GSK-Chair of Infectious Diseases
(Chaire GSK de Maladies Infectieuses / GSK-Leerstoel in Infectieziekten)
a joint academic activity of the
Université catholique de Louvain **and the** *Katholieke Universiteit Leuven*

Pharmacodynamics of Antibiotics: How it can save the life of your (future) Patients

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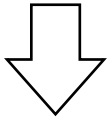
Pharmacodynamic Parameters

- Like Pharmacokinetic parameters or like serum levels, Pharmacodynamic parameters are only numbers and have no absolute meaning
- They may correlate with something meaningful; If so, they derive great utility from these correlations
- Usually, the correlate is microbial killing, although there may also be a correlate to clinical outcome, in settings where the bacterial isolate is the cause of disease and its symptoms
- Examine the elements of ABX cure and response

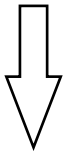
Clinical Use of Antimicrobials

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

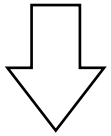
Antibiotic



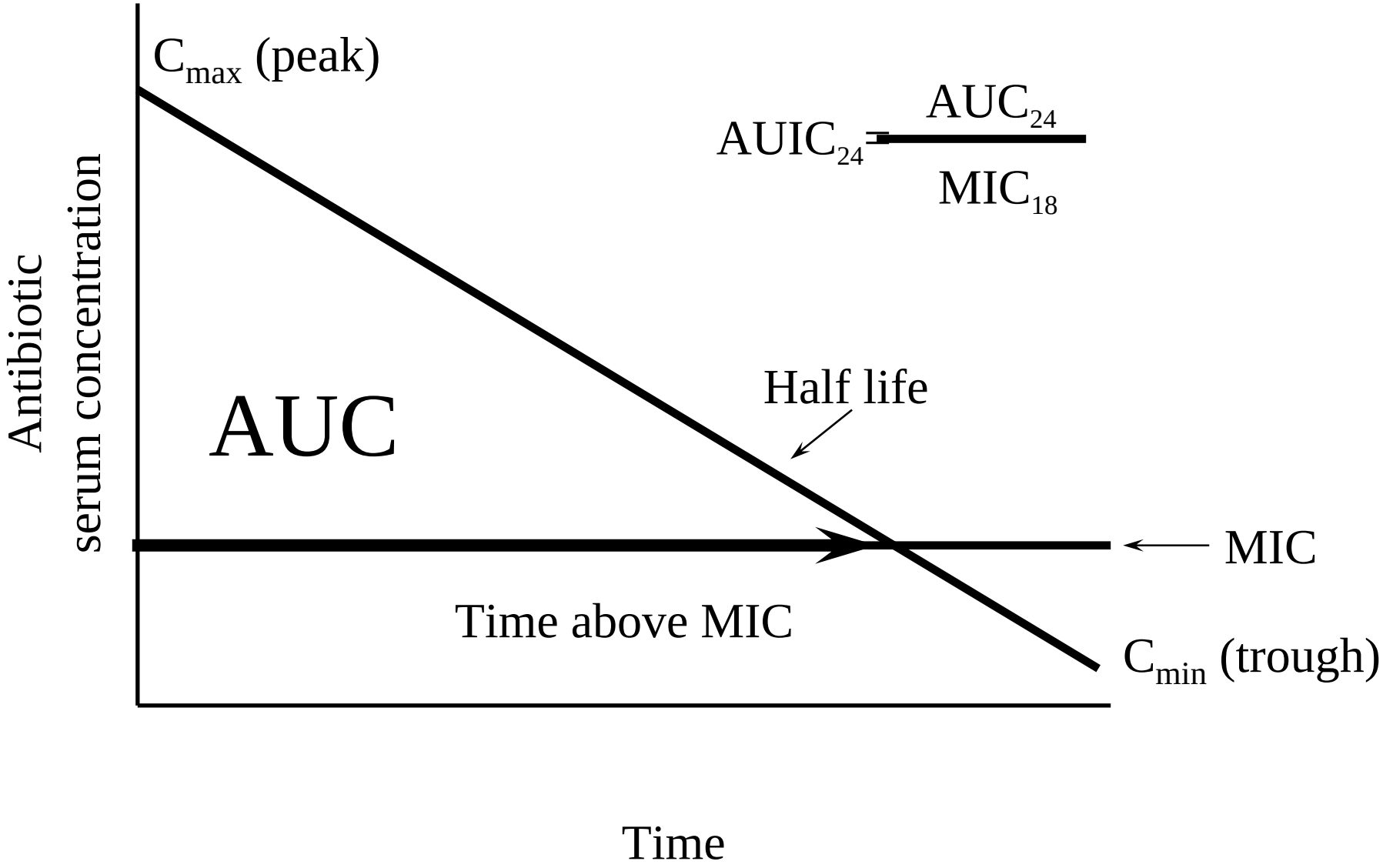
Infected Patient



Bacterial Eradication



Clinical Cure

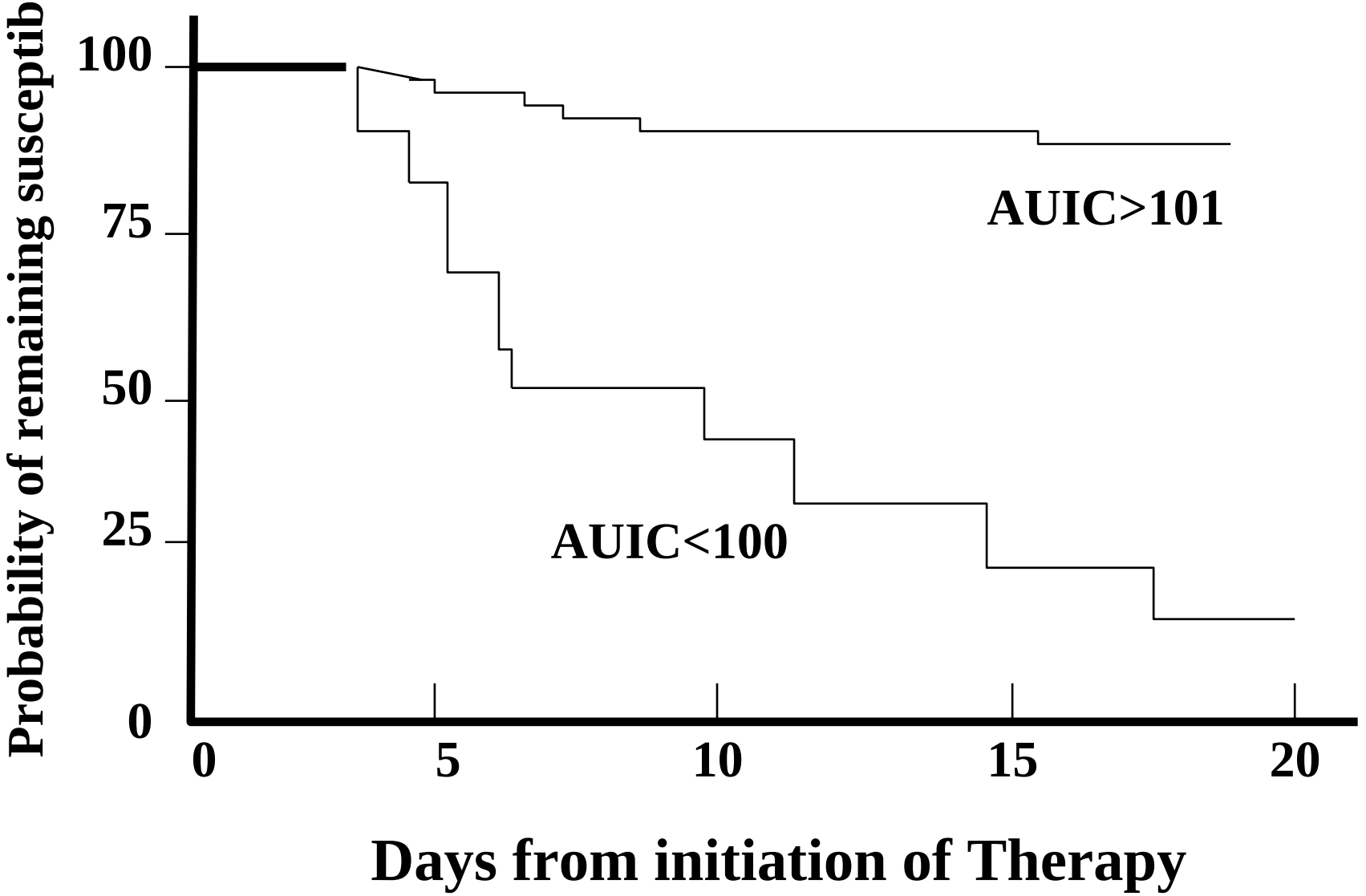

C_{max} (peak)
$AUIC_{24} = \frac{AUC_{24}}{MIC_{18}}$
Antibiotic serum concentration
AUC
Half life
MIC
Time above MIC
C_{min} (trough)
Time

Optimal PK and PD attributes

- **For optimal antimicrobial effect:**
  - **C_{max}/MIC ratio should be > 8 to 10**
  - **AUC/MIC ratio should be > 125**
- **To minimize resistance development:**
  - **AUC/MIC ratio should be >100**

