
# Clinical Pharmacy and Optimization of Antibiotic Usage: The experience of the American Pharmacists

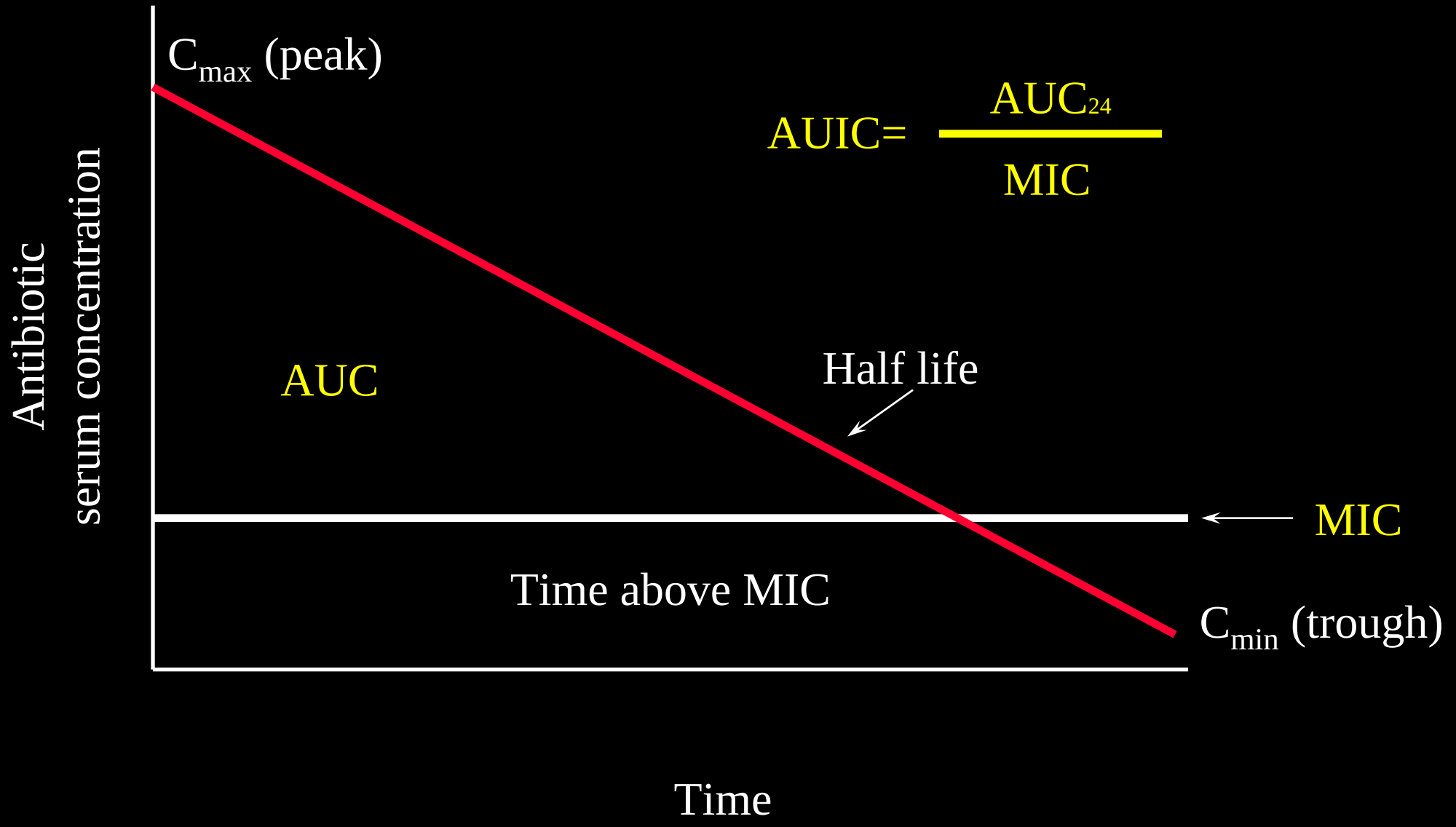
**Jerome J Schentag, Pharm D**

Presented at UCL on Monday February 25th

# Systems Approach to Antibiotics

- **Value: Making sure every patient receives excellent care, every time..**
- **The “Hammer” is the computer….**
- **“To a man with a hammer, everything starts to look like a nail that needs pounding…”**

