The (important) role of the pharmacist in the handling of COPD

- H. Lode -

Free University Berlin

The Emerging Health System

- Oriented Towards Health
- Population Perspective
- Intensive Use of Information
- Knowledge of Treatment Outcomes
- Focus on the Consumer
- Expectations of Accountability
- Growing Interdependence of Practitioners

Practice Level Strategies for Clinical Pharmacy-Oakbrook ‘98

- Reach out to the community to demonstrate the services that pharmacists are capable of providing
- Establish good working relationships with other members of the health care team
- Communicating better and more often to decision makers, the fiscal and practical patient care values that Pharmacists offer

Truths and/or Realities

- The Product-Specific Roles of the pharmacist are becoming increasingly Outmoded
- Pharmacy Needs to Adapt or change
- Clinical Pharmacy is the Way for our Survival and Growth in the New Order.
- Informatics is Crucial to our Success
- We must Reorganize our Curriculum to Enhance our Clinical Roles in Patient Care

Practice Level Strategies for Clinical Pharmacy- Oakbrook ‘98

- Guiding the improvement of networked computer systems to allow for the full integration of drug information between the inpatient and outpatient settings
- Conducting outcomes research that measures the end results of health care services in clinical, economic, and human terms

Preparation for Health Care Team Outcomes Management

- The Focus will be on Group Activity to Achieve Overall Favorable Outcomes
- Departmental Barriers will Fade Away
- Drug Treatments are Tools, Not Endpoints
- Formularies will Decline as Informatics (and Individualized Care Focus) Ascends.
- Pharmacy, Like most Professions, is Poorly Prepared for these Changes.

Necessary Coursework for the Future Pharmacy Practitioner

- High Level Mastery of Pathophysiology
- Pharmacotherapeutics (Disease States)
- Pharmacoepidemiology and Informatics
- Pharmacokinetics
- Pharmacodynamics
- Pharmacoeconomics
- Advanced Communications Skills

Compared to what we train as BS Pharmacists, Pharm Ds Must have:

- Orientation to the Patient, rather than the Products or their Handling.
- Training in Disease State Management, rather than Business Management
- Effective skills in Informatics, and unique Reaearch roles like Pharmacoeconomics.
- Communications skills to Thrive in Interdisciplinary Team Patient Care Roles

Antibiotic Strategies in Hospitals

- **Use of guidelines or protocols**
- **Limit or restrict hospit. formularies**
- **Avoid unnecessary use**
- **Establish / use unit specific antibiograms**
- **Antibiotic rotation / cycling**
- **Consider use of strategies – heterogeneity / mixing**
- **Cost / benefit (outcome) analysis**

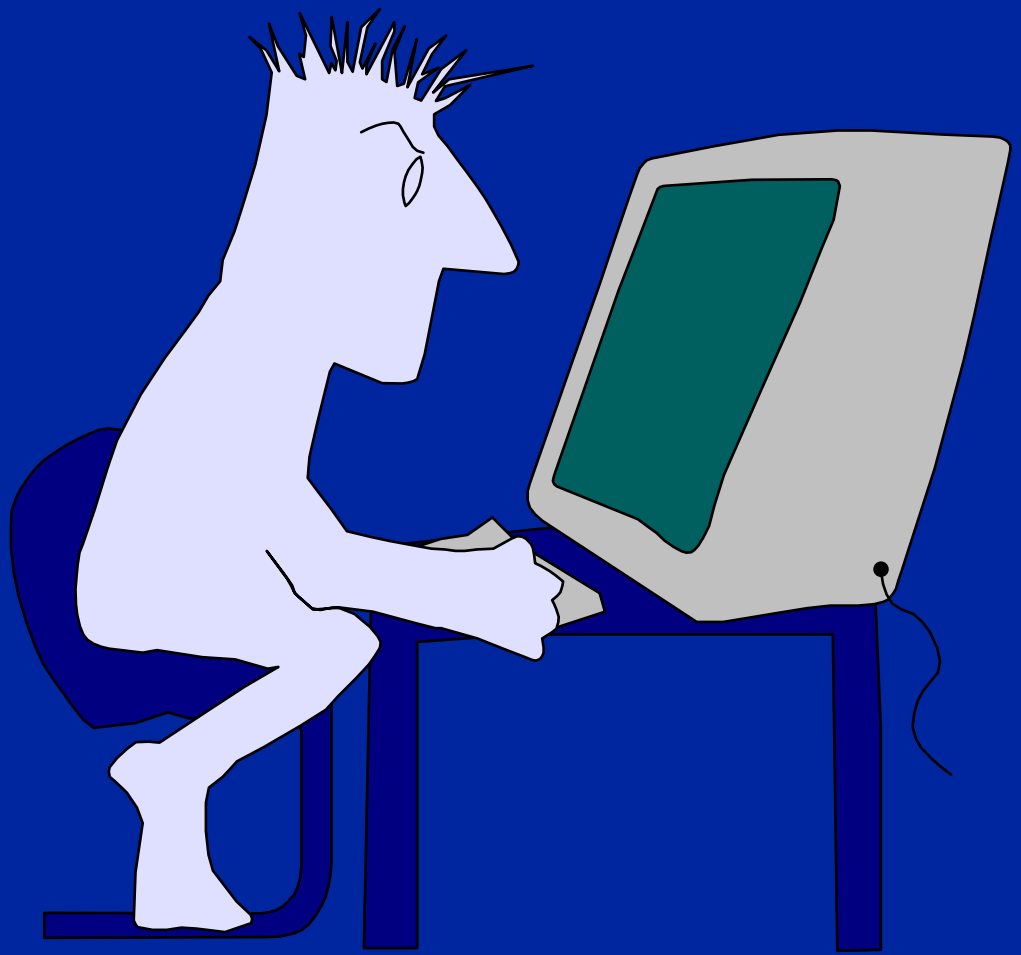
Roles in Therapeutic Optimization

- Virtually all Drugs have sufficient variability in Outcomes at the same dose, so as to justify some individualization
- The clinical pharmacist is best prepared to assume these roles
- Monitoring the impact of therapeutic substances is the additional challenge