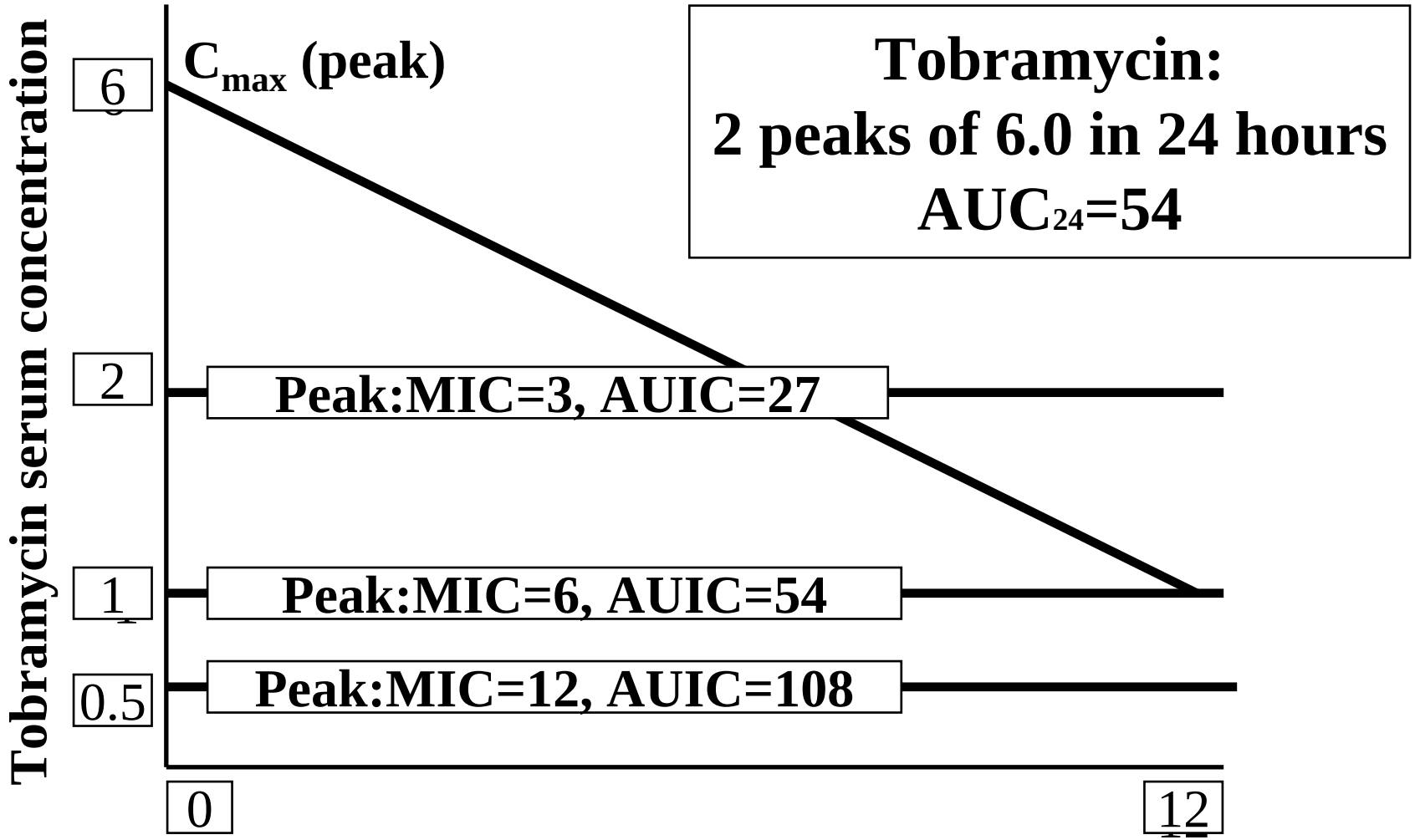
AUIC vs Resistance

Thomas JK, Antimicrobial Agents Chemother. 42: 521-527, 1998.