  **–Mark Twain**


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

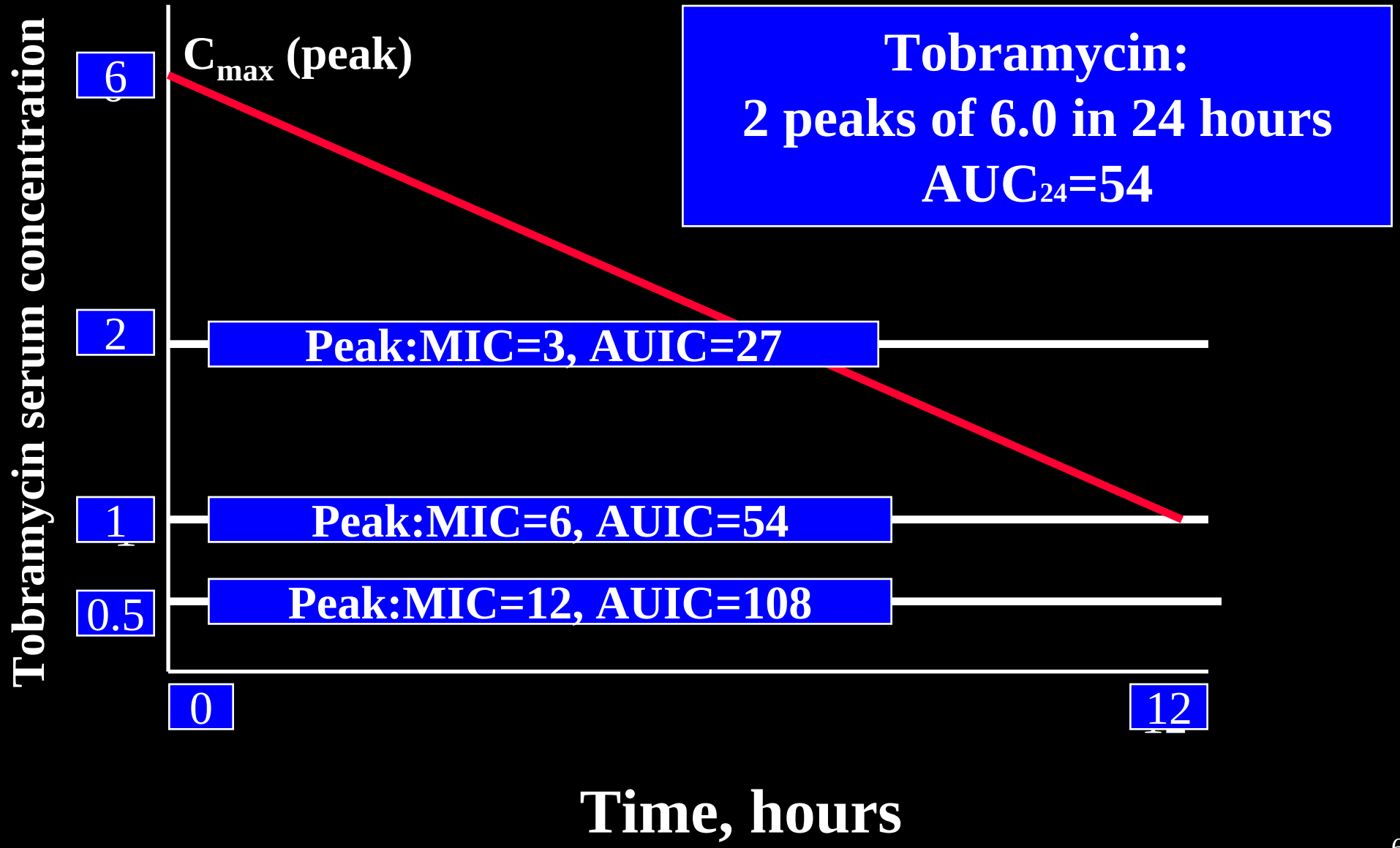
# Antibiotic PK and PD attributes

- **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**

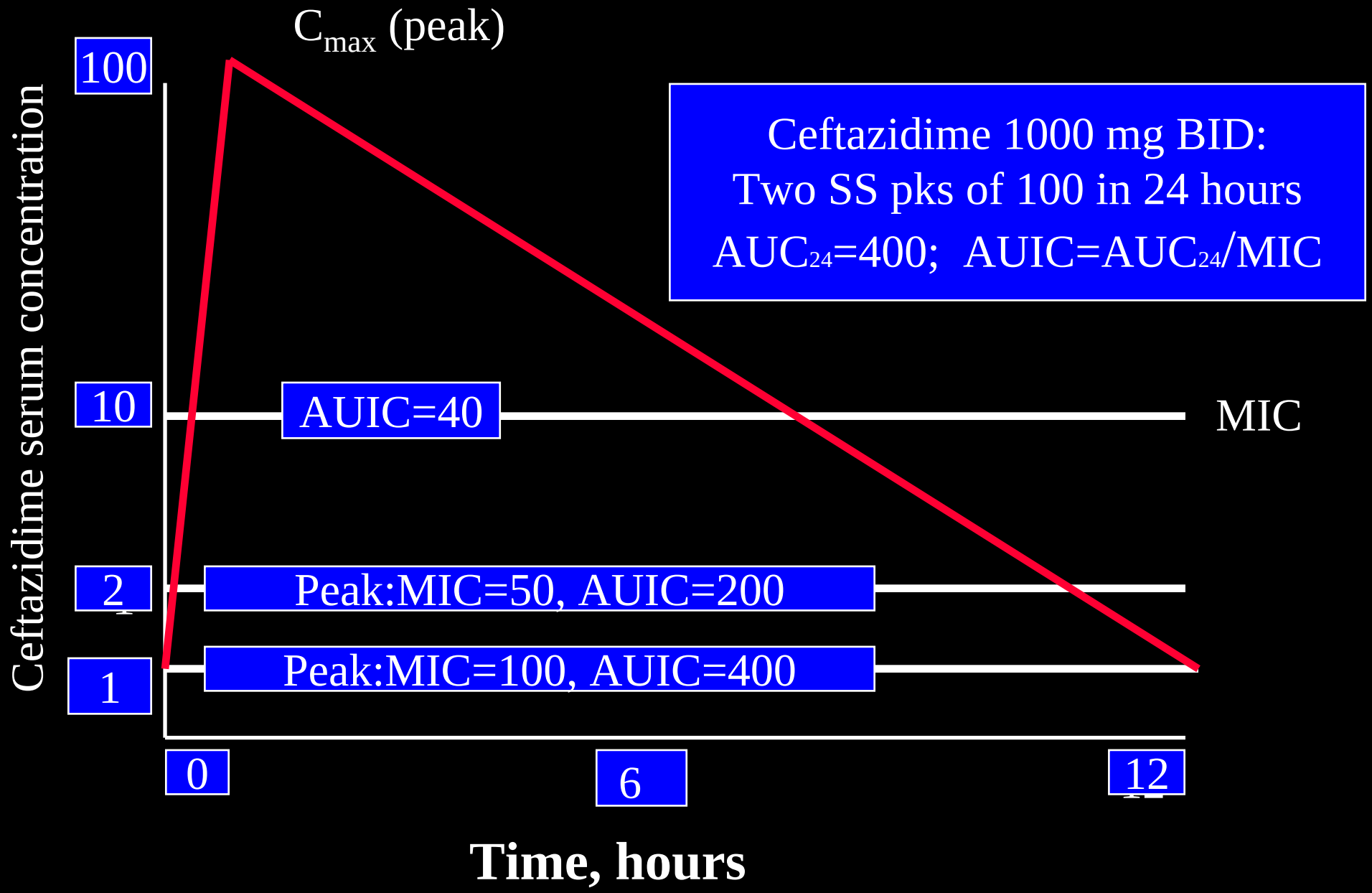

Tobramycin serum concentration
6
2
1
0.5
0
12
$C_{max}$ (peak)
Tobramycin:
2 peaks of 6.0 in 24 hours
$AUC_{24}$=54
Peak:MIC=3, AUIC=27
Peak:MIC=6, AUIC=54
Peak:MIC=12, AUIC=108
Time, hours

