



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

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



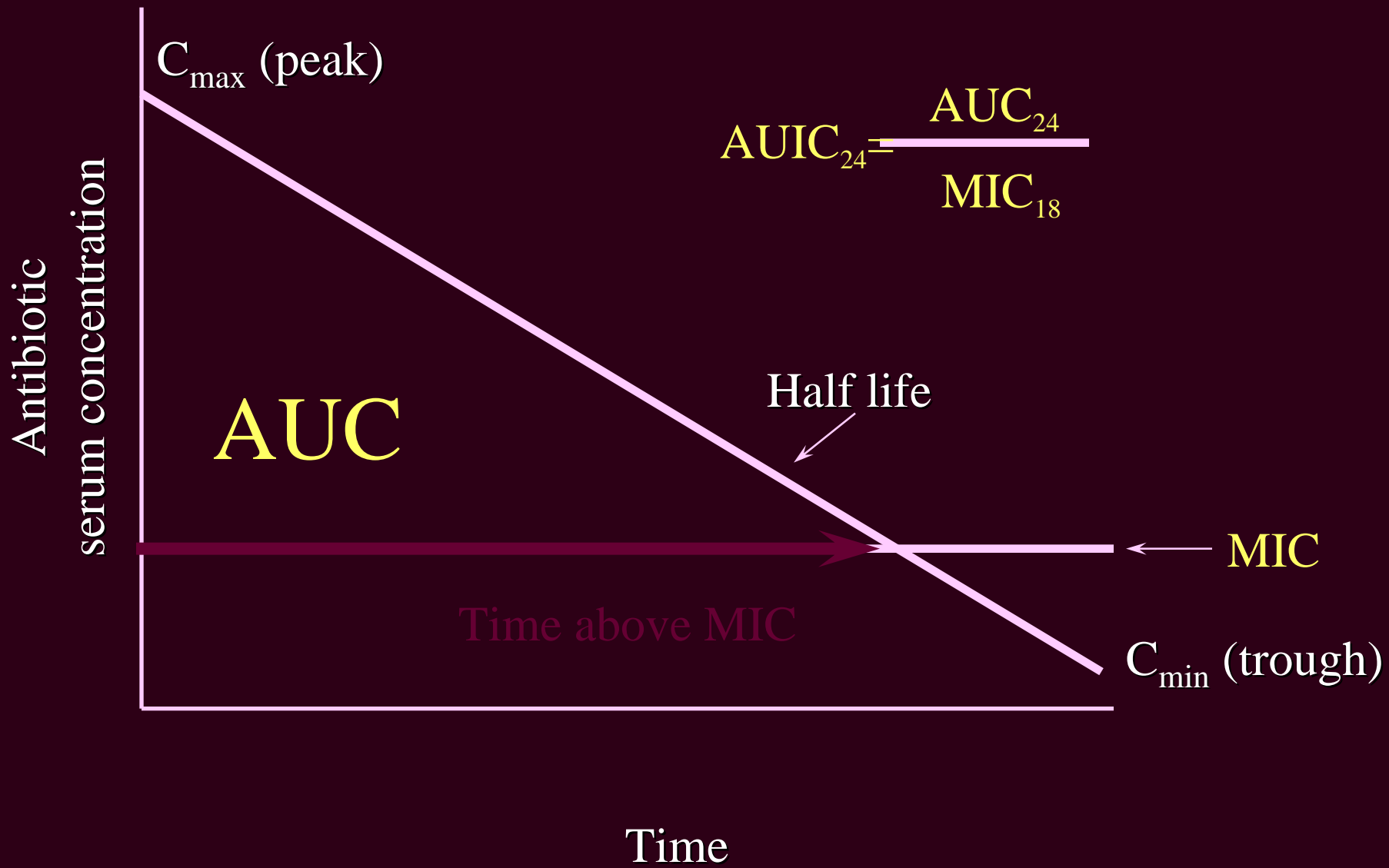
Infected Patient



Bacterial Eradication



Clinical Cure