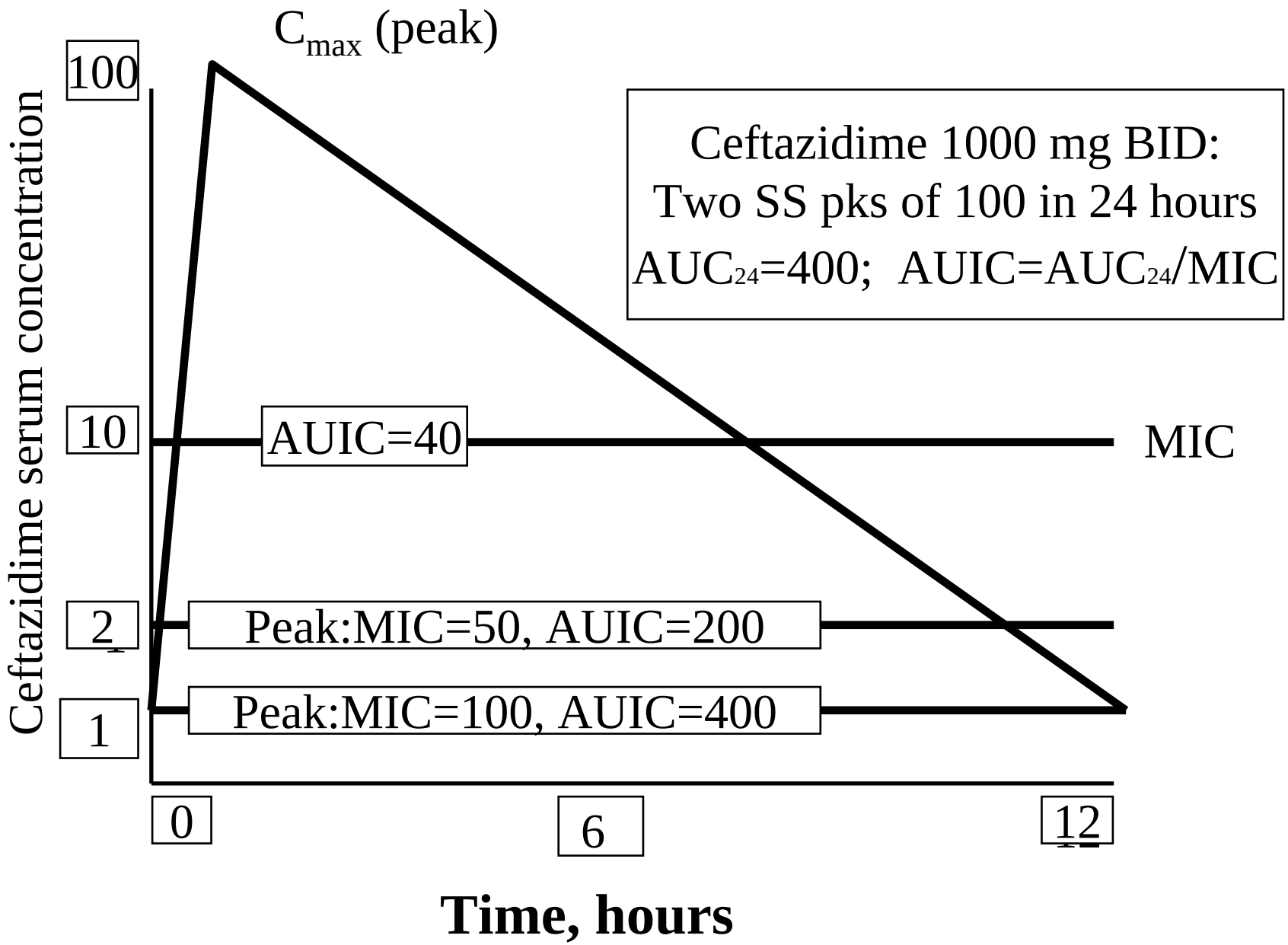
Antibiotics for Study in LRTI

- **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


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

Antibiotic Combinations

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

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

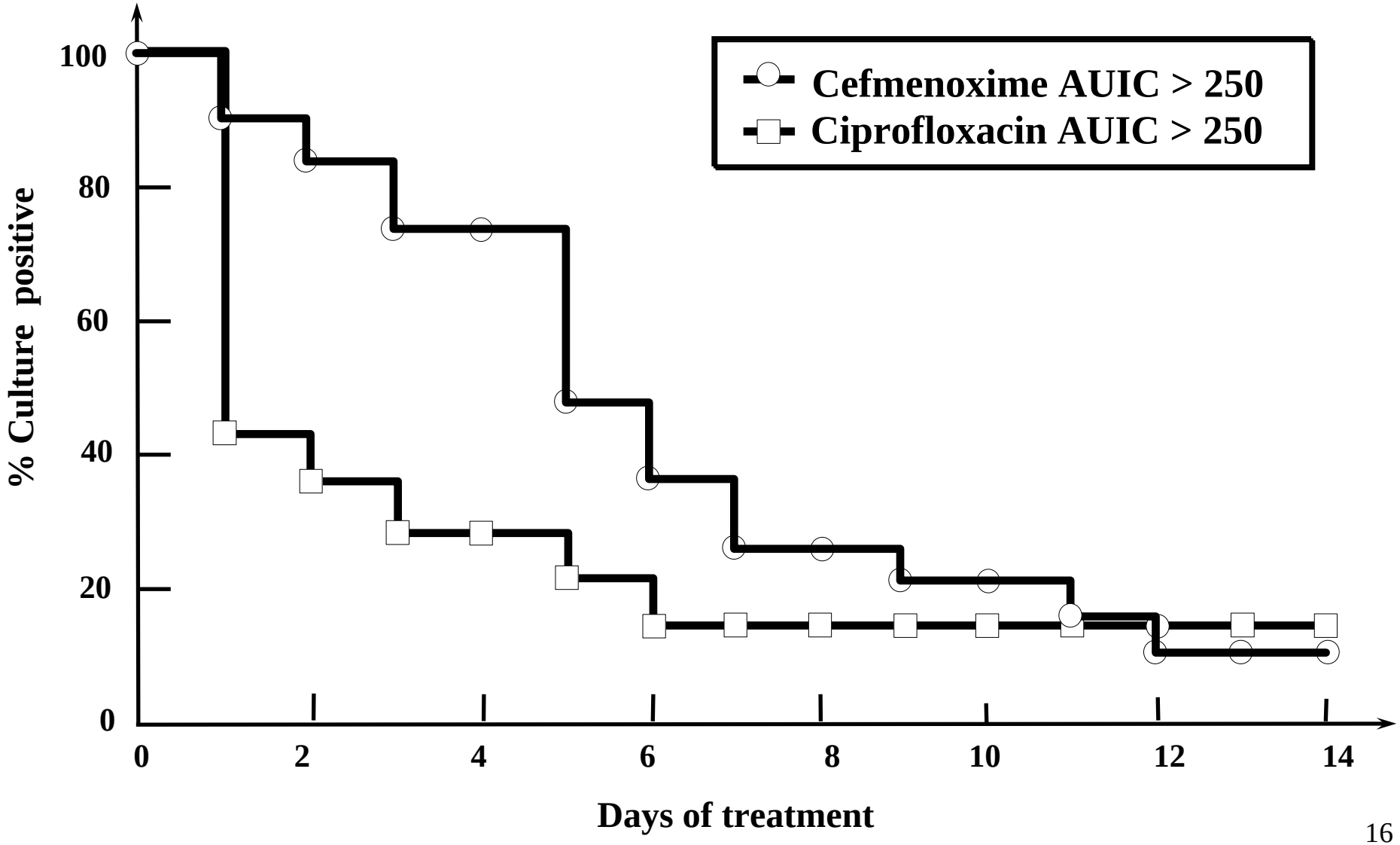
Measures of Antimicrobial Action

