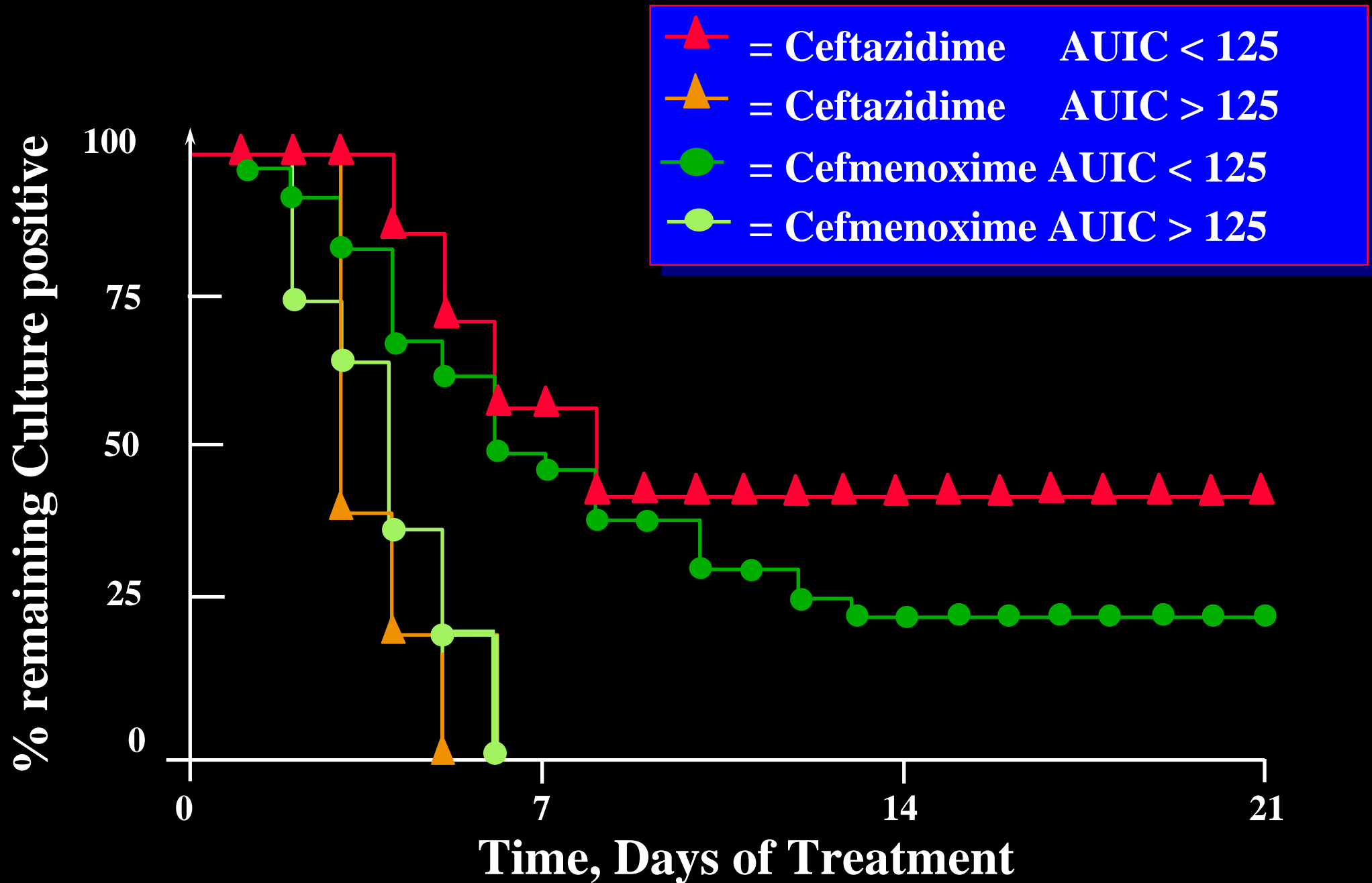
Aminoglycosides

- Low AUIC with typical dosing and levels
 - breakpoint MIC is 0.25 mcg/ml for AUIC of 125
- We say their activity is decreased
 - with the infection site pH below 6.0
 - at urine sites due to cations
 - with decreased PO_2
 - due to binding at the infection site
- Combination Therapy is necessary in most situations, because of a low AUIC

Antibiotic Combinations

Compound	AUC ₂₄	MIC	
		P.aerug	AUIC ₂₄
Tobramycin	54	1.0	54
Ceftazidime	400	2.0	200
Total (Tob+Ceftaz)			254