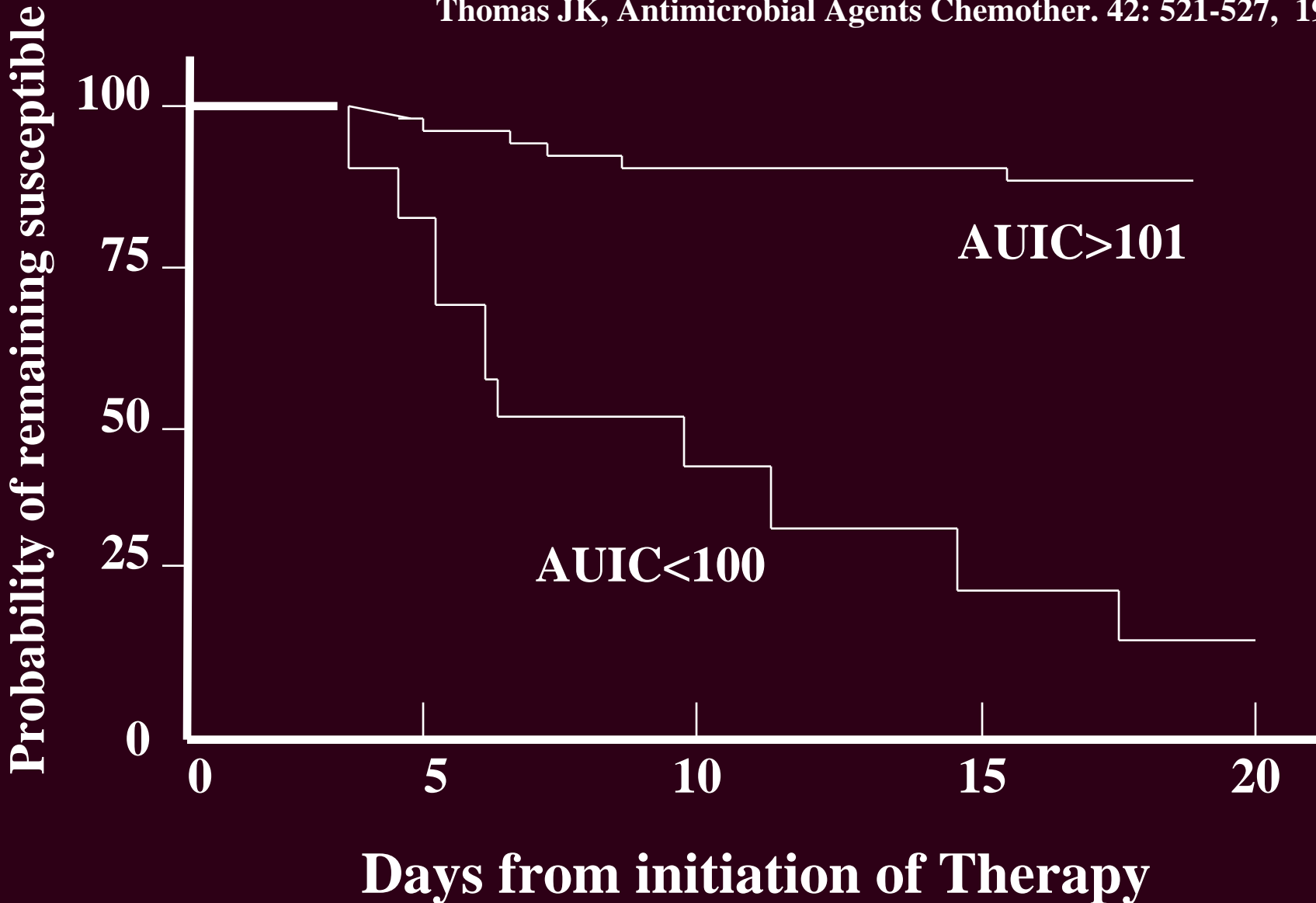


Optimal PK and PD attributes

- **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**

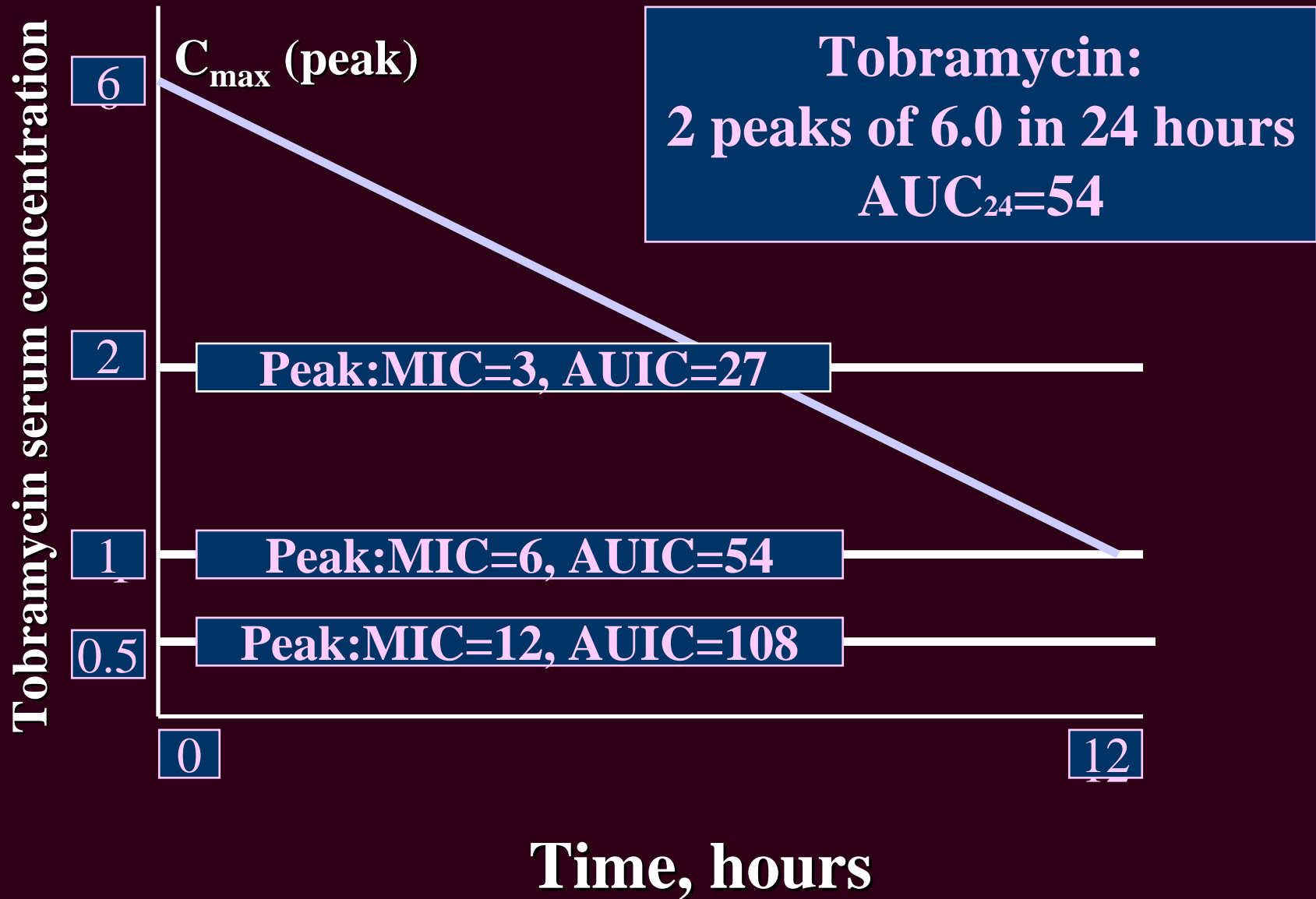
AUIC vs Resistance