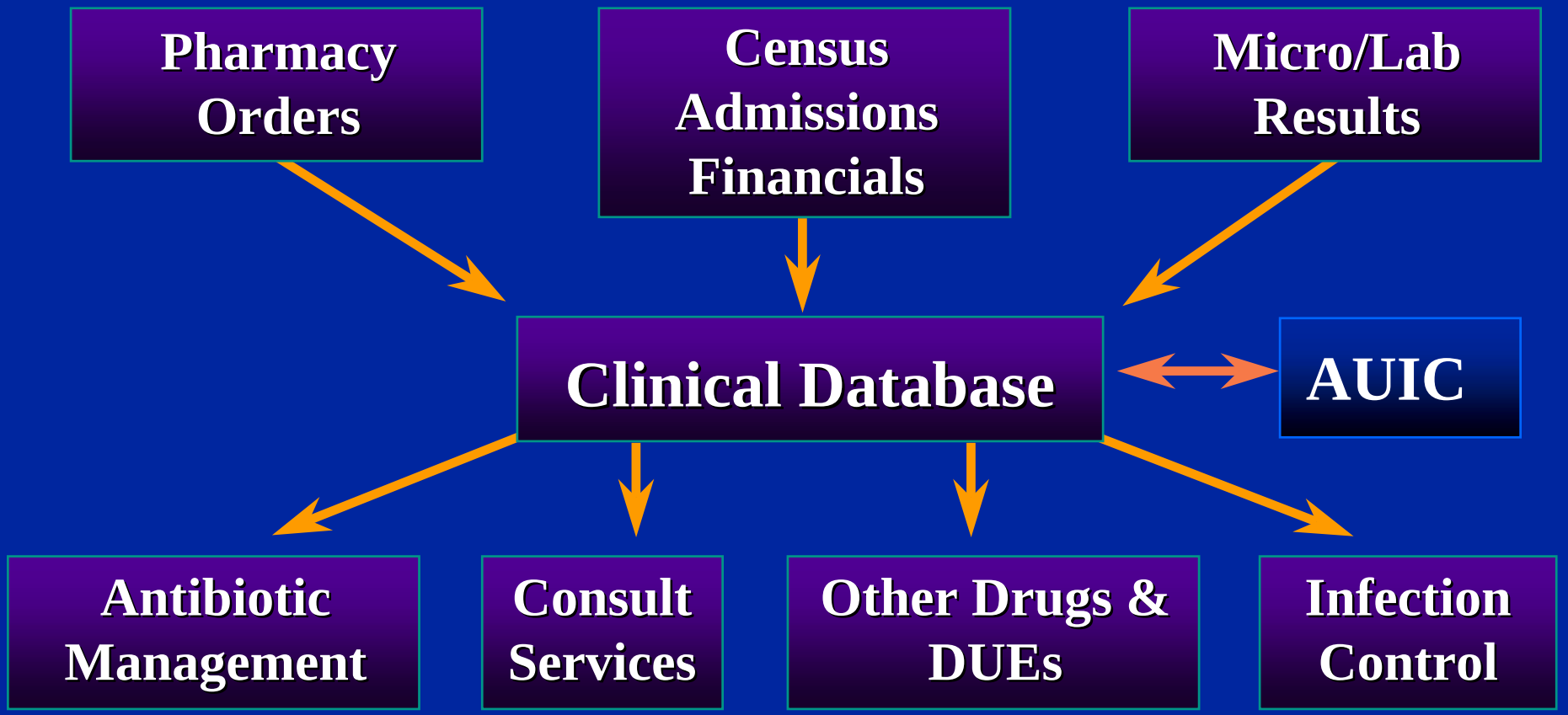
Missions of The Clinical Pharmacokinetics Laboratory

- **Research**
- **Education**
- **Patient Care**
  - Traditional inpatient cost management
  - Outpatient medication cost management, and optimization of therapy for target disease states

Informatics in Action



Computer Assisted Outcomes Management



Problem Detection and Intervention to Optimize Care

- Computerized Sorting and Screening to Identify Potential Problems before they Occur.
  - Detect Patterns of Care which are associated with Suboptimal Outcomes.
  - Database Mining as the Business Folks Call it.
  - Identified Patterns are Immediately Output to an Intervention Specialist for Resolution
- The above Behavior is not Limited to Drugs, but Our Opportunity is There.

Clinical Specialist Pharmacists

- Each responsible for DSM area
  - Conduct Research
  - Patient Interface to Physician Care
  - provide Informatics to organized care review committees
- Day to Day responsibility for regimens with committee guidance.
- Connected at home and in the office

Still True

- Students need Postdoctoral training if they are to assume a Clinical Specialist role
- One to three years in addition to the 6 year Pharm D degree
- Role of Research in this Postdoctoral Program
  - Note the Medical Model

Transitions

- The Formulary ➡ Patient Specific Care:
  - Prescriptive Authority (under MD)
  - Increased Need for Personnel
- The Pharmacy Computer ➡ Health Care Information System:
  - Decreased need for Dispensing Personnel, Increased Need for Patient Care Practitioners.
  - Activities Move to Implementation at the Bedside

Practical Approaches for Implementation of Pharmacodynamic Studies into Clinical Practice

H. Lode

Berlin, Germany

Predominant Respiratory Tract Pathogens

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*

Outpatient clinical studies in respiratory tract infections

- High-rate spontaneous resolution makes it difficult to show differences between agents
- Bacteriologic outcome studies are not often performed due to necessity for invasive procedure (ear, sinus or lung tap) to obtain specimen
- Most studies are therefore designed to show equivalent clinical outcome between established and new agents
- Inadequacies of agents studied are therefore often not apparent

Impact of limited clinical data and increasing pathogen resistance on choice of antibacterial therapy

- There is a need for:
  - accurate prediction of efficacy
  - newer dosage regimens
  - newer antibacterials
  - revised susceptibility breakpoints
  - statistically valid clinical studies

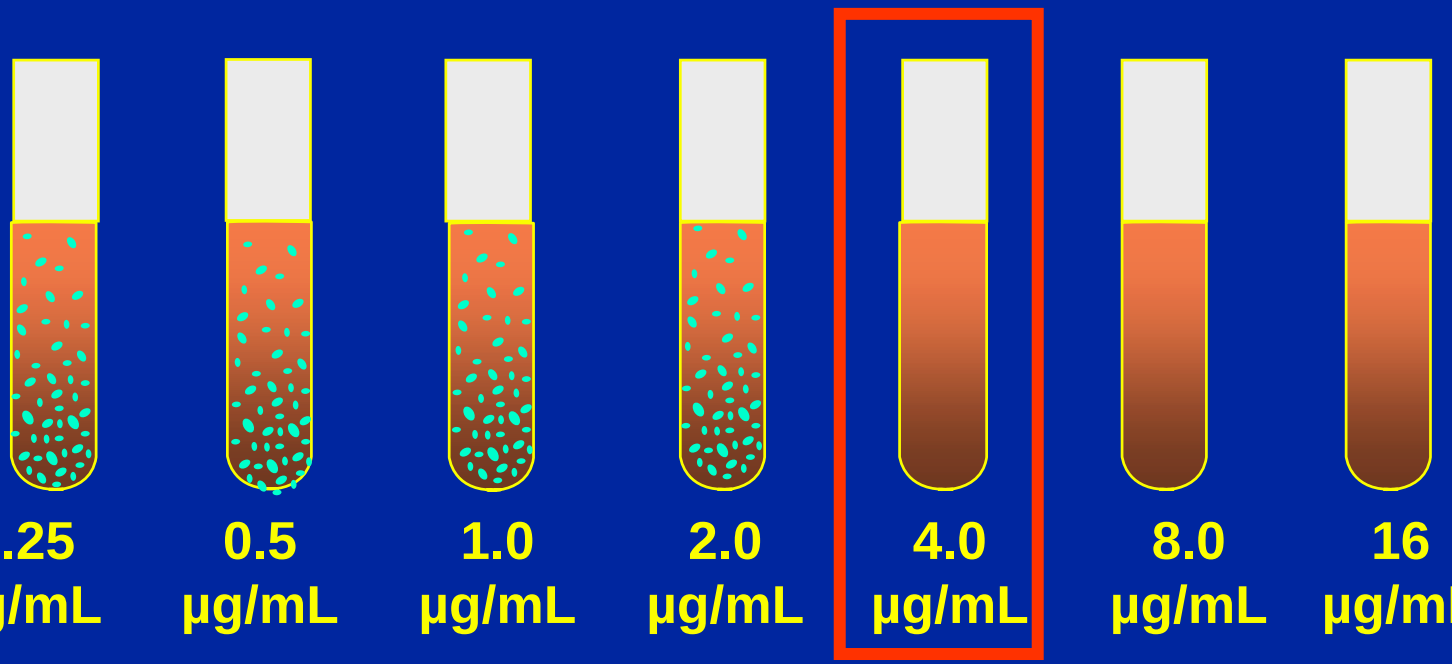
The role of antibiotics is to eradicate the causative organisms from the site of infection