- 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

Measures of Antimicrobial Action

- On the bacteria
  - Bacteriological cure (contains no time sensitive information)
  - Time of bacterial eradication in relation to the time that therapy (dosing) starts

Time to Eradication vs AUIC



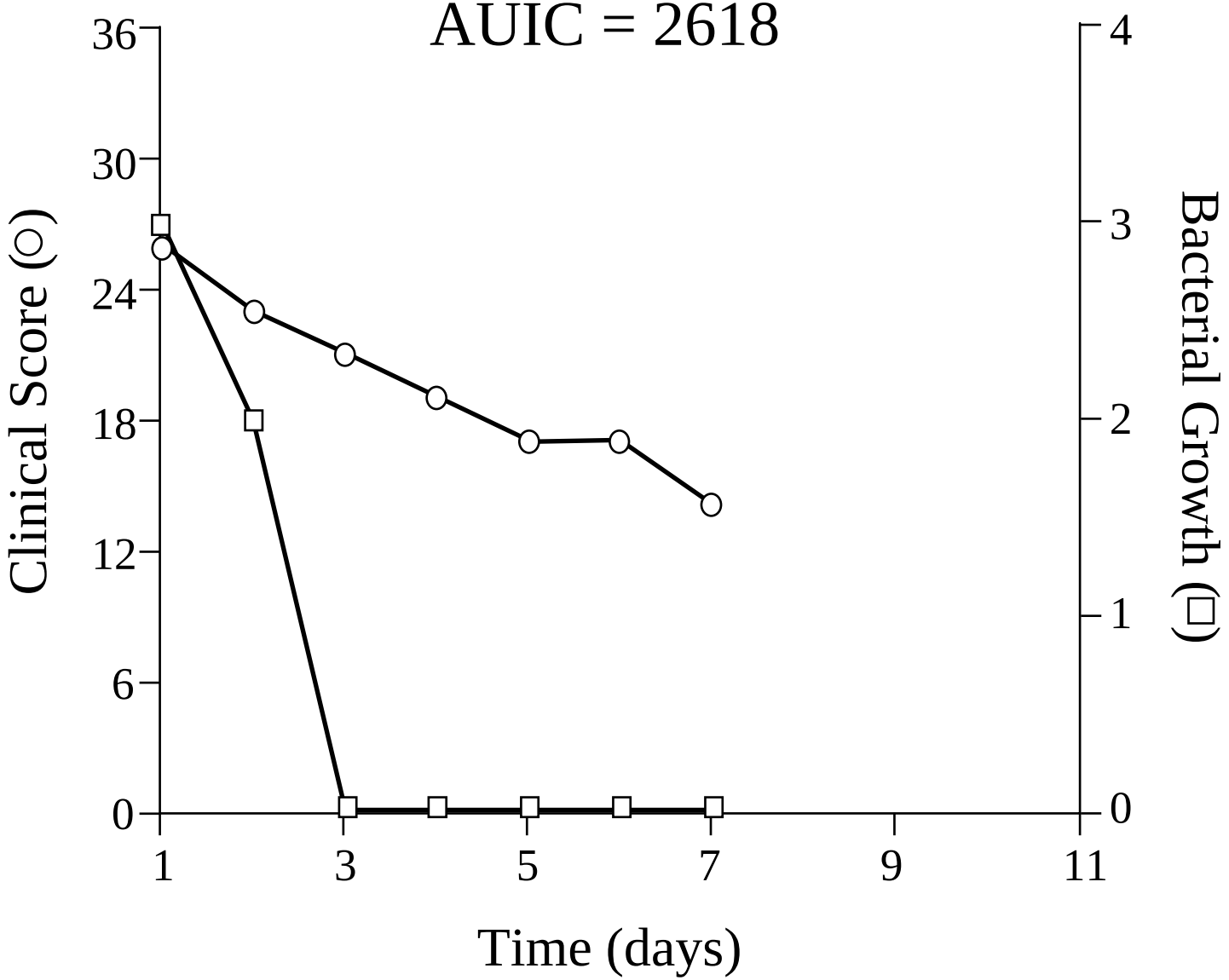
Challenges in Antibiotic Monitoring

- 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.