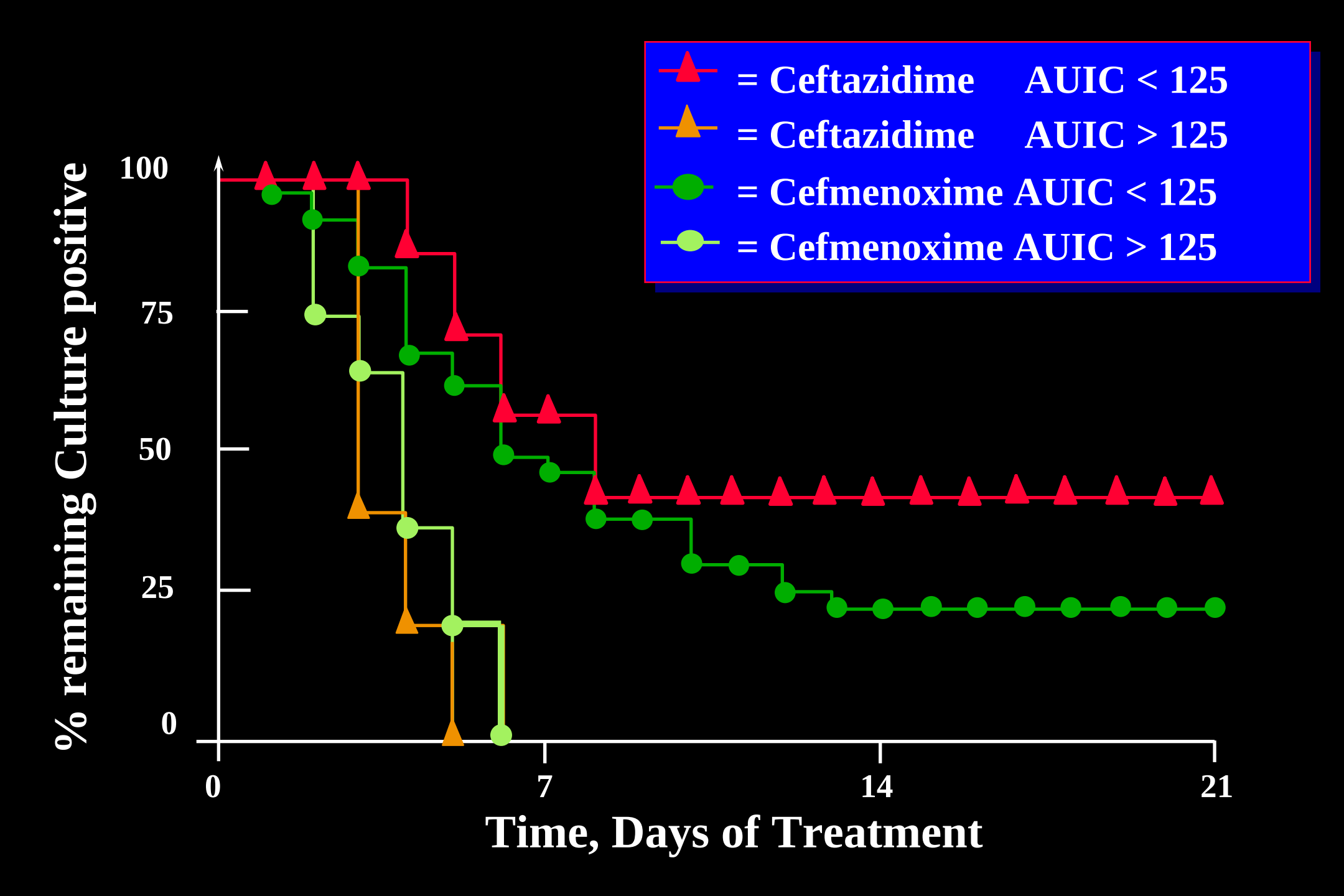
# Aminoglycosides

- 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

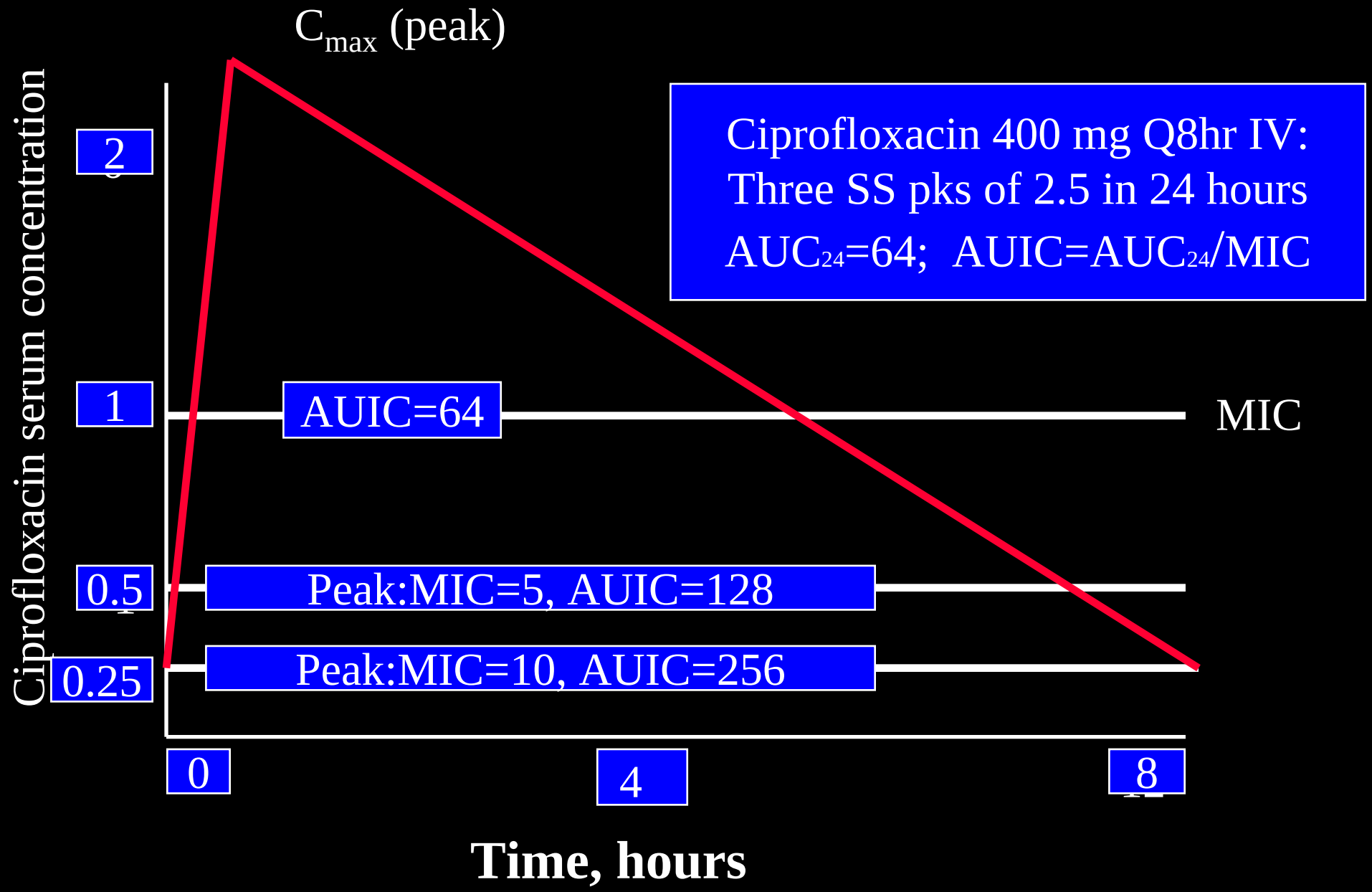
| Compound | $AUC_{24}$ | MIC P.aerug | $AUIC_{24}$ |
|---|---|---|---|
| **Tobramycin** | 54 | 1.0 | 54 |
| **Ceftazidime** | 400 | 2.0 | 200 |
| **Total (Tob+Ceftaz)** | | | 254 |


$C_{max}$ (peak)
100
10
2
1
Ceftazidime serum concentration
Ceftazidime 1000 mg BID:
Two SS pks of 100 in 24 hours
$AUC_{24}$=400; AUIC=$AUC_{24}$/MIC
AUIC=40
MIC
Peak:MIC=50, AUIC=200
Peak:MIC=100, AUIC=400
0
6
12
Time, hours


= Ceftazidime AUIC < 125
= Ceftazidime AUIC > 125
= Cefmenoxime AUIC < 125
= Cefmenoxime AUIC > 125
% remaining Culture positive
100
75
50
25
0
0
7
14
21
Time, Days of Treatment

# 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….


$C_{max}$ (peak)
Ciprofloxacin 400 mg Q8hr IV:
Three SS pks of 2.5 in 24 hours
$AUC_{24}$=64; AUIC=$AUC_{24}$/MIC
Ciprofloxacin serum concentration
2
1
0.5
0.25
AUIC=64
MIC
Peak:MIC=5, AUIC=128
Peak:MIC=10, AUIC=256
0
4
8
Time, hours