Evaluating antibiotic efficacy using pharmacokinetics and pharmacodynamics

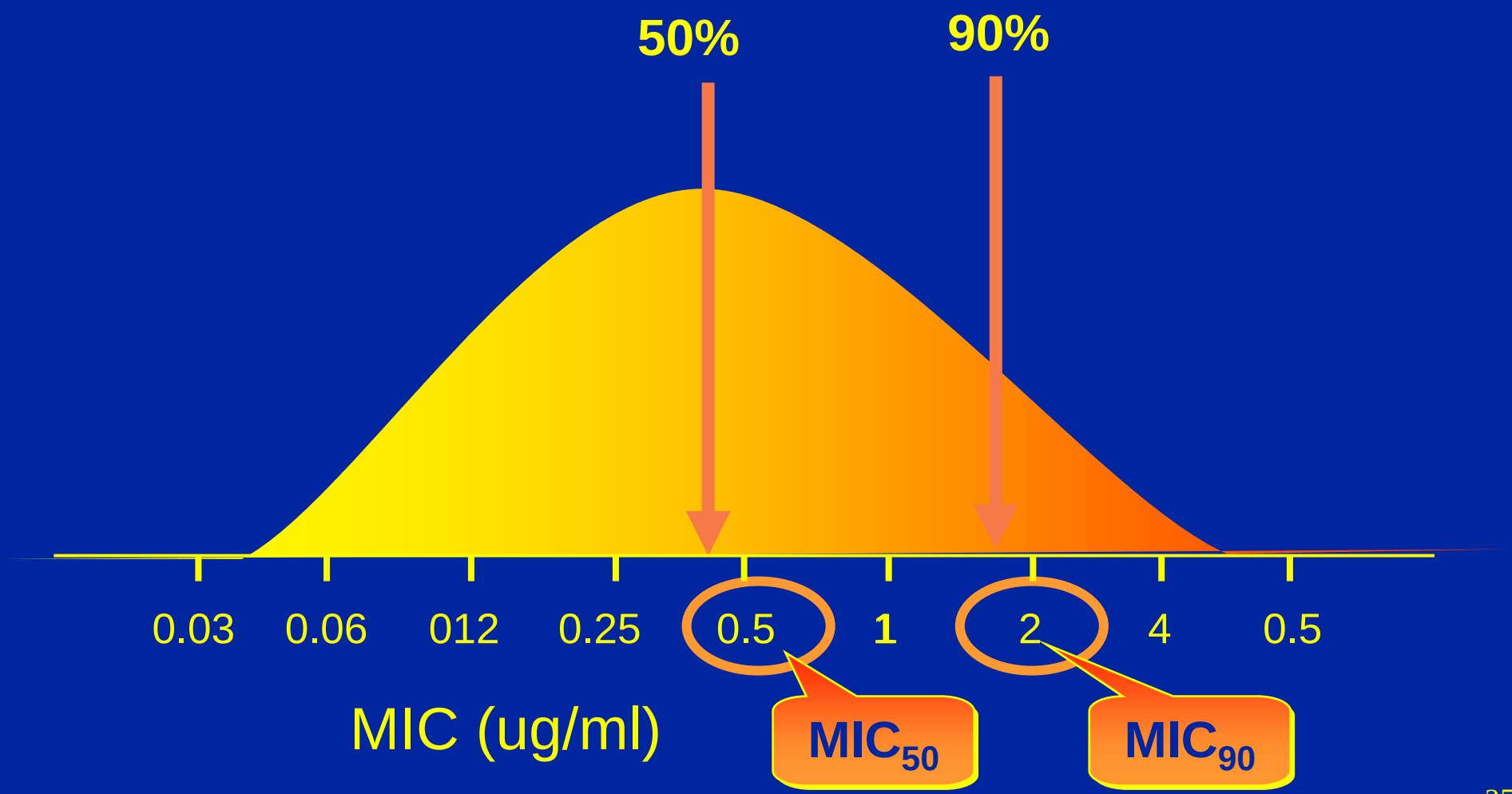
- Pharmacokinetics
  - serum concentration profile
  - penetration to site of infection
- Pharmacodynamics
  - susceptibility – MIC (potency)
  - concentration- vs. time-dependent killing
  - persistent (post-antibiotic) effects (PAE)

Drug potency is measured by determining lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism after overnight exposure

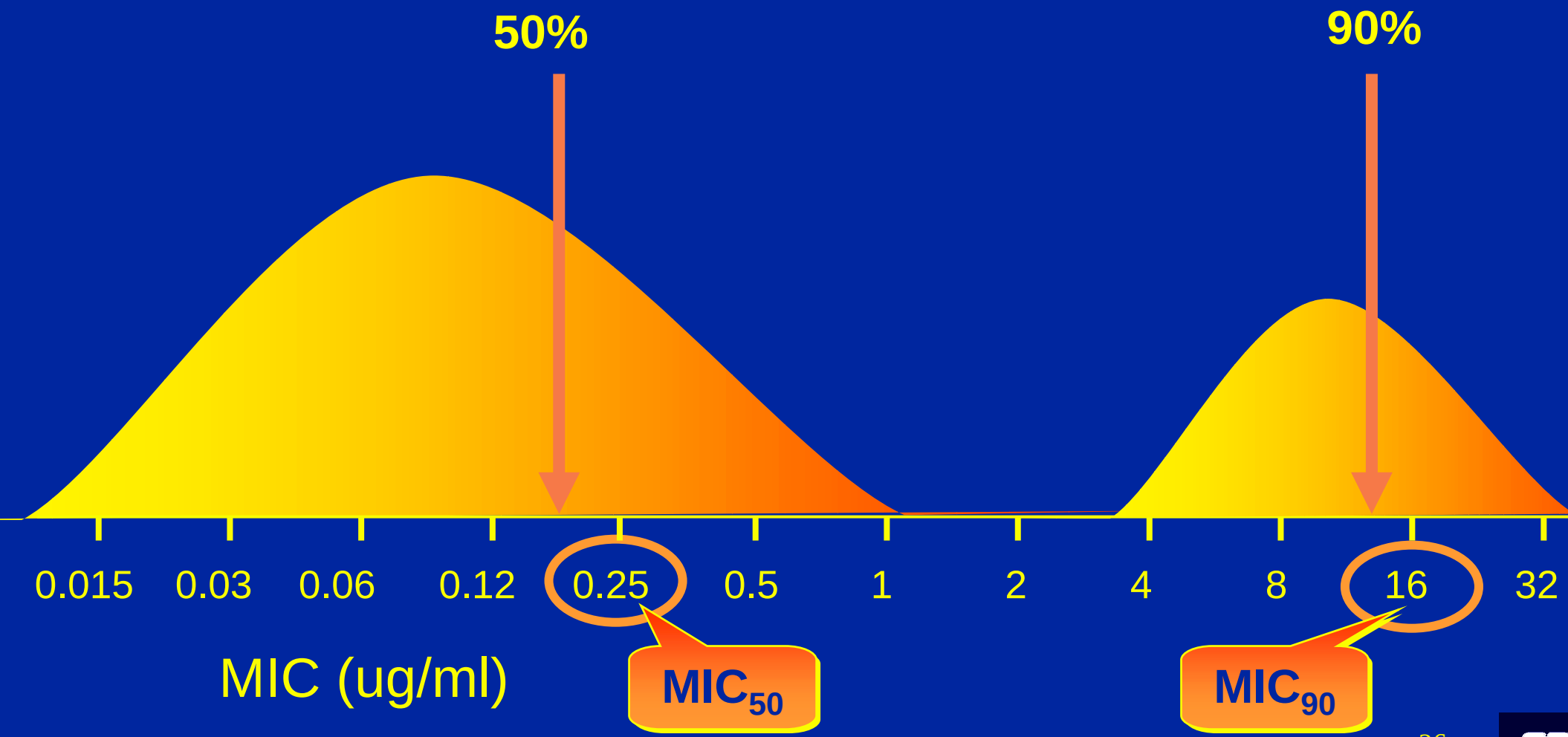
Known bacterial inoculum placed into each tube