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



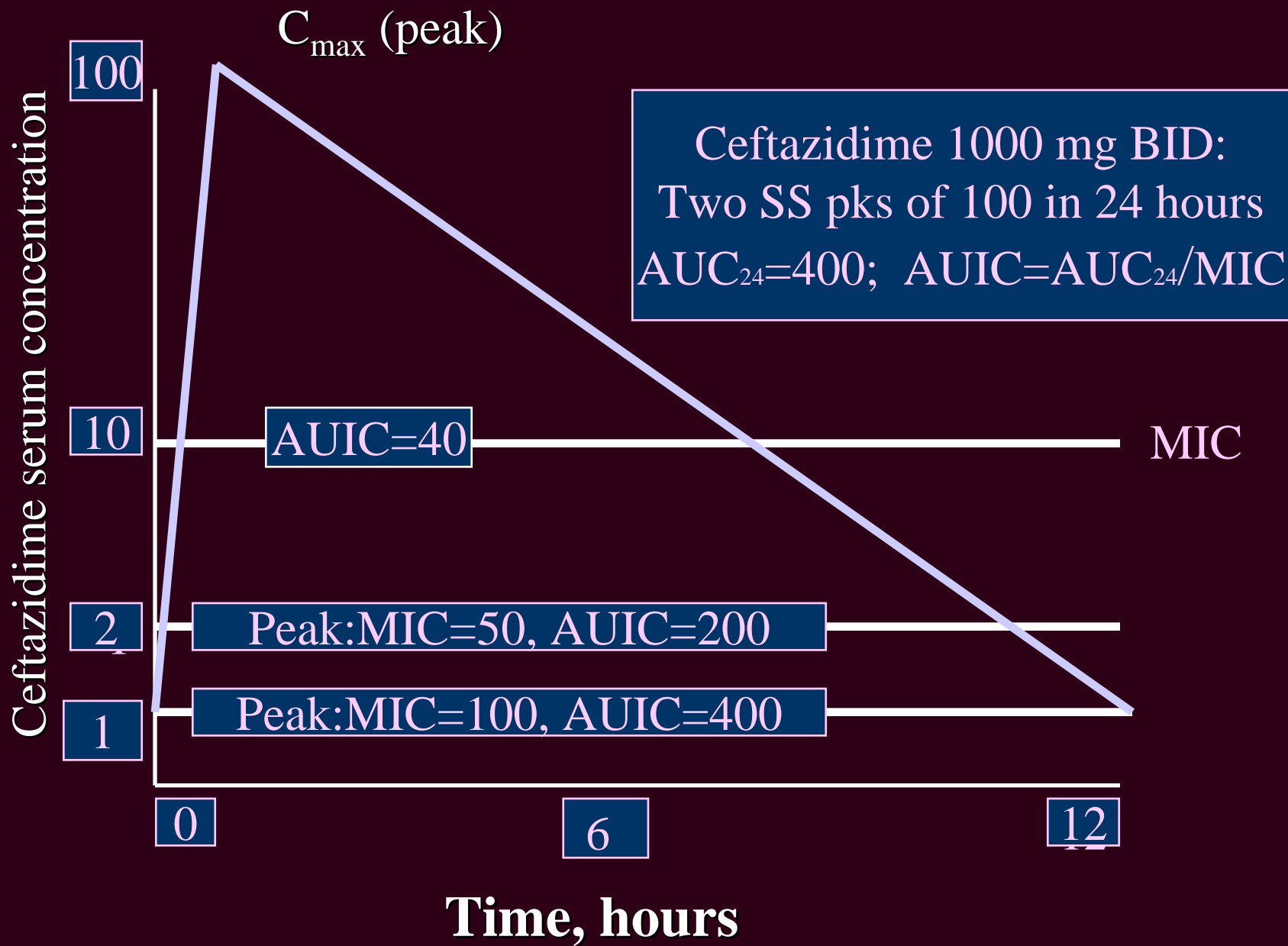
Antibiotics for Study in LRTI

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



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