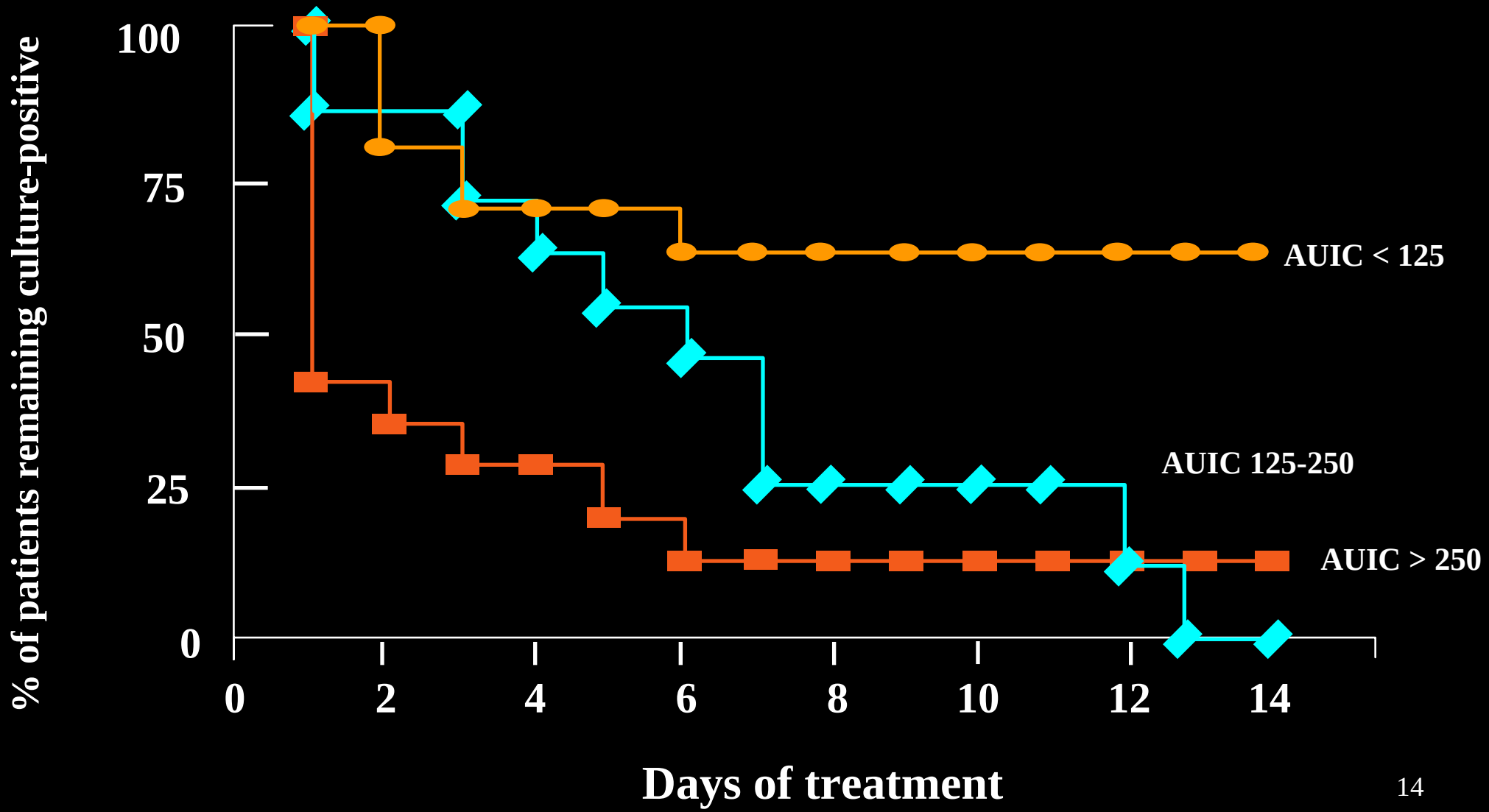
# Cure vs Ciprofloxacin AUIC

| | | Cure Rate | |
|---|---|---|---|
| AUIC | No. | Bacteriologic | Clinical |
| 0-125 | 19 | 29% | 42% |
| 125-250 | 16 | 81% | 88% |
| 250-1000 | 14 | 78% | 71% |
| 1000-5541 | 15 | 87% | 80% |

Forrest A, Antimicrob Agents Chemother 37:1073-1081, 1993.

# Ciprofloxacin: Eradication vs AUIC

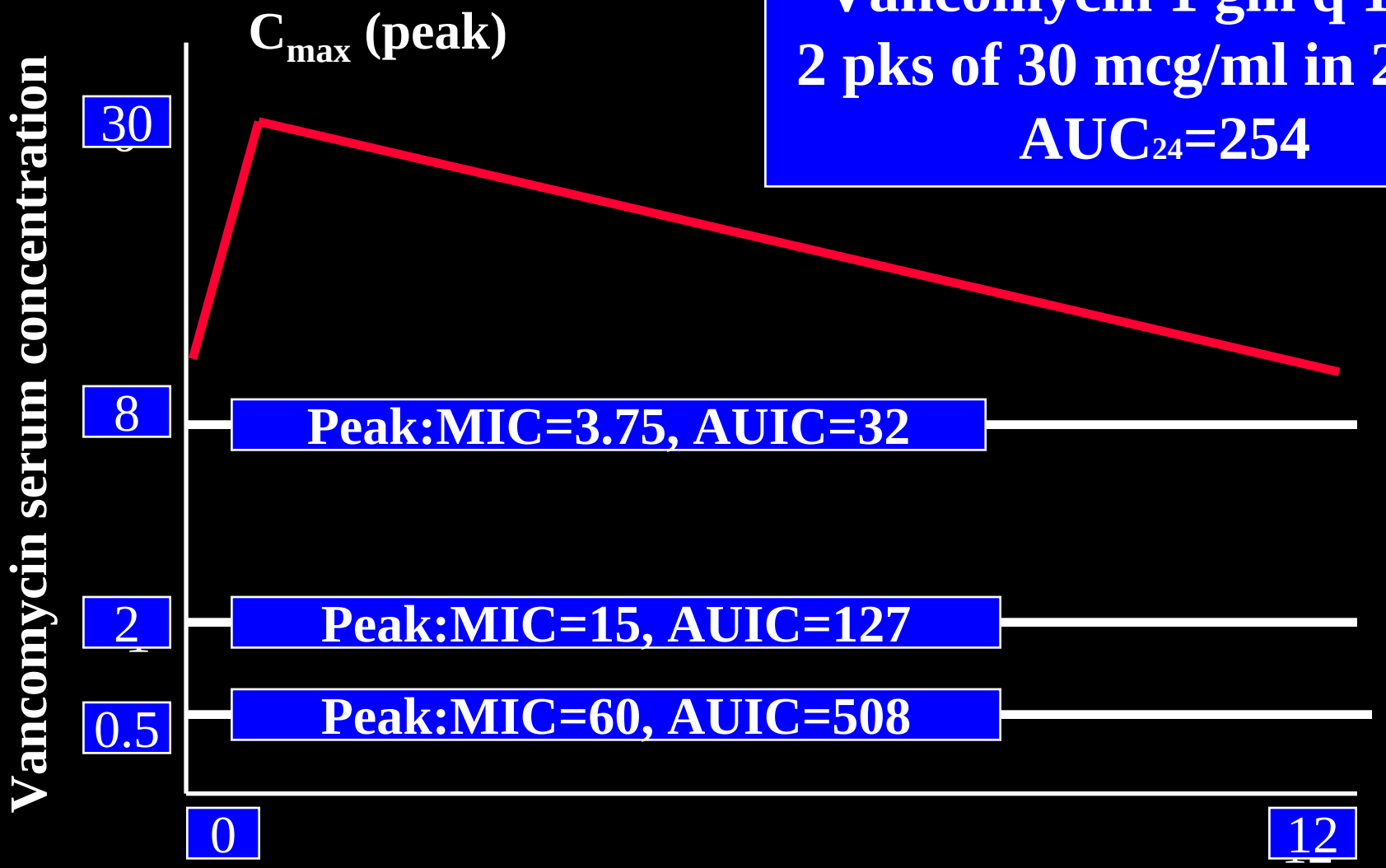
Forrest A, Antimicrobial Agents Chemother 37:1073–1081, 1993.



# AUIC Targets for Concentration Independent Antibiotics

- Examples: Beta-Lactams and Vancomycin.
- AUIC of 125 achieves the Maximal Rate of Bacterial Killing.
- At 125, 80% of the total AUC is above the MIC. Provided that dosing intervals are realistic, most of the time is above MIC.