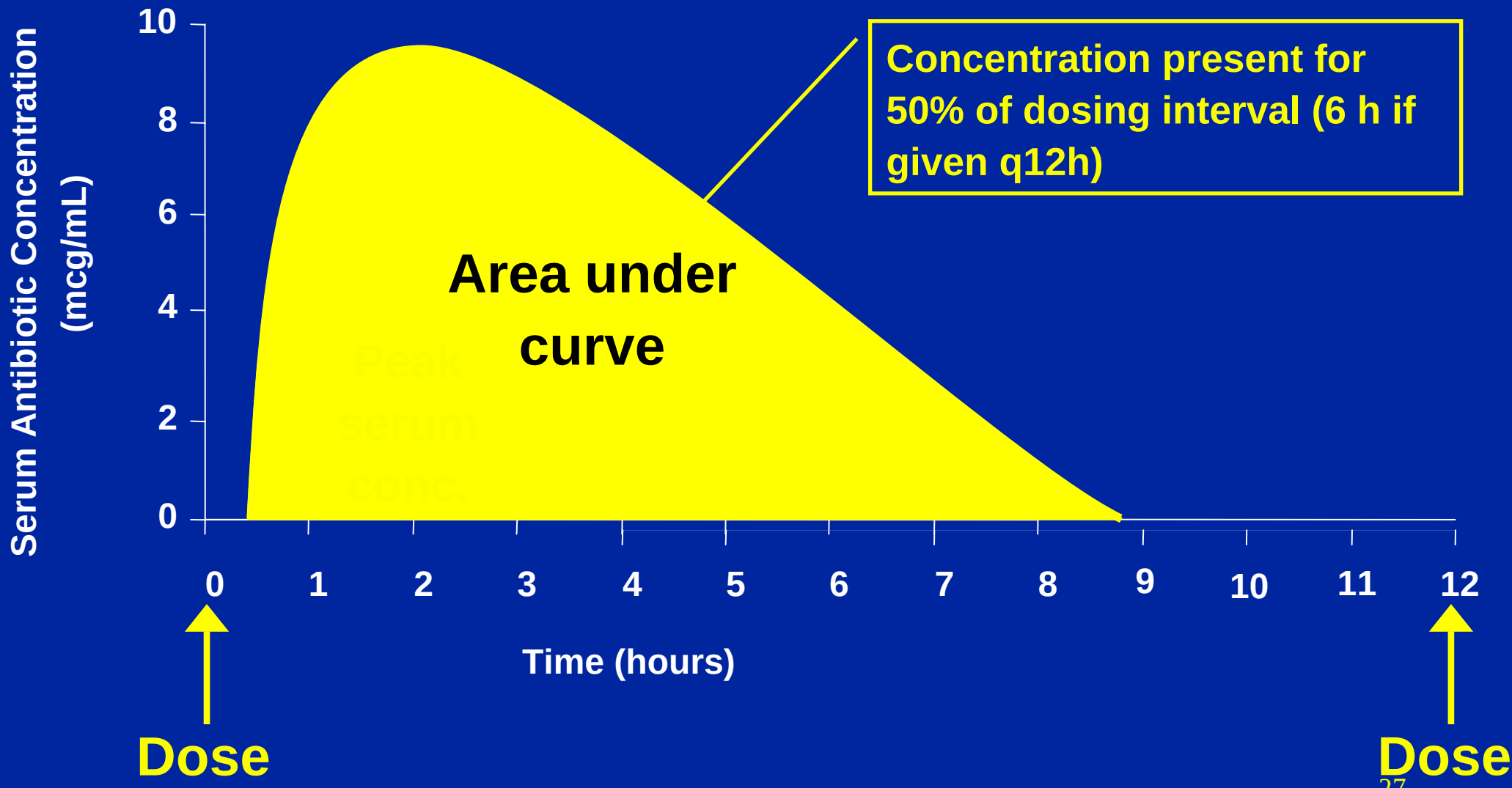
MIC_{50} and MIC_{90} unimodal population



MIC_{50} and MIC_{90} bimodal population



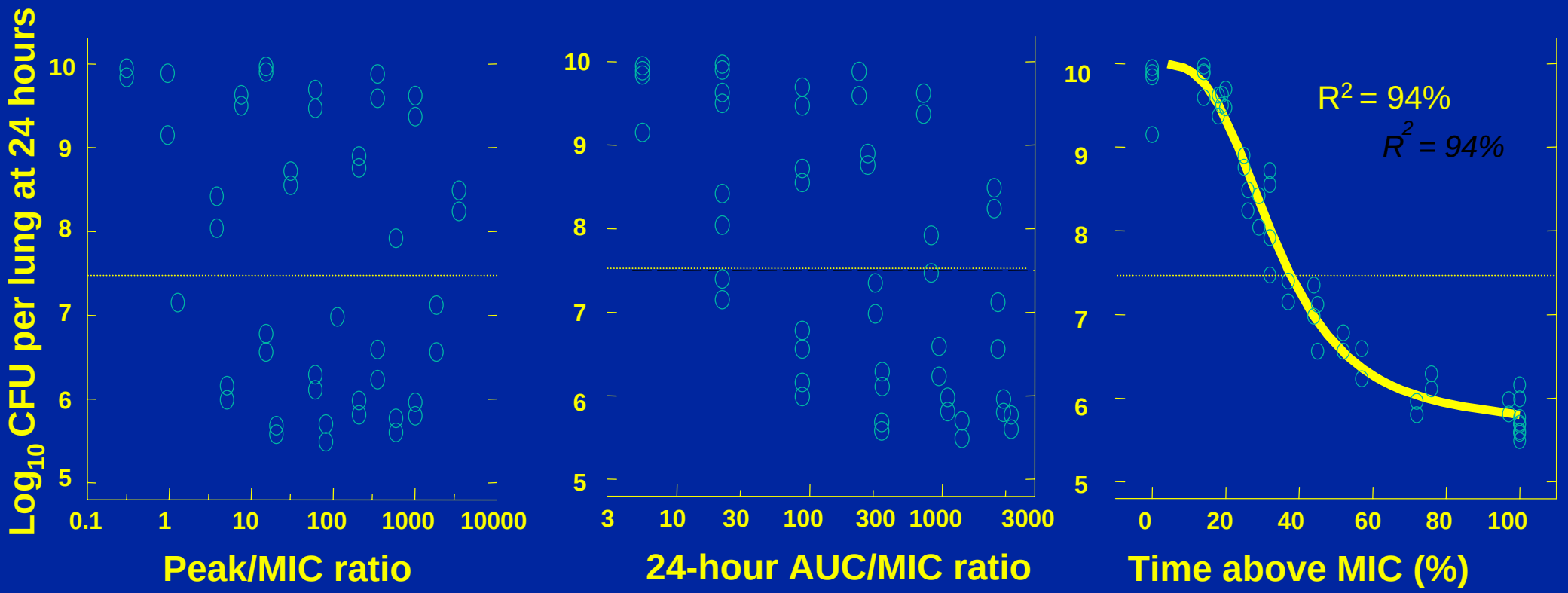
Pharmacokinetic Parameters



Patterns of Antimicrobial Activity

- Time-dependent killing and minimal to moderate persistent effects ➔ Time above MIC (T>MIC)
- Time-dependent killing and prolonged persistent effects ➔ AUC/MIC ratio
- Concentration-dependent killing and prolonged persistent effects ➔ AUC/MIC or Peak/MIC ratio