Development of a Scoring System for Nosocomial LRTI patients

- Monitoring elements that are time-sensitive:
  - fall in body temperature
  - fall in WBC
  - Improvement in hypoxia
  - fall in the frequency of suctioning
  - declines in # of WBCs on serial gram stains
  - declines in # of bacteria on serial gram stains
- Scored Items rated 1-4. The top Score of 40= Severe Disease

Ciptaz #38 (*E.cloacae* eradicated)
Ceftaz/Tobra
AUIC = 2618



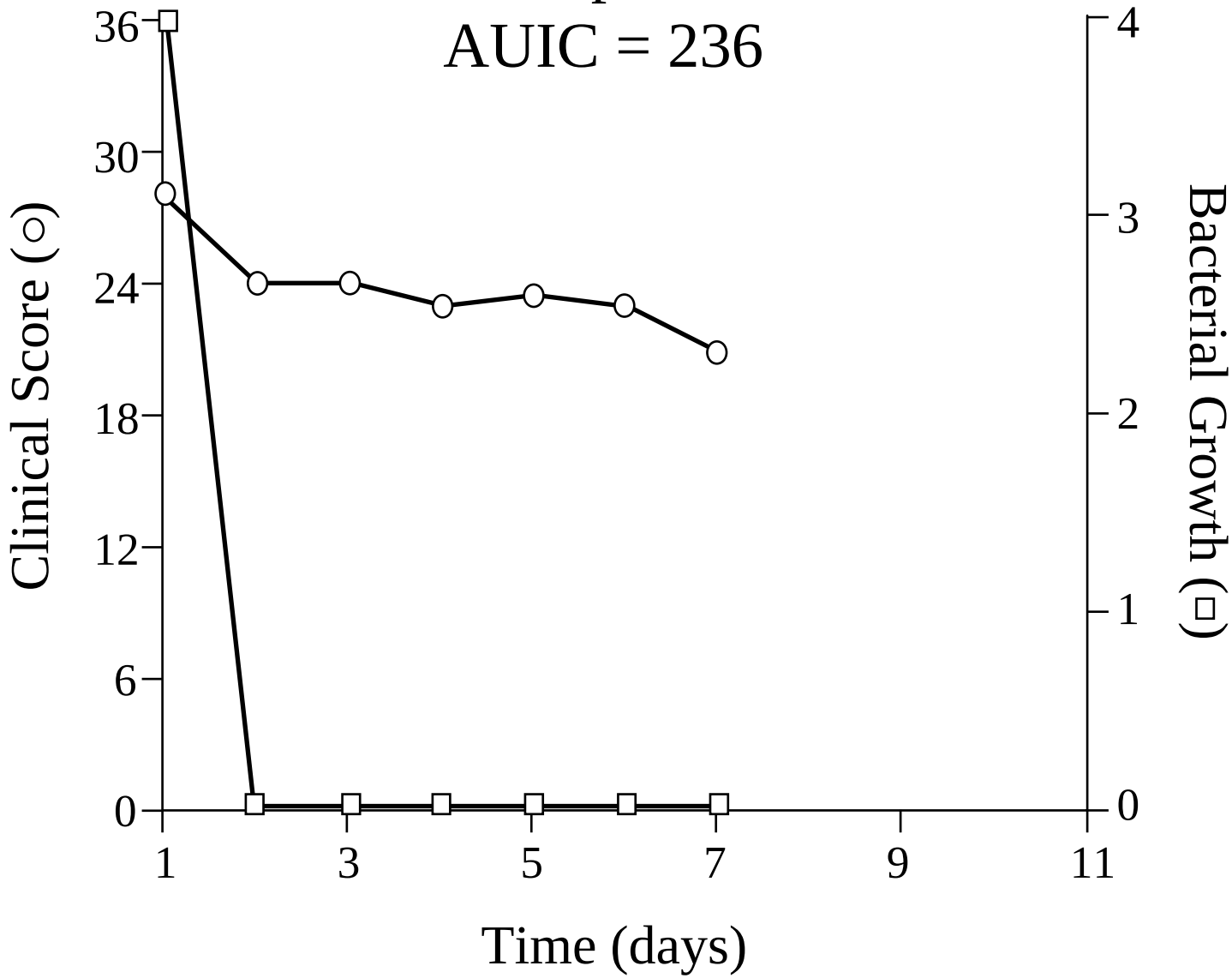