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

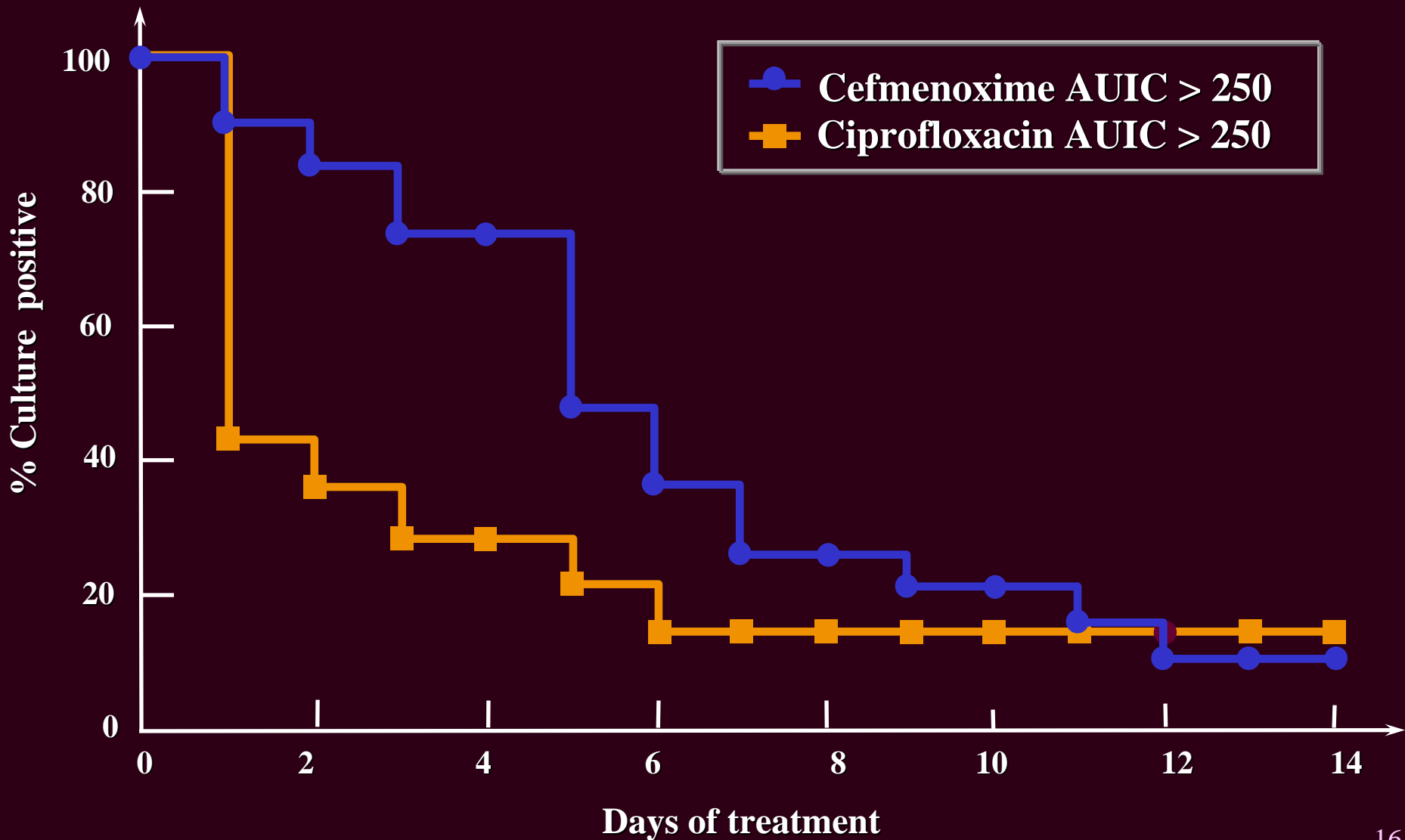
Measures of Antimicrobial Action

- 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 AUC