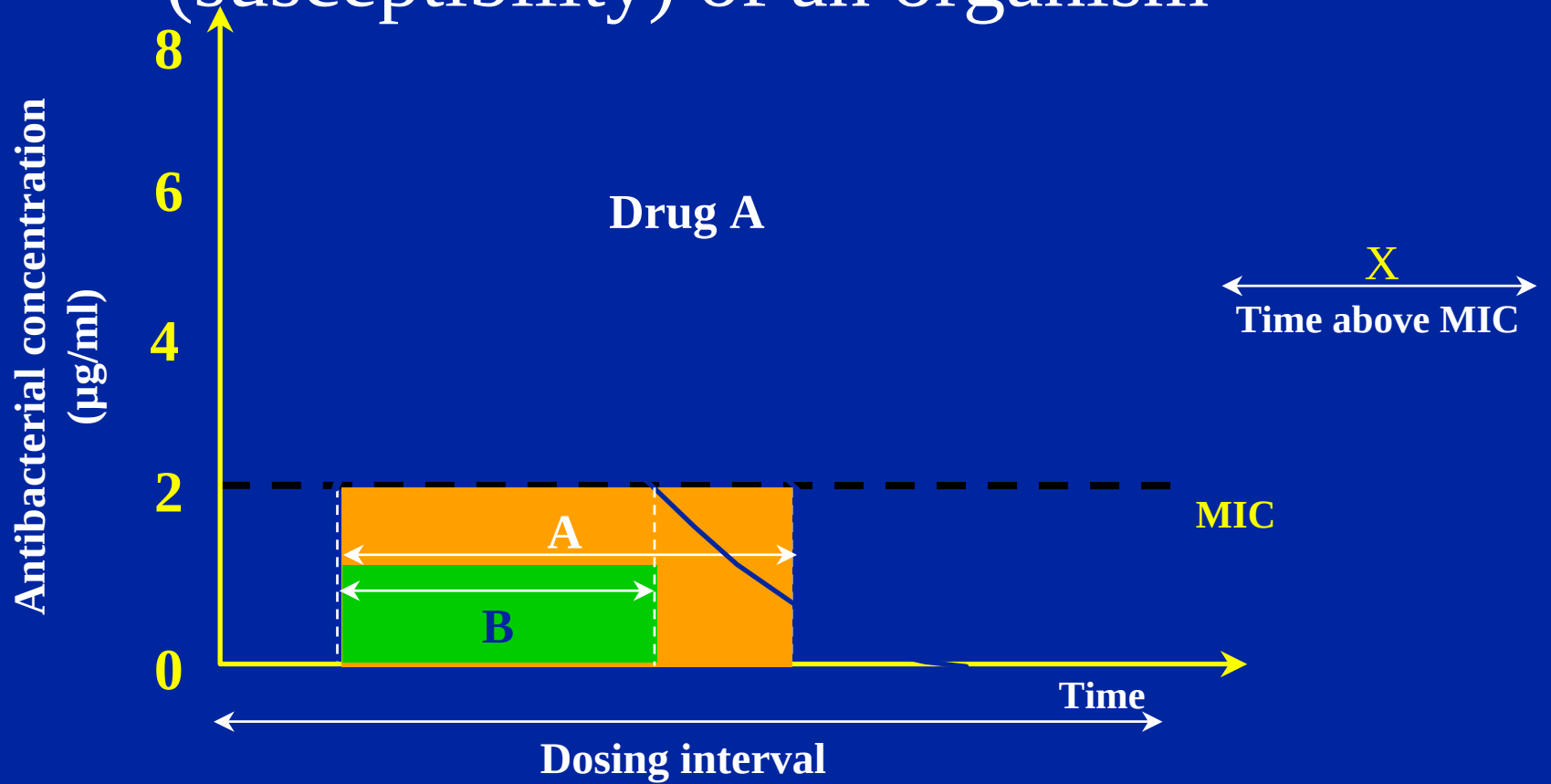
Relationship between PK/PD parameters and efficacy for cefotaxime against *Klebsiella pneumoniae* in a murine pneumonia model



Craig. *Clin Infect Dis* 1998; **26**:1–12

Time above MIC

Correlation of serum pharmacokinetics with MIC (susceptibility) of an organism



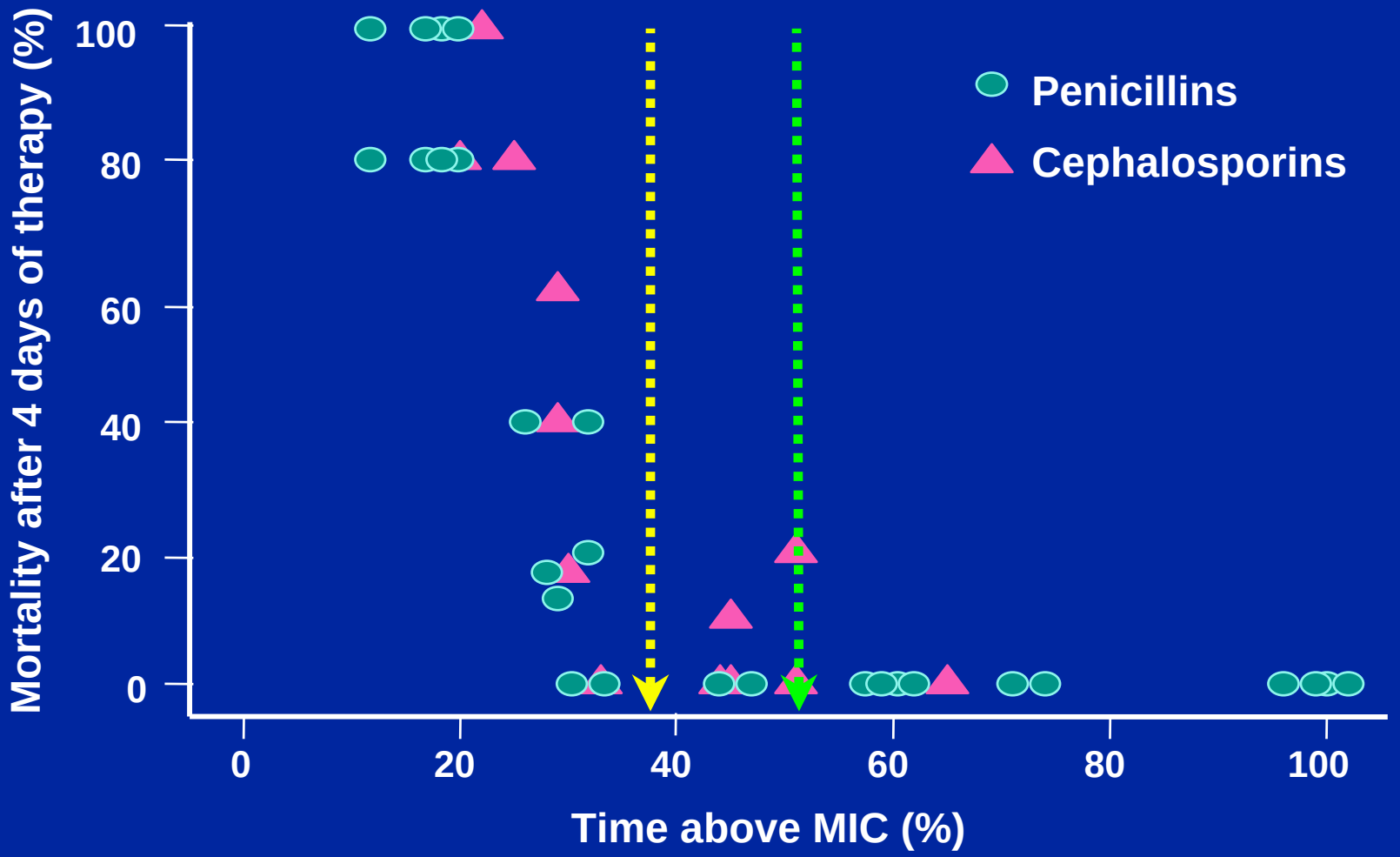
Drug A present at concentration of 2 µg/ml for 50% of dosing interval

Drug B present at concentration of 2 µg/ml for 30% of dosing interval

Time Above MIC: β-Lactams

- T>MIC (% of dosing interval) required for the static dose against most organisms in neutropenic mice vary from 25-35% for penicillins and from 30-45% for cephalosporins
- The presence of neutrophils reduces the T>MIC required for efficacy by 5-10%
- Free drug levels of penicillins and cephalosporins need to exceed the MIC for 35-50% of the dosing interval to produce maximum survival

Relationship between Time above MIC and efficacy in animal infection models infected with *S. pneumoniae*