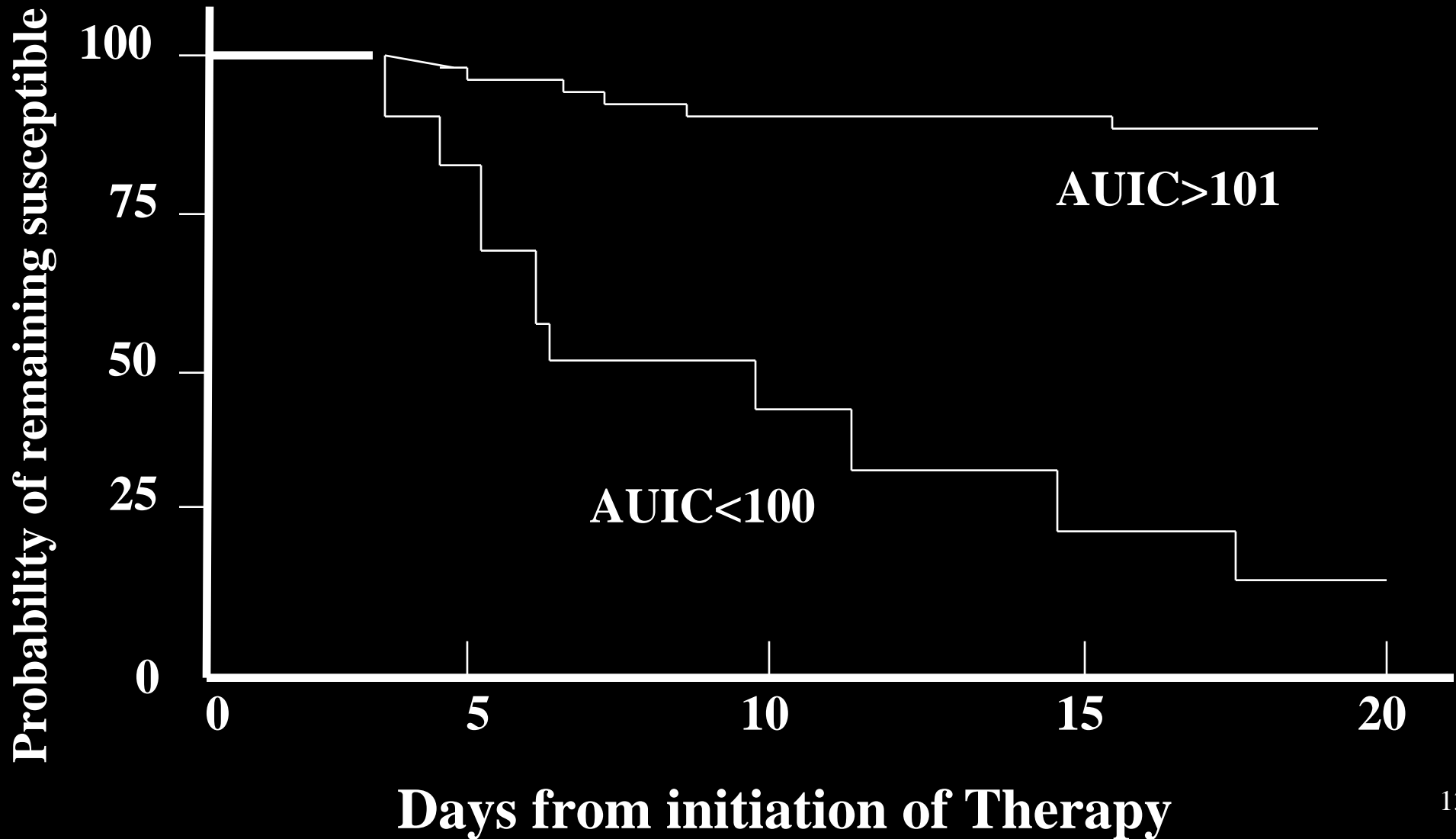
Do Aminoglycosides protect against Resistance?

- Activity against the pre-existing sub-population that is resistant to the concomitant beta lactam?
- If so, then AUIC drives the action and additivity laws are served
- Protection only when the aminoglycosides contribute enough to bring total AUIC above 125....