Challenges in Antibiotic Monitoring

- AUC 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.

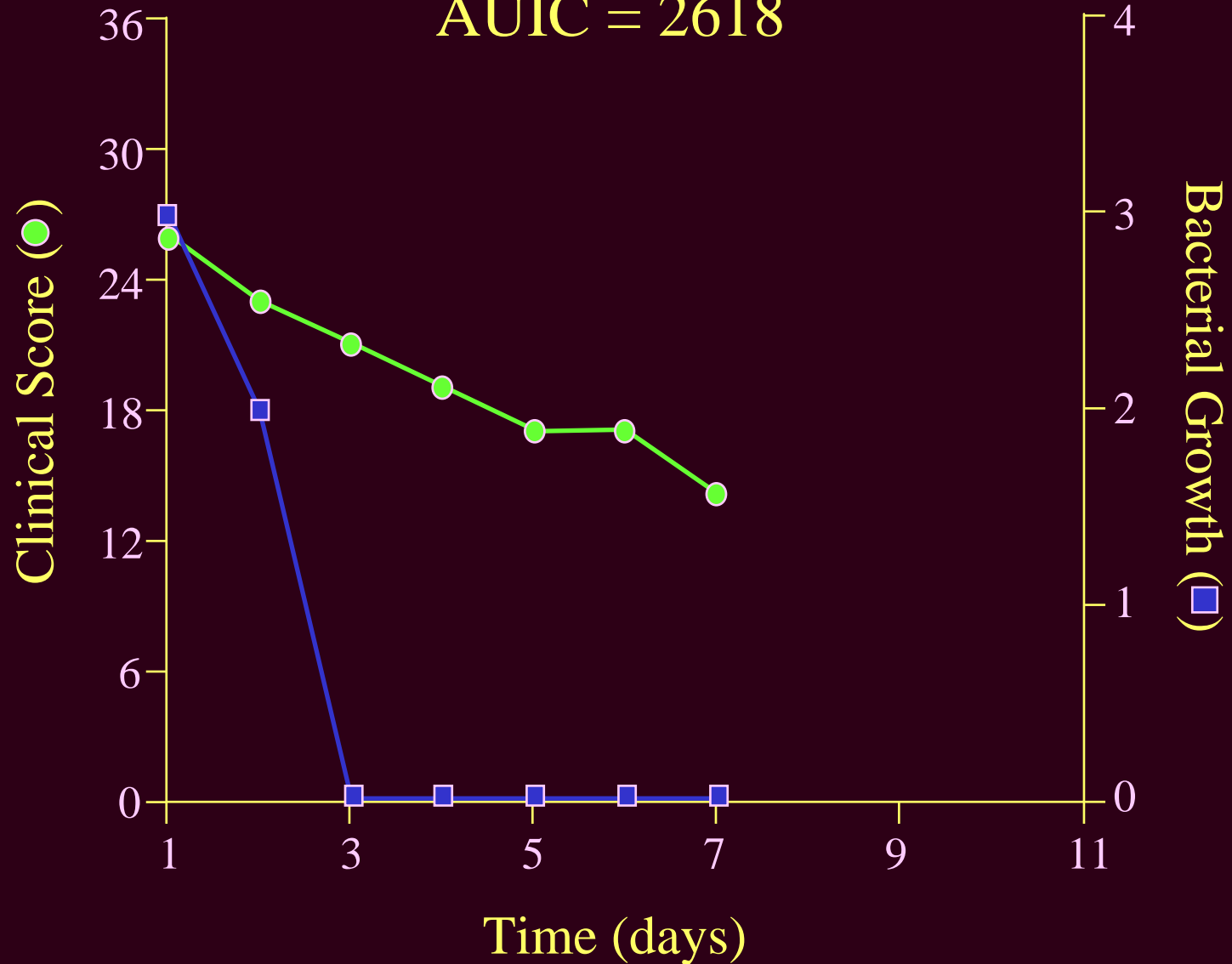
Development of a Scoring System for Nosocomial LRTI patients