**Vancomycin 1 gm q 12hr:**
**2 pks of 30 mcg/ml in 24 hrs**
**$AUC_{24}$=254**

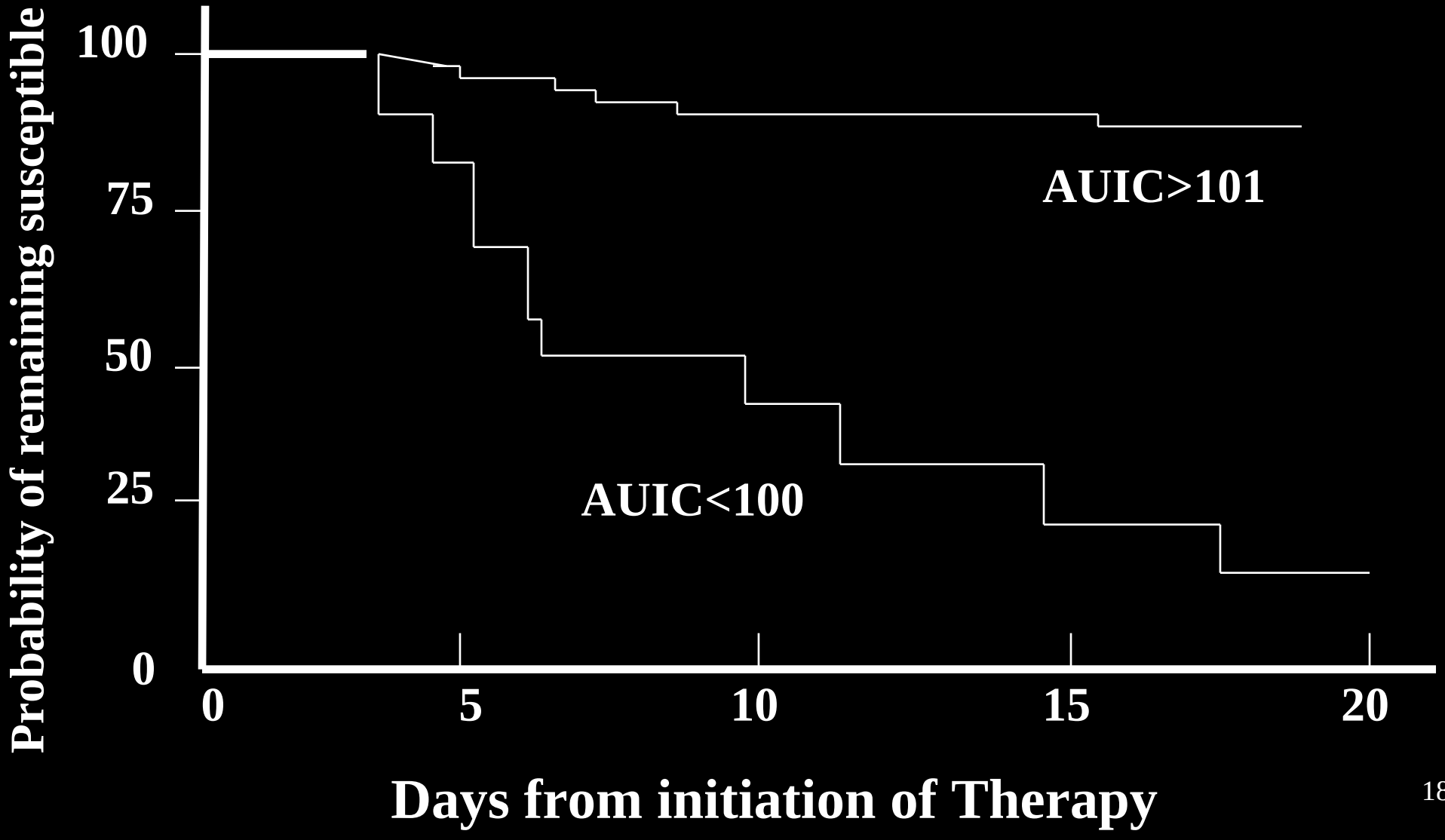


# Consequences of Under-dosing with Antibiotics

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

Thomas JK, Antimicrobial Agents Chemother. 1998.

# AUIC vs Resistance



# Emergence of Resistance

- **Protected Compartment**
- **Bacteria in this compartment are heterogeneous or resistant at baseline...**
- **Two Factors then rule:**
  - **Initial Inoculum**
  - **Antibiotic AUIC (exposure)**

# 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 AUIC 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

- $DOSE_{24}/Clearance=AUC_{24}$
- Clearance = CCr(x) +Clnr
- Adjust AUC for 24 hr of Dosing if not already done
- MIC as Default or Exact value?
- $AUIC_{24}=AUC_{24}/MIC_{18}$

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

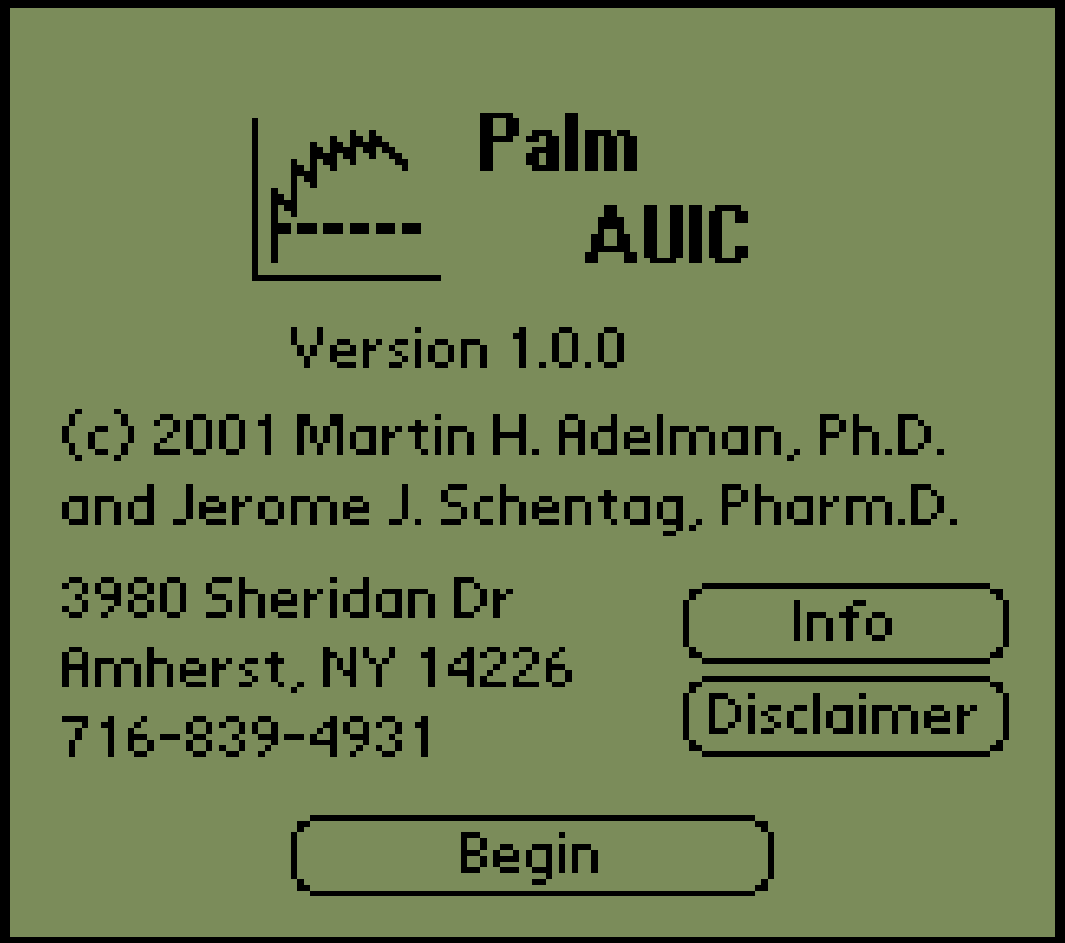
**ANTIBIOTIC UTILIZATION INFORMATION AND CONSULTATION**
**ANTIBIOTIC UTILIZATION INFORMATION AND CONSULTATION**
**ANTIBIOTIC UTILIZATION INFORMATION AND CONSULTATION**
**ANTIBIOTIC UTILIZATION INFORMATION AND CONSULTATION**
**ANTIBIOTIC UTILIZATION INFORMATION AND CONSULTATION**
**ANTIBIOTIC UTILIZATION INFORMATION AND CONSULTATION**
**ANTIBIOTIC UTILIZATION INFORMATION AND CONSULTATION**