Consequences of Under-dosing with Antibiotics

- **Failure to Eradicate**
- **Long Eradication Time**
- **Resistance develops when
AUC is below 100**

AUIC vs Resistance



Linkage between dosing and Antibiotic Resistance

- **Marginal Organisms (MIC at the breakpoint) are the first organisms to express resistance**
- **Emergence by selective pressure occurs when dosing is lowered below MIC. Example: Ofloxacin resistant *Pseudomonas aeruginosa***
- **Individual patients with foreign bodies and low doses are reservoirs for these resistant pathogens, once these conditions occur**

Clinical Approaches

- **Dose to Trough above MIC**
- **Increase doses for high MIC organisms and patients with high CCr**
- **When in doubt, combine antibiotics. When sure of isolates, refine regimens**
- **Gram Stain is the best monitoring tool**
- **Computer software to Estimate AUICs**

Computerized Estimation of AUIC

- **Selected patients who are now undertreated will benefit from the addition of a second antibiotic, or higher doses**
 - **Less resistance, fewer failures, shortened therapy**
- **Most cephalosporin doses will be lowered (elderly patients, low MIC organisms)**
 - **Cost Savings in the antibiotic budget**

Use of AUC in Patient Care

- **77 yoM, 70 in, 155 lb, with COPD, Lung Ca, and Diabetes, 7 days post-op LLL resection.**
- **Now with new S&S of LRTI, on a Ventilator**
- **Cefazolin for prophylaxis day 1, currently receiving no ABX. Serum creatinine is 1.2 mg/dl**
- **Cx taken, Ceftazidime 1.0 gm Q12hr is ordered.**
- **You were consulted for antibiotic management**

Calculation of AUICs

- $\text{DOSE}_{24}/\text{Clearance}=\text{AUC}_{24}$
- $\text{Clearance} = \text{CCr}(\mathbf{x}) + \text{Clnr}$
- Adjust AUC for 24 hr of Dosing if not already done
- MIC as Default or Exact value?
- $\text{AUIC}_{24}=\text{AUC}_{24}/\text{MIC}_{18}$

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

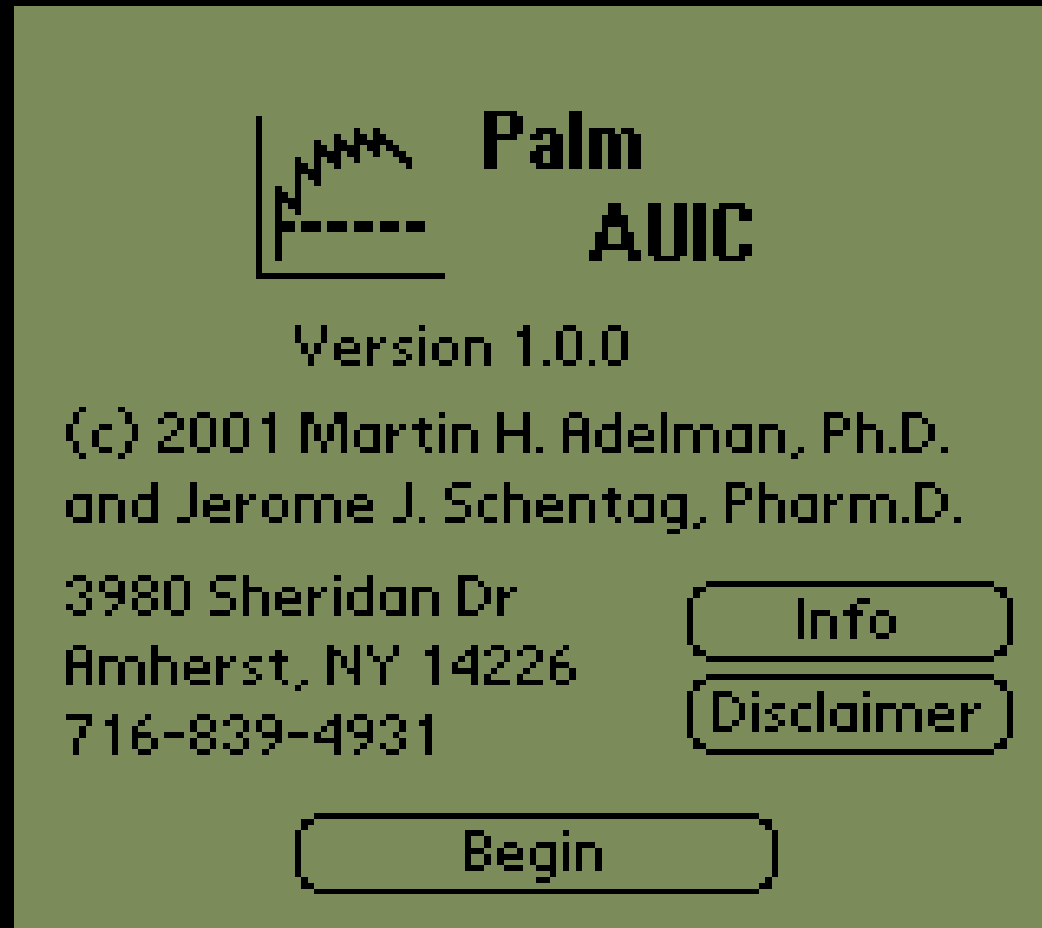
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Buffalo NY**