- 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



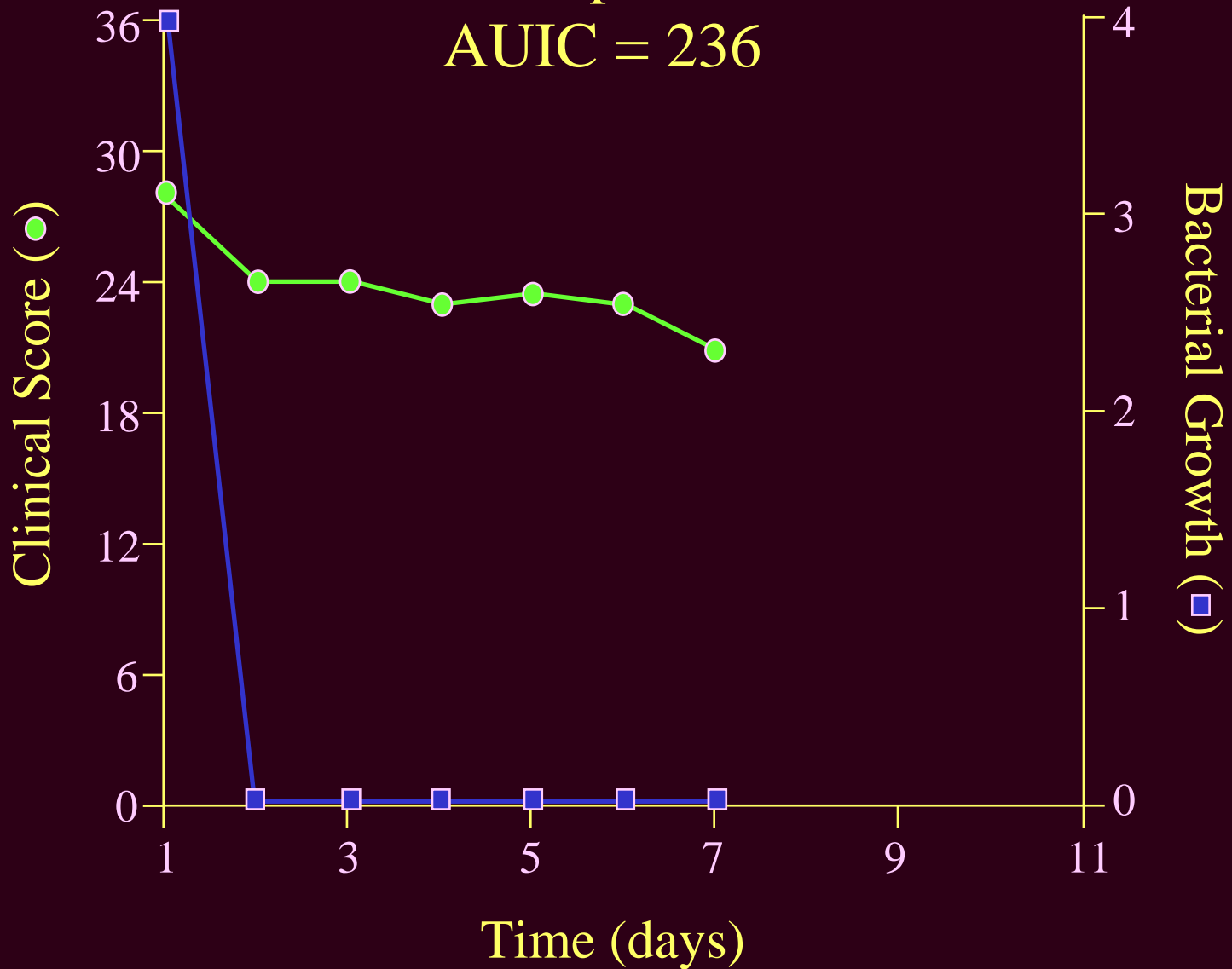
Observations in Scoring

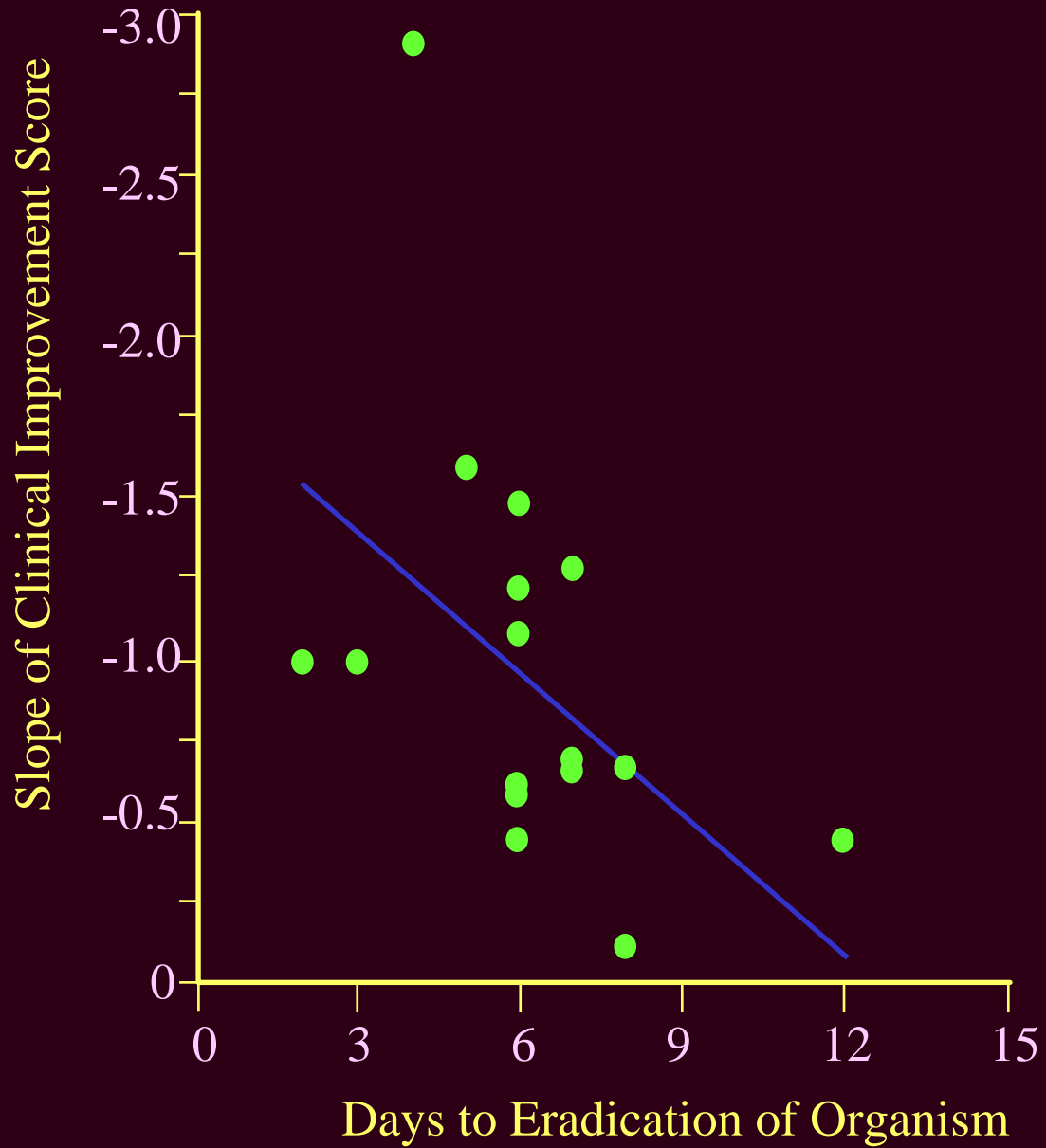
- Patients with nosocomial LRTI have a high pre-treatment score
 - Maximum score is 40, and many of these are in the high 30s
- High initial scores drop rapidly in the first few days, especially with 24-48 hr bacterial eradication
- Falls to a high baseline are common, with no further improvement regardless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