**Version 1.0.0a**


**Jerome J Schentag and Martin H Adelman**
**Buffalo NY**

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

# Home Screen-Palm AUIC



# Millard Informatics

**Jerome J Schentag Pharm D**

**Martin H Adelman PhD**

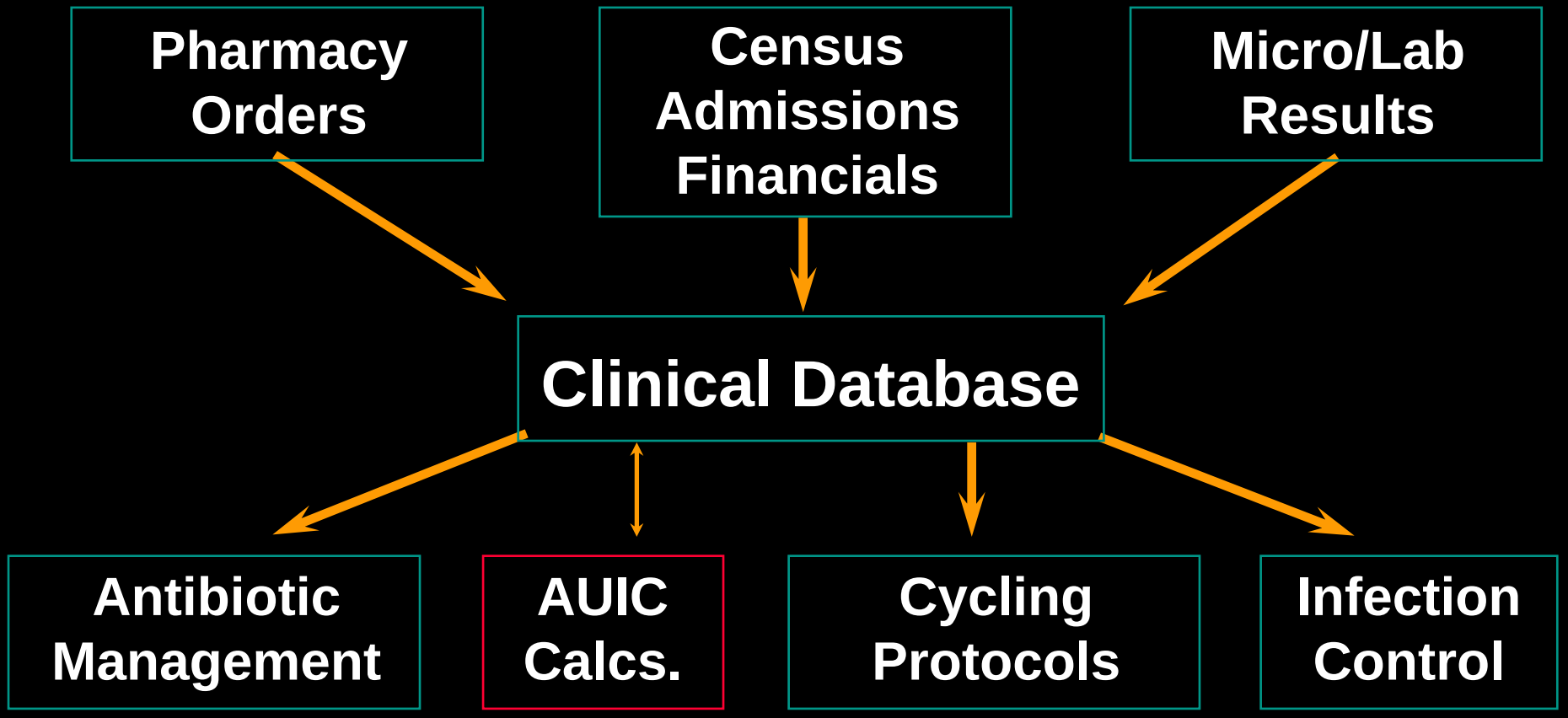
**Millard Fillmore Health System**

**Buffalo NY**

# 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

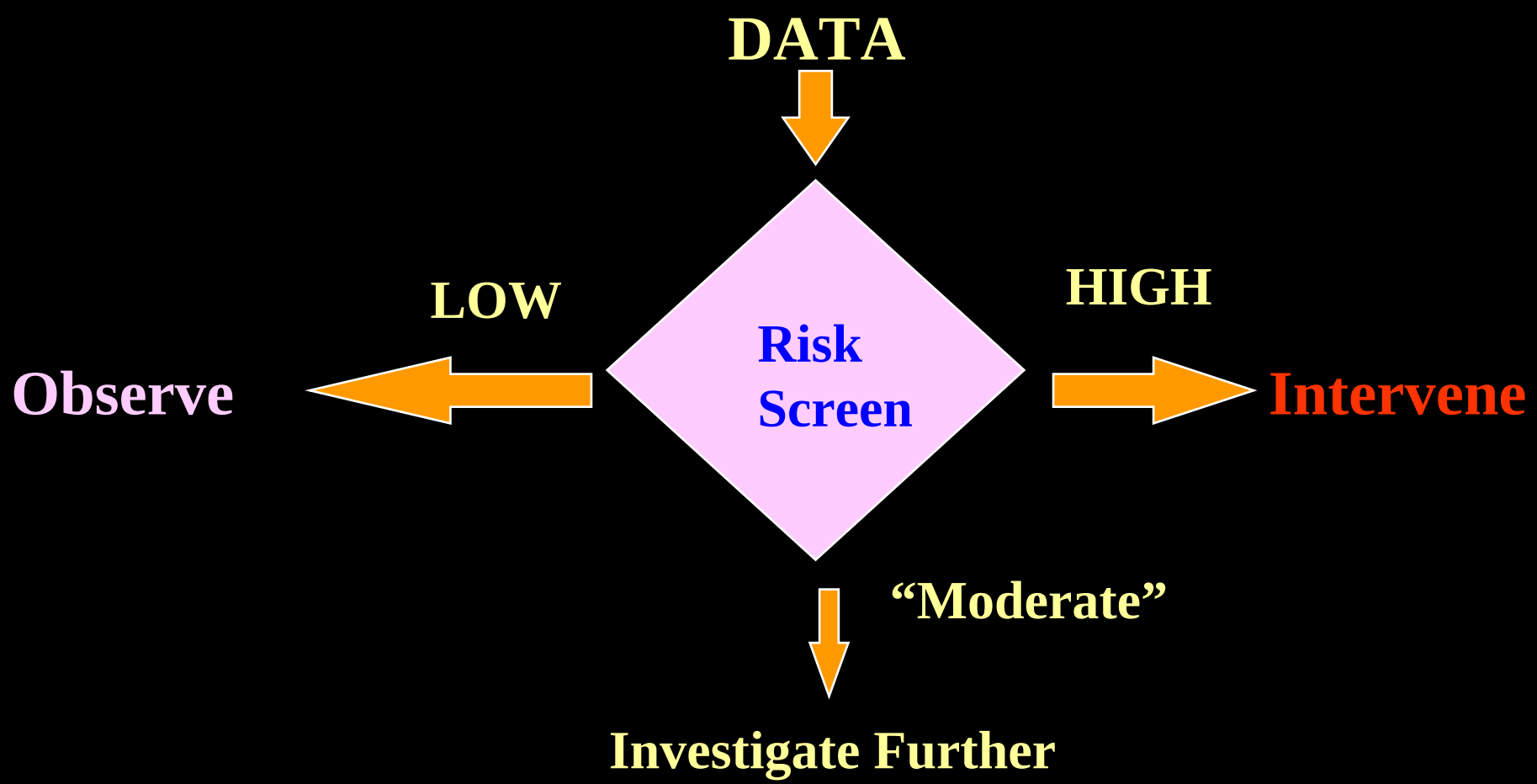
# Computer Assisted Antibiotic Management



# Risk Screening Tools

- **Survey Instruments**
  - **actuarial, population based**
  - **SF 36**
- **Algorithms**
  - **Model designed first, then applied to the data**
- **Predictive Modeling**
  - **Data Driven, case specific**