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and Jerome J Schentag, PharmD**

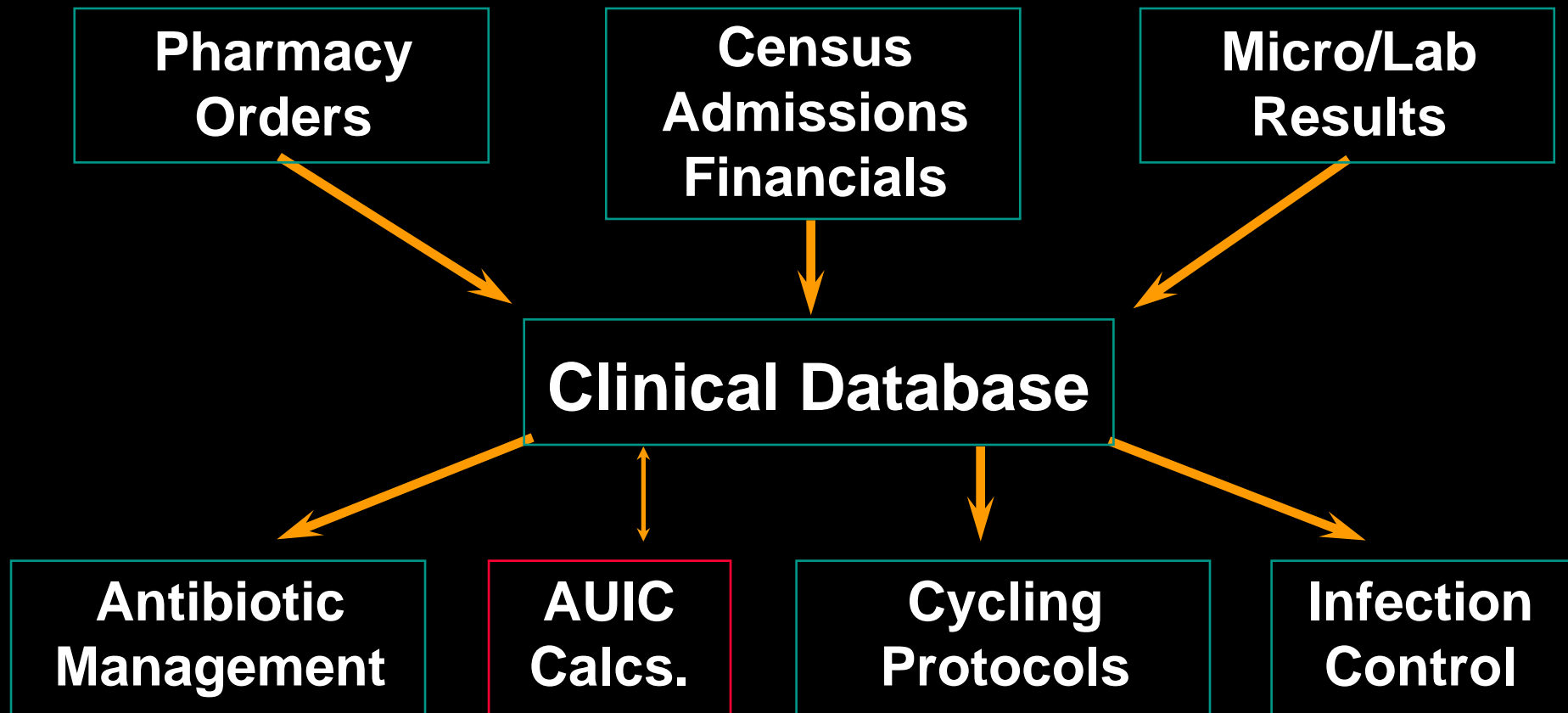
Home Screen-Palm AUIC



AUIC Screening by Computer

- Selected patients who are now under-treated will benefit from the addition of a second antibiotic, or from the use of higher doses
 - Less resistance, fewer failures, shortened therapy
- Most cephalosporin doses will be lowered (elderly patients, low MIC organisms)
 - Cost Savings in the antibiotic budget
- Requires integrated computer datafiles