Craig. *Diagn Microbiol Infect Dis* 1996; **25**:213–217

Time above MIC for β-lactams

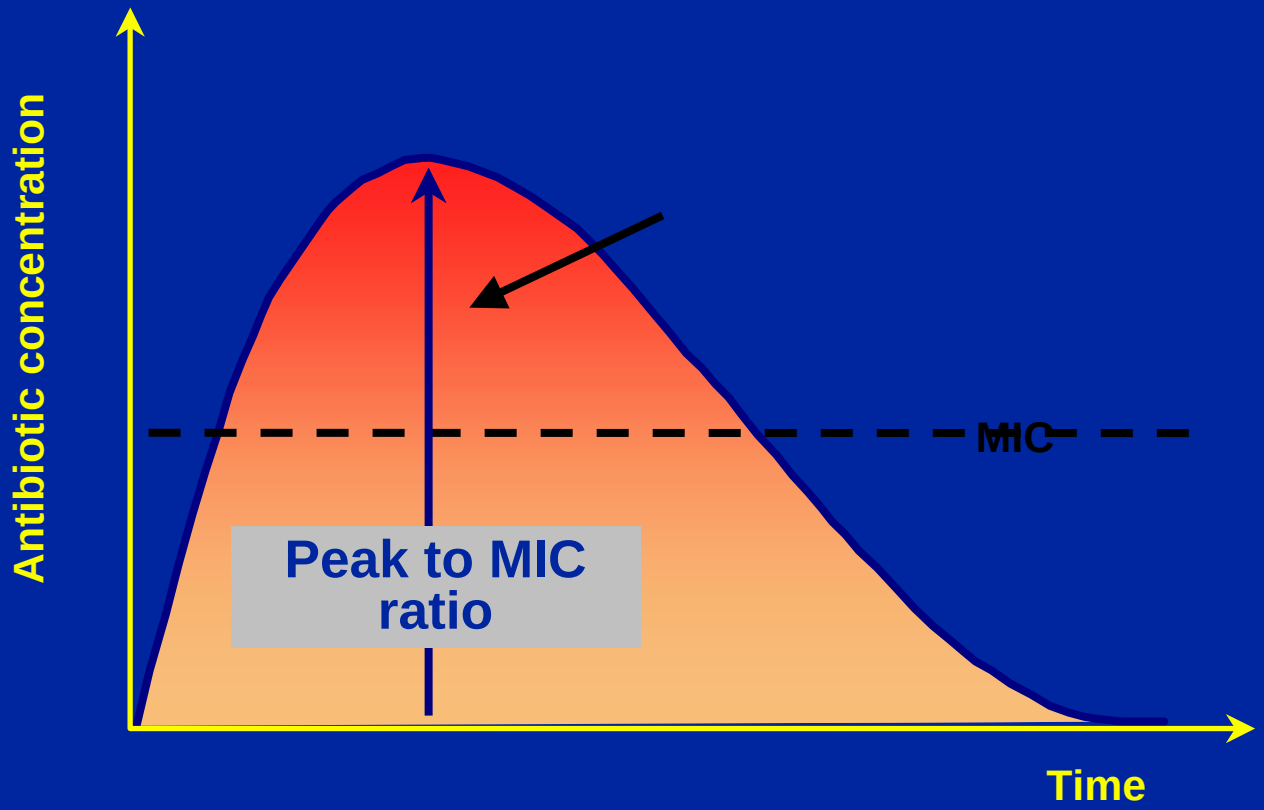
- Is the magnitude of the parameter required for efficacy the same in different animal species including humans? YES
- Does the magnitude of the parameter vary with:
  1. the dosing regimen? NO
  2. different sites of infection (e.g. blood, lung, peritoneum, soft tissue)? NO
  3. different drugs within the same class?
     Penicillins less than cephalosporins; no difference within groups providing free, unbound drug levels are used
  4. different organisms including resistant strains?
     FOR SOME; no difference for penicillin-resistant pneumococci

Craig. *Diagn Microbiol Infect Dis* 1996; **25**:213–217
Craig. *Clin Infect Dis* 1998; **26**:1–12
Craig. *Ear Nose Throat J* 1998; **77**:7–11