Observations in Scoring

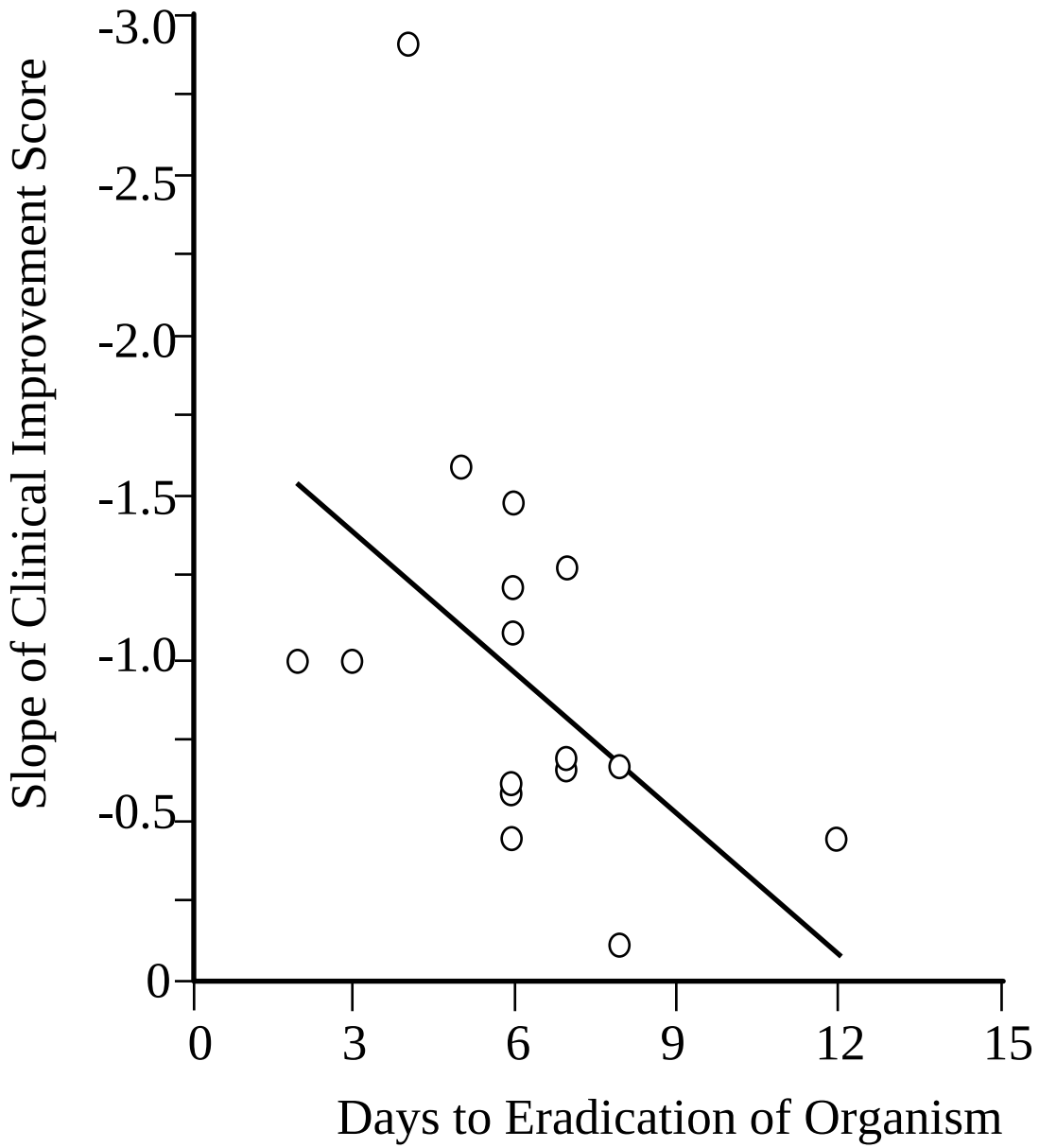
- Patients with nosocomial LRTI have a high pre-treatment score
  - Maximum score is 40, and many of these are in the high 30s
- High initial scores drop rapidly in the first few days, especially with 24-48 hr bacterial eradication
- Falls to a high baseline are common, with no further improvement regardless of the duration of antibiotic therapy

Ciptaz #24 (*P.aeruginosa* eradicated)