Ciptaz #24 (*P.aeruginosa* eradicated)

Cipro

AUIC = 236





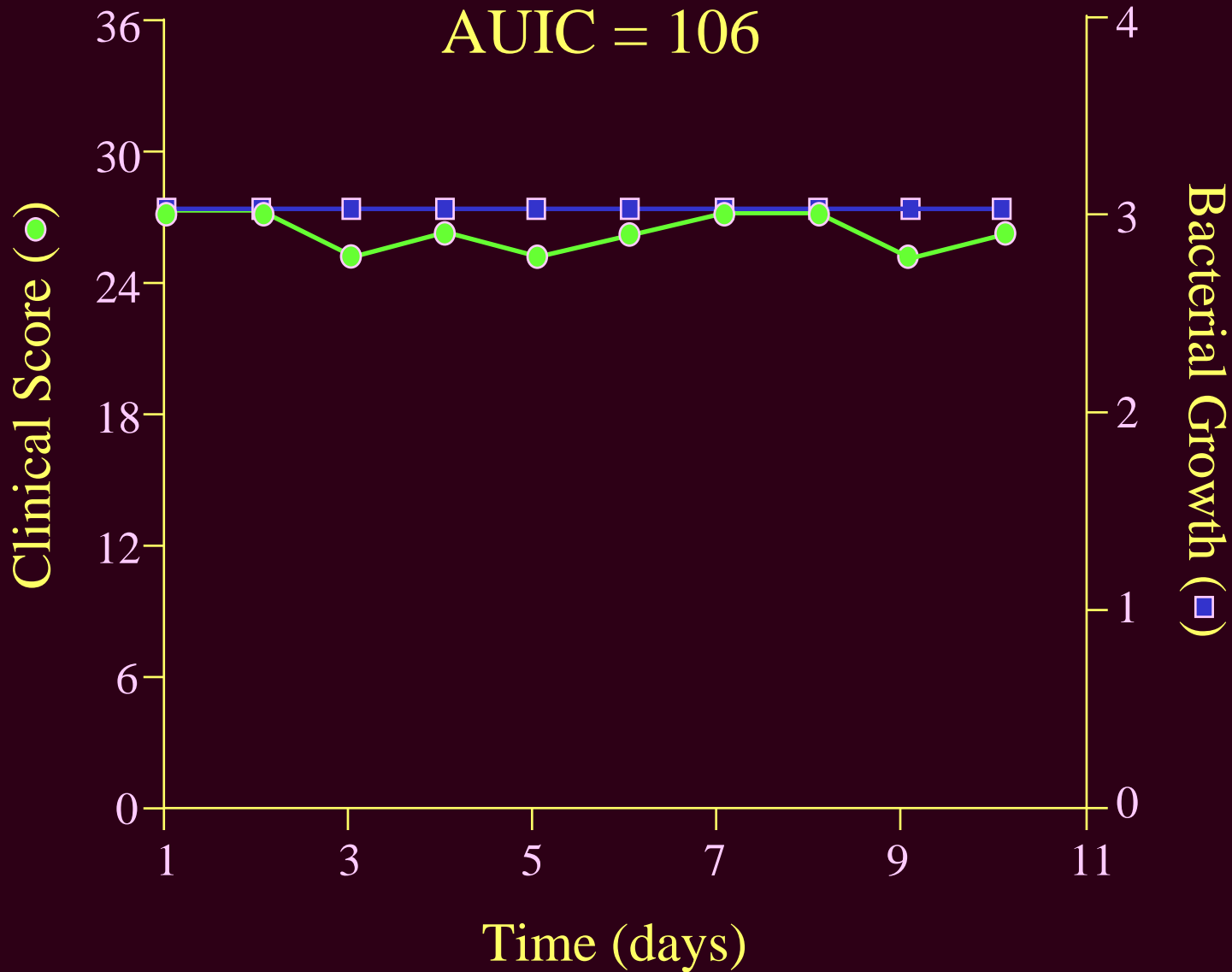
Correlations between scoring and Bacterial Eradication

- 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



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**