Concentration-dependent agents

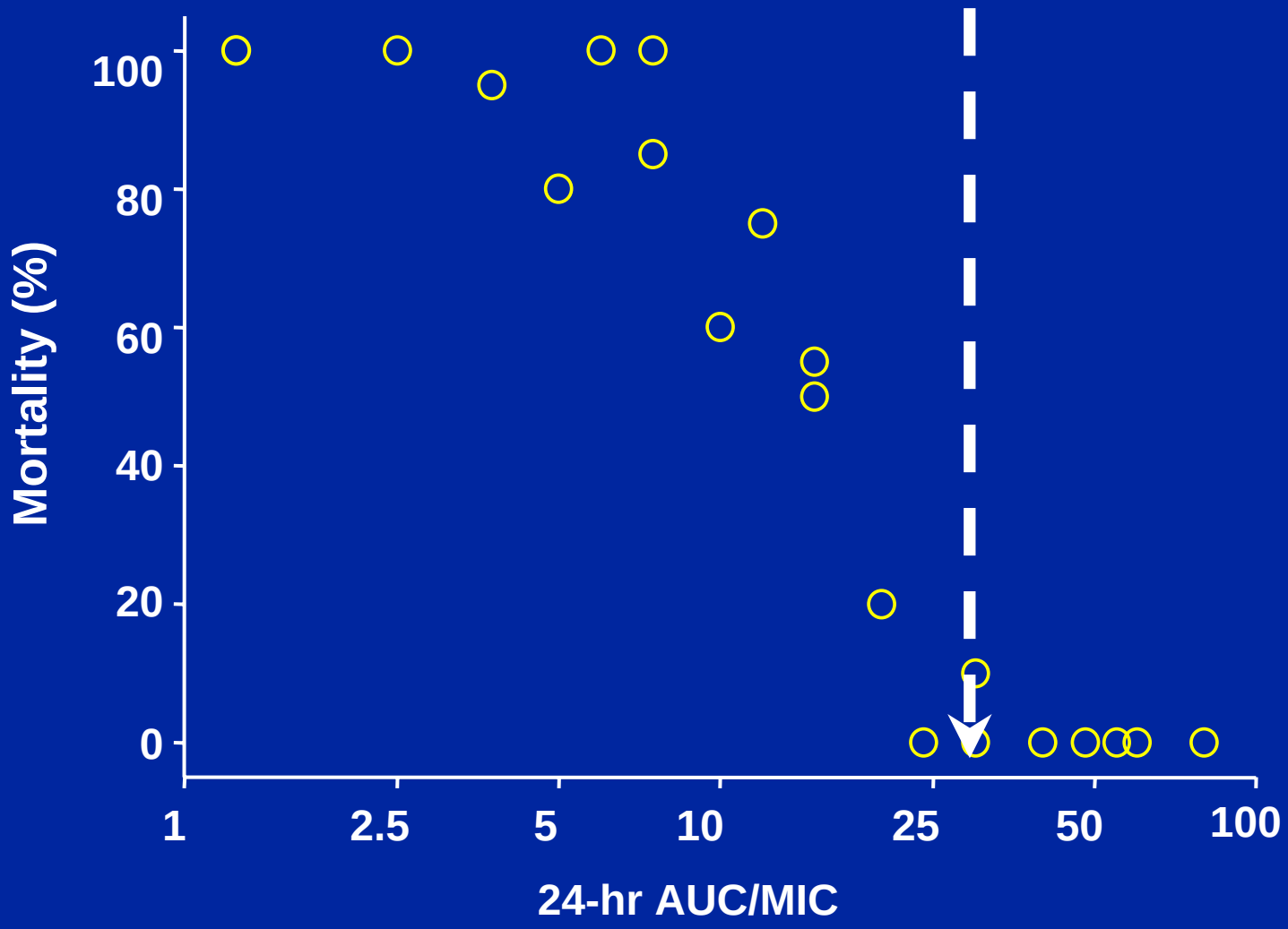
24-hr AUC/MIC and Peak/MIC Ratios

Correlation of serum pharmacokinetics with MIC (susceptibility) of an organism

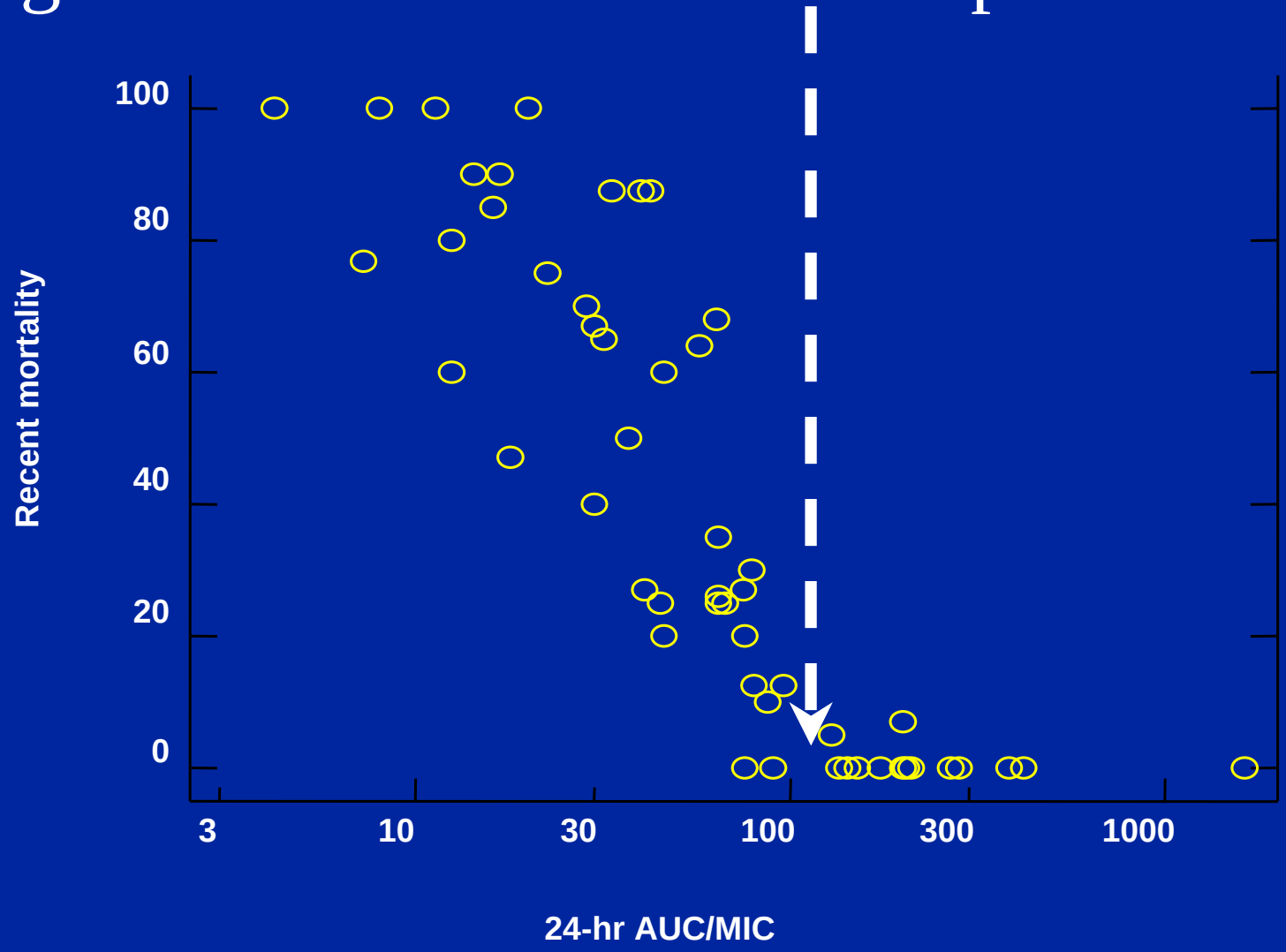


24-hr AUC/MIC is correlated with outcome of infection, the magnitude required for success and MIC at which this occurs becomes the PD breakpoint

Relationship between 24 Hr AUC/MIC and mortality for fluoroquinolones against *S. pneumoniae* in immunocompetent animals

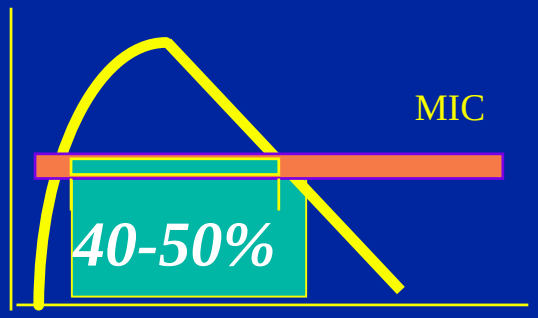


Relationship between 24 Hr AUC/MIC and mortality for fluoroquinolones against Gram-negative bacilli in immunocompromised animals



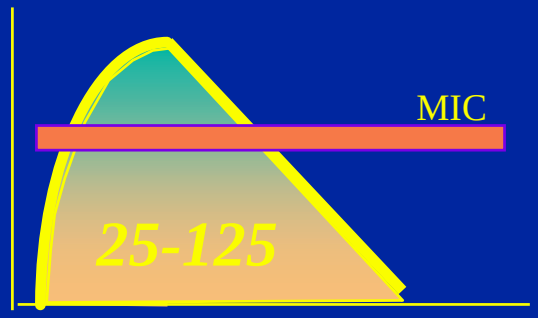
Predictors of Bacterial Eradication:
Pharmacokinetic/Pharmacodynamic profiles