# Risk Stratification



# 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

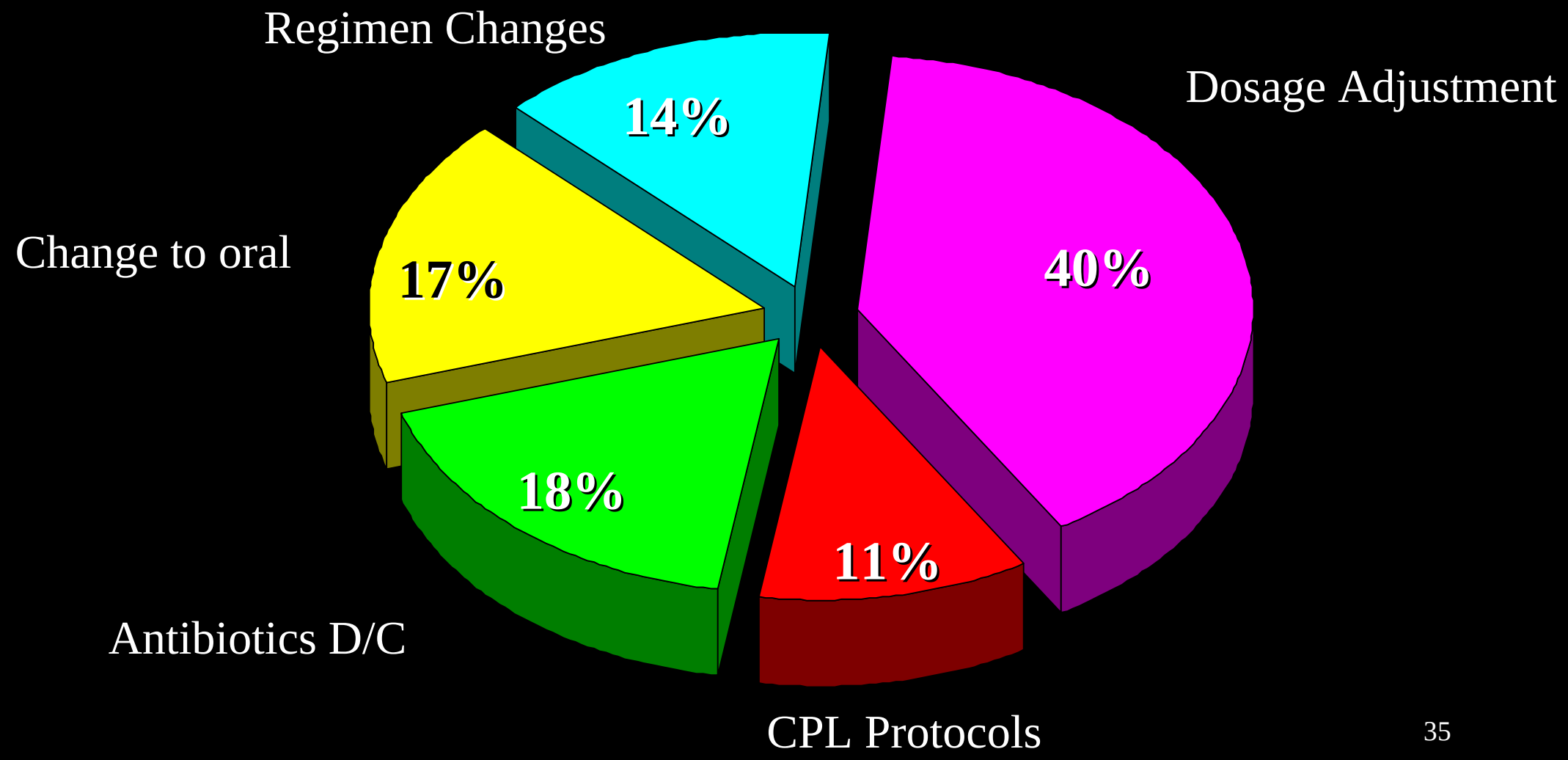
# Secrets of the reminder cult...

- **Actionable content**
- **Patient and Task Specific**
- **Available at the time of care**
- **Makes the task easier**
- **Reasonable at least 50% of the time**
- **Appropriate to the available data**

# Clinical Pharmacy Goals

- **Implement AUIC 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**

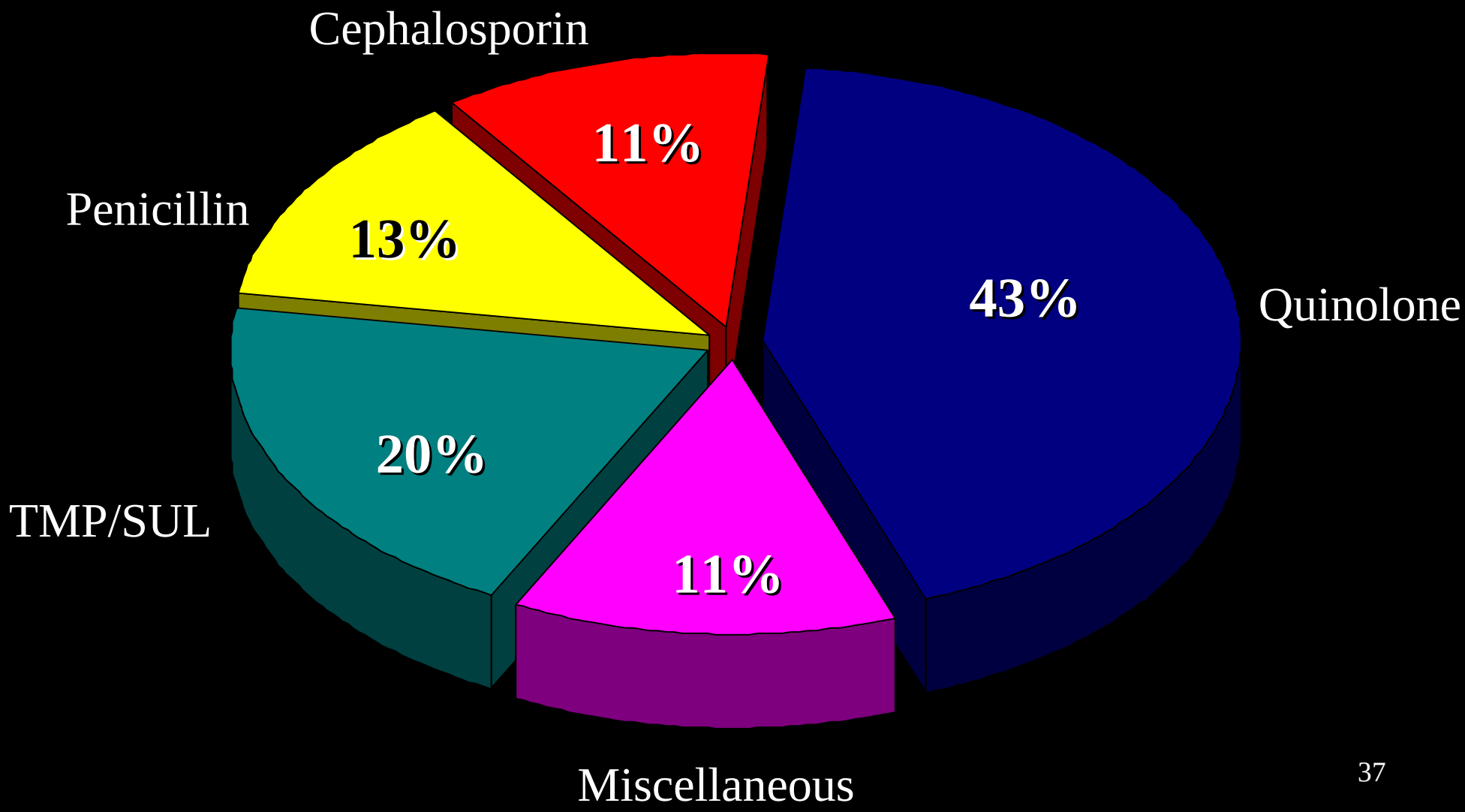
# Type of Antibiotic Interventions



# 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**

# Oral Antibiotics Recommended



# Clinical Response to Therapy

| | Parenteral | Parenteral + Oral Cipro |
|---|---|---|
| Satisfactory | 48 (77.4%) | 50 (89.3%) |
| Complete Success | 30 | 43 |
| Partial Success | 18 | 7 |
| Unsuccessful | 13 | 4 |
| Indeterminate | 1 | 2 |