Cipro

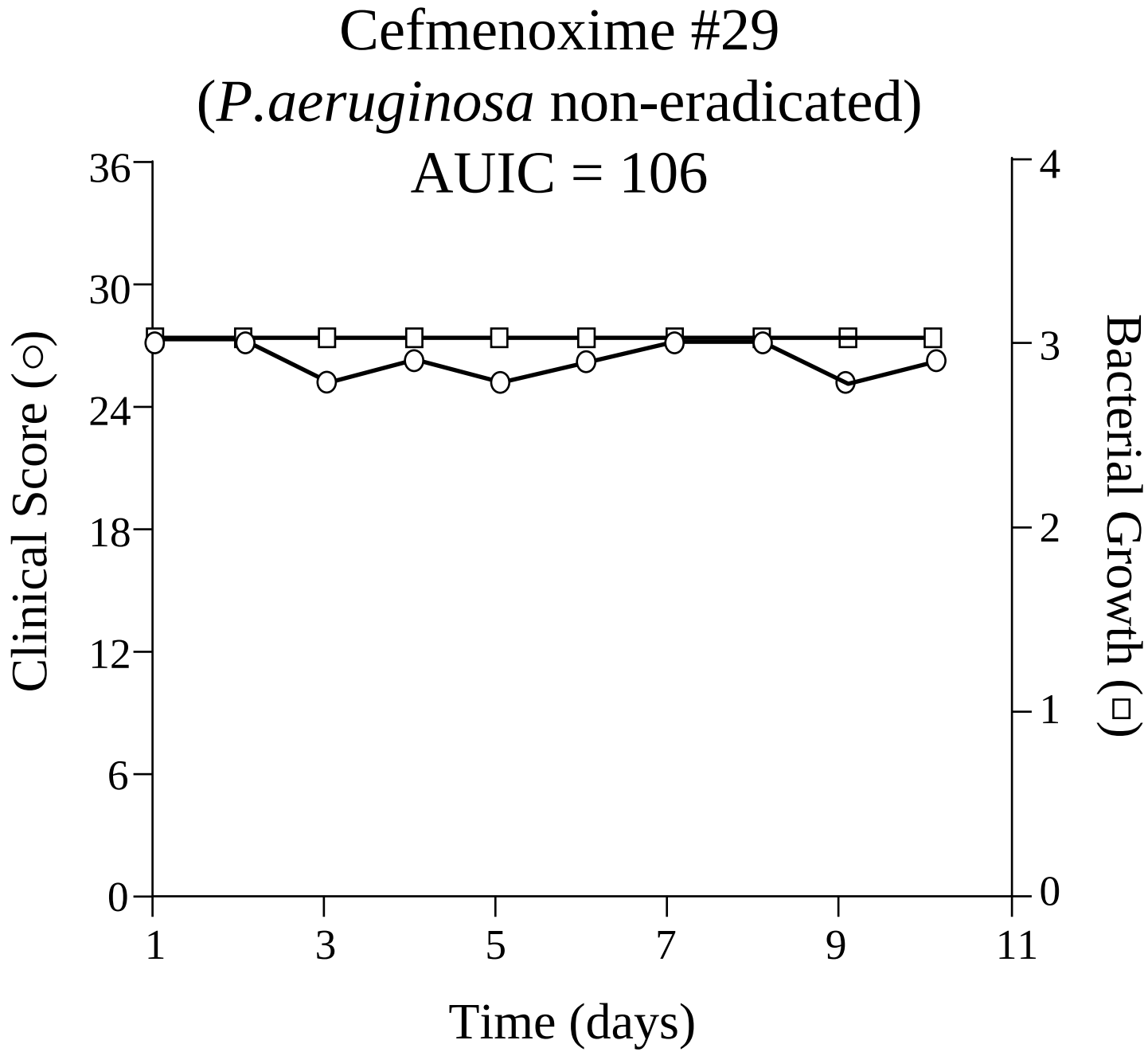
AUIC = 236




Slope of Clinical Improvement Score
-3.0
-2.5
-2.0
-1.5
-1.0
-0.5
0
0
3
6
9
12
15
Days to Eradication of Organism

Correlations between scoring and Bacterial Eradication

- Patients with rapid bacterial eradication have a rapid initial decline in score
  - i.e. the slope declines quickly
- The score may then flatten out, as the patient approaches his baseline
  - Low baseline is an indicator of no underlying respiratory pathology; This will be uncommon.
  - High baseline usually indicates underlying pathology


Cefmenoxime #29
(*P.aeruginosa* non-eradicated)
AUIC = 106
Clinical Score (○)
Bacterial Growth (□)
Time (days)
36
30
24
18
12
6
0
4
3
2
1
0
1
3
5
7
9
11

Observations

- Scoring is feasible in nosocomial LRTI patients
- Scoring is only effective when used daily in LRTI patients: This is not for diagnosis, only for monitoring drug effect
- Elements of the score were chosen to detect fast clinical response, if it occurred
- AUIC predicted the slope of the improvement score, especially with quinolones that kill bacteria in a concentration dependent manner

Summary

- **AUIC fixes problems with combination therapy and multiple organisms**
- **AUIC allows clinicians to optimize therapy to decrease resistance**
- **Pick a good dose, for each patient, as early in the regimen as possible**
- **Speeds time to eradication for the concentration dependent antibiotics**
- **Scoring changes in clinical response is feasible, and results correlate with AUIC**