Computer Assisted Antibiotic Management



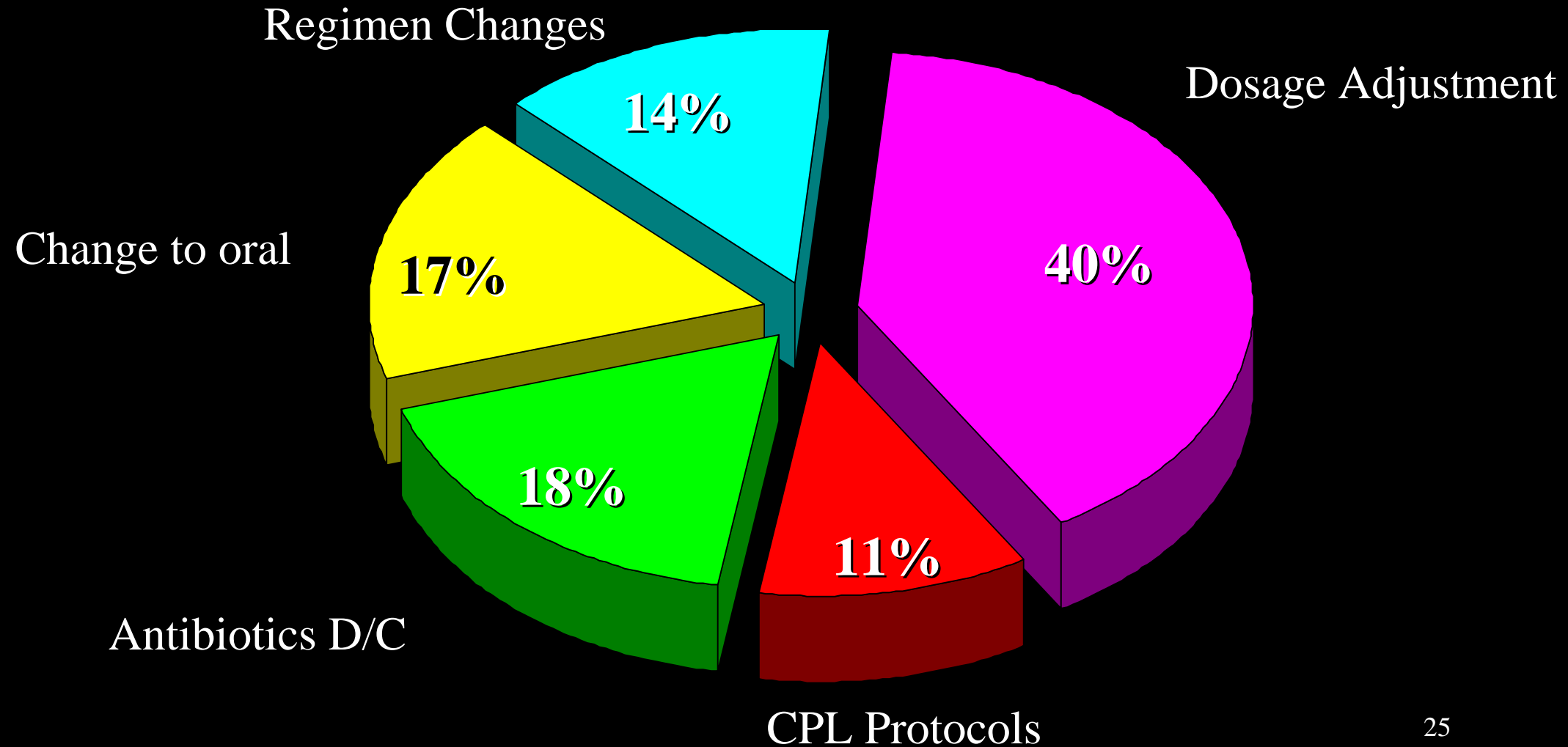
Antibiotic Management and Infection Control

- **Custom Reports for Specialists**
- **List of Target Organisms**
- **Antibiograms by unit or even by room, with ABX Use data**
- **Target Sites of Infection**
- **Resistance surveillance functions**

Clinical Pharmacy Goals

- **Implement AUC dosing adjustment program for improvement of clinical outcomes. Raise doses for high MICs**
- **Implement regimen refinement program to lower costs after first 3 days of Intravenous therapy**

Type of Antibiotic Interventions



Antibiotic Modifications

- **By day 3 of treatment, most patients:**
 - **Have improved clinically**
 - **Have an Identified organism in cultures taken on day 1**
 - **Have organism eradication or inoculum reduction**
 - **Are taking oral diets and/or Medications**