# Comparative costs of the two regimens

| | Parenteral | Parenteral + Oral Cipro |
|---|---|---|
| Day 1-3 (per day) | $68.34 | $68.34 |
| Day 4+ (per day) | $60.65 | $7.93 |
| Total per case | $1,269.28 | $314.34 |
| Savings per case | | $954.94 |

**Paladino JA, Am J Med. 1991**

# Benchmarking Program

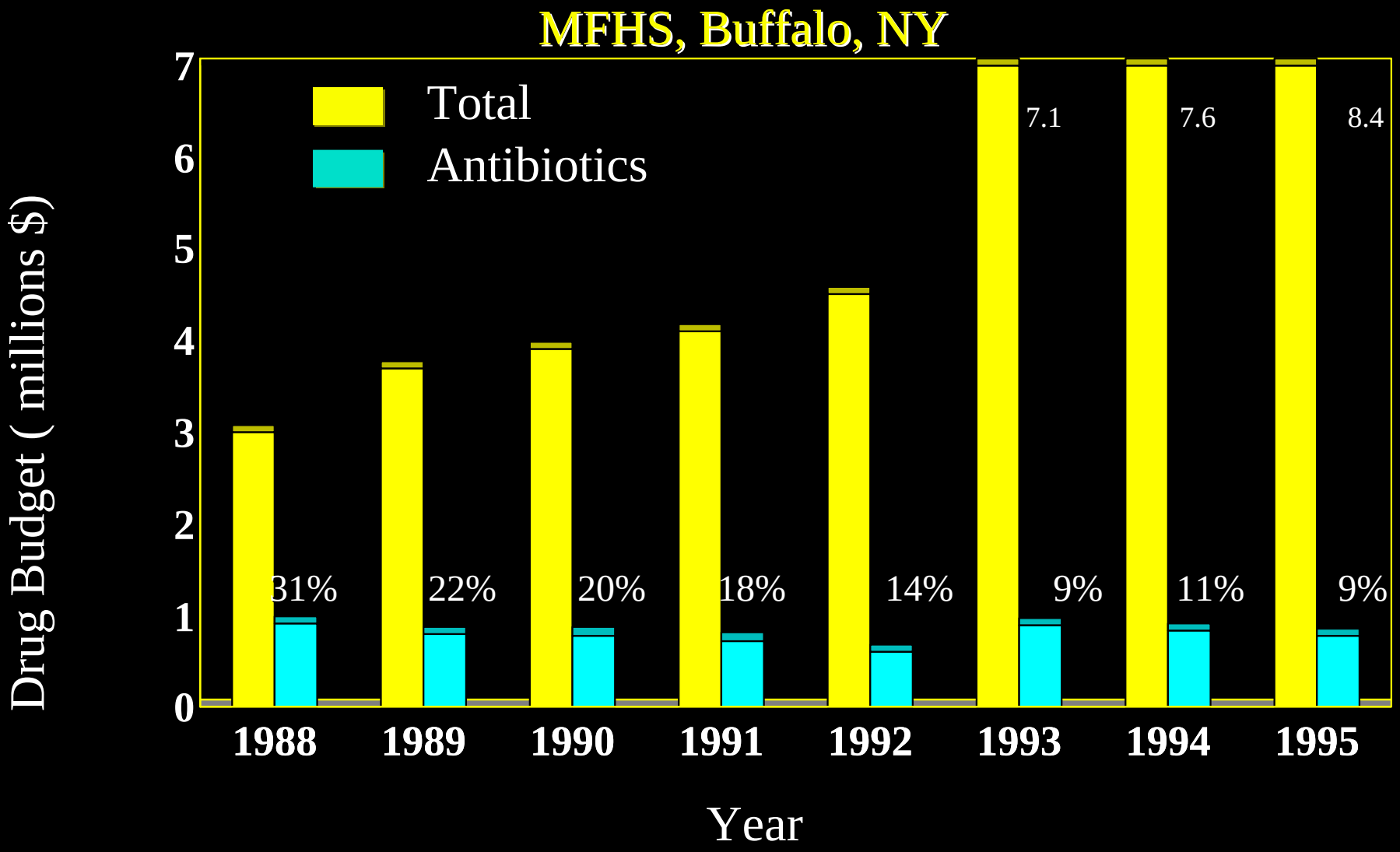
- **Goal: To identify antimicrobial management practices, expenditures, resistance trends, and overall pharmacy expenditures across hospitals**
- **Voluntary participation of >140 Hospitals across the US and Canada**
- **Information from 1993-1996:**
  - **Hospital demographics**
  - **Drug Utilization Patterns**
  - **Antibiograms**

# Methods

- Data Collected (1993-1996):
  - Hospital size (OB)
  - Ciprofloxacin IV/PO expenditures
  - Ofloxacin IV/PO expenditures
  - Anti-pseudomonal antibiotic expenditures
  - Overall antibiotic expenditures
  - *Pseudomonas aeruginosa* resistance
- Baseline (year 1), year 2, year 3, year 4

**Rifenburg RP, Hanson SC, Tuttle JA, Paladino JA, Schentag JJ. Use of benchmarking techniques to analyze the strategies hospitals use to control antibiotic expenditures. Am J Health Syst Pharm. 53: 2054-2062, 1996.**

# Changes in total and in antibiotic drug budgets



# Reasons for lower antibiotic expenditures at MFHS

1. Target low AUIC patients early, to increase dose or antibiotic potency
2. Pharmacy focus on intervention
3. Streamlining when cultures come back
4. Early cessations
5. IV ➔ oral switch

# The Story Is In The Practice Pattern

- **Focus On Day 3 (As Opposed To Day 1)**
- **Use AUIC to prevent Underdosing And Failure Early In Therapy, And To Lower The Cost/Day In Responders**
- **Oral Switch Alone Is Worth Over $500,000. Much of The Credit Goes To Our Medical Staff, The Early Adopters Of Oral Switch**

# Antibiotic Management

- **IV to Oral Switch Candidates**
- **Streamlining Candidates**
- **Early Cessation Candidates**
- **AUIC based dosage calculations on all patients**
- **Mismatches in Dosing for Organism**
  - **Dose too high or low for MIC or CCr**

# Implementation

- Make a bargain with physicians:
  - Consider a change in antibiotic regimen when cultures come back, in trade for less restriction at the beginning
- Shorten courses of antibiotics
  - Oral switch as soon as possible
  - Negative cultures = 5 days maximum
  - Five days after negatives cultures is the maximum duration for patients who improve

# Resistance Is A Pharmacy Problem

- Formulary-Driven Rigidity. The Associated Monopolistic Use Gives Bacteria The Advantage Over The Antibiotic
- We Lower Doses For patients With Decreased CCr, Ignoring MIC Differences
- We Do Not Increase Antibiotic Doses, Even When The Regimen Could Not Possibly Exceed AUIC Targets

# Cost Benefit for Informatics

- Computer power is inexpensive compared to the costs of people power
- An extreme shortage of gifted clinicians
- Expert System functions allow less specialized personnel to perform higher level intervention activities
- Lessen the time spent looking for patients and expand contact time with Caregivers
- Humans in the loop at all Decision Points

# Clinical Challenges that are UNIQUELY Solved by the use of AUICs

- Comparison of regimens within classes
- Comparisons across antibiotic classes
- Monotherapy vs Combination Regimens
  - Specific to a Patient
  - Specific to an Infecting Pathogen
  - With Sensitivity to real costs
- Design of Empiric Regimens
- Design of Step-down or Oral Switch Therapy