Time > MIC



- Penicillins
- Cephalosporins
- Erythromycin
- Clarithromycin

AUC_{24}/MIC



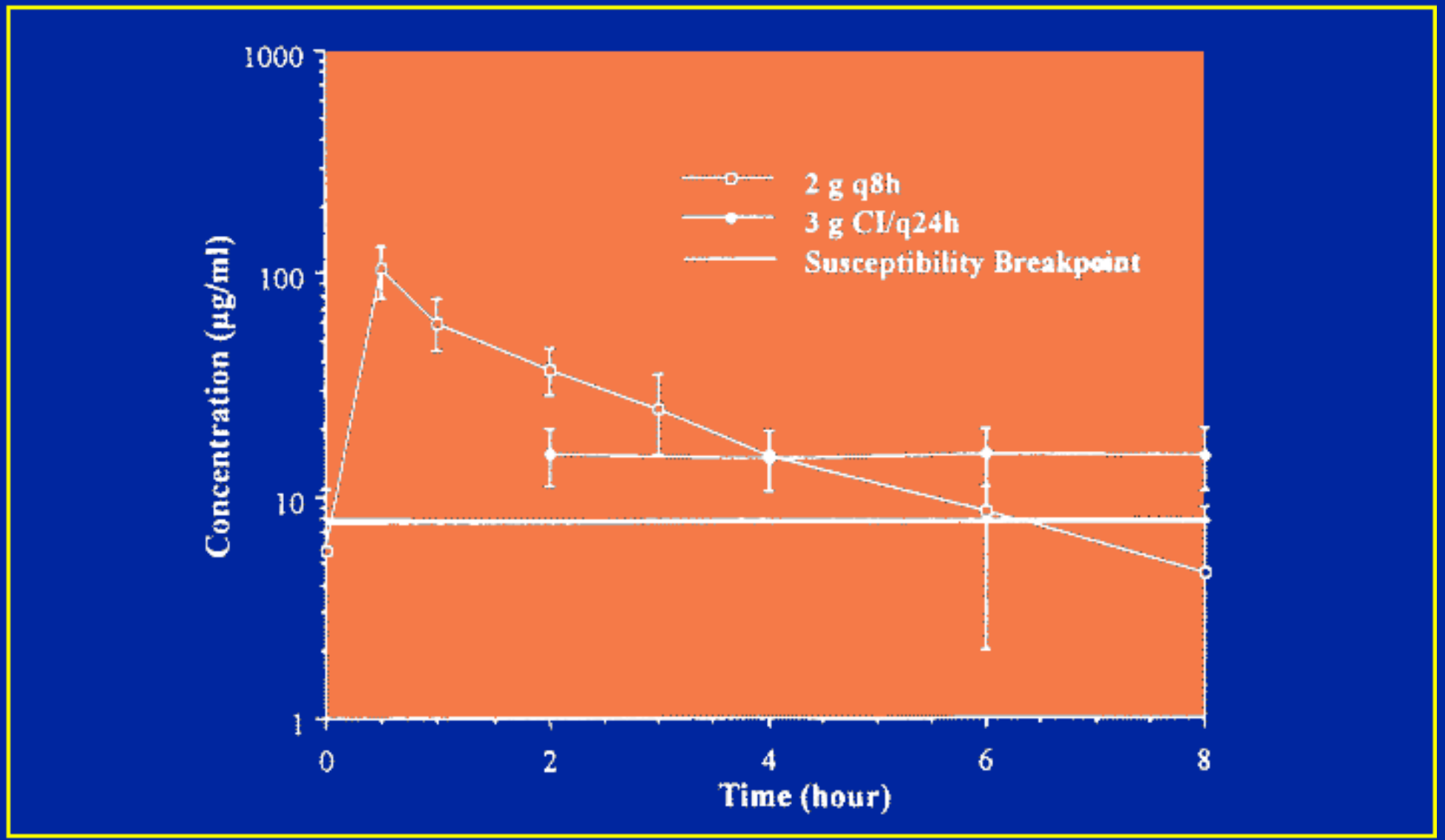
- **Quinolones**
- **Aminoglycosides**
- **Azithromycin**
- **Telithromycin**

Pharmacokinetics of Continuous and Intermittent Ceftazidime in Intensive Care Unit Patients With Nosocomial Pneumonia

David P. Nicolau, Melinda K. Lacy, JoCarol McNabb, Richard Quintiliani, and Charles H. Nightingale

***Infectious Diseases in Clinical Practice* 1999; 8:45-49**

Steady-state Ceftazidime Serum Concentrations



Nicolau DP et al. *Infectious Diseases in Clinical Practice* 1999; 8:45-49

Pharmacokinetic Parameters of Ceftazidime 2 g IV q8h and 3 g Cl over 24 Hours in Patients With Normal Renal Function

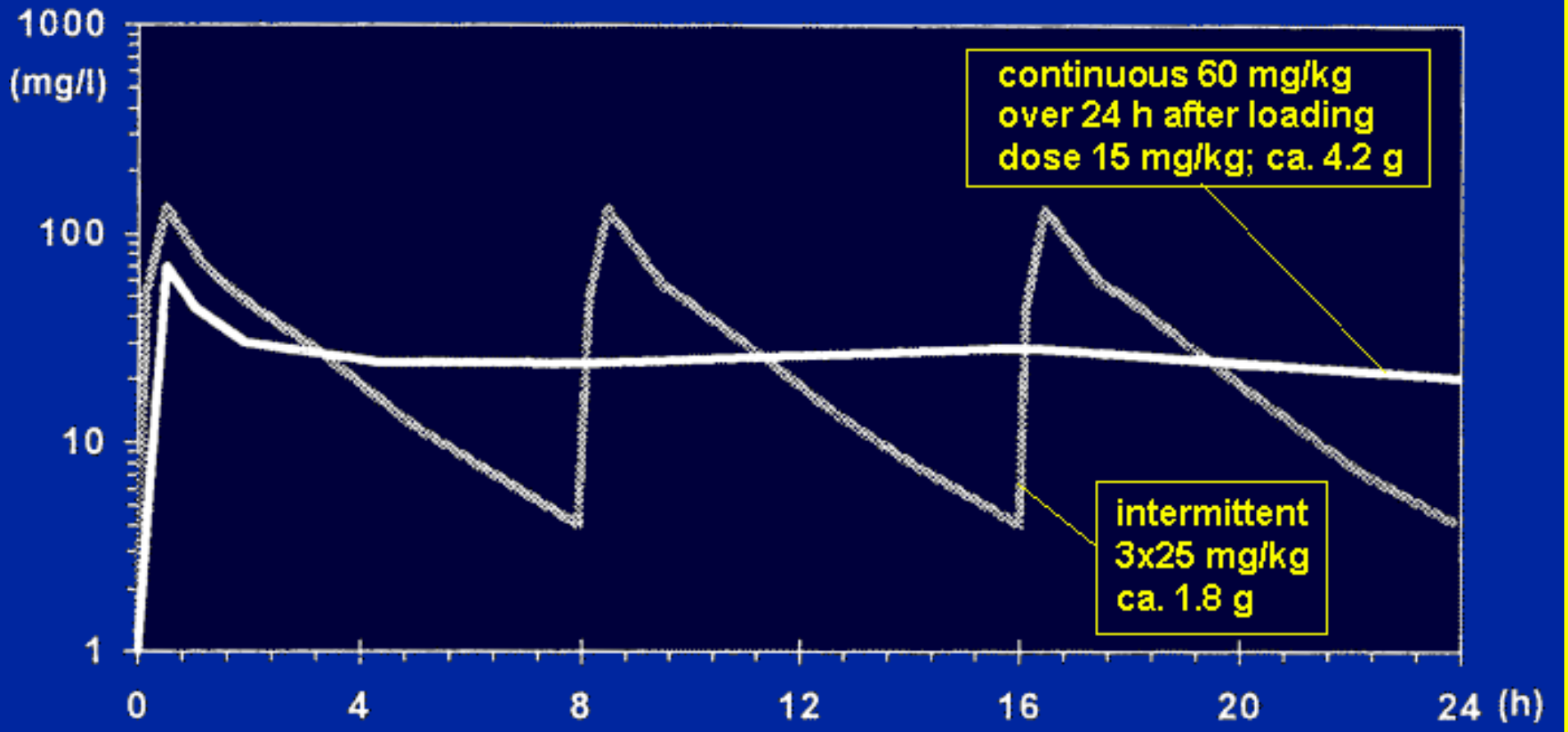
	II (n = 11)	Cl (n = 10)
Weight [kg]	69.9 ⇧ 9.3	69.0 ⇧ 13.7
C_{max} [µg/mL]	105.3 ⇧ 28.0	15.9 ⇧ 4.5
C_{mean} [µg/mL]	...	15.3 ⇧ 4.2
$t_{1/2}$ [h]	1.9 ⇧ 0.6	...
AUC $_{0-24}$ [µg*h/mL]	651.7 ⇧ 163.4	365.6 ⇧ 104.7
Cl_T [mL/min]	162.8 ⇧ 42.7	143.6 ⇧ 30.1

Note: Normal renal function is defined as creatinine clearance ⇩50 mL/min.

Nicolau DP et al. *Infect Dis Clin Pract* 1999; 8:45

Continuous Infusion of Ceftazidime

Serumconcentration with 8 volunteers in a crossover trial



Mod. after Mouton JW *et al. Antimicrob Ag Chemother* 1990; 34:2307-2311

Calculated Steady-state Concentrations of β-Lactams Administered by Continuous Infusion to Subjects With Normal Renal Function

Antimicrobial	Dose [g/24h]	Concentration [µg/mL]
Aztreonam	2	15 - 18
Cefazolin	2	12 - 16
Cefotaxime	2	10 - 14
Ceftizoxime	2	10 - 14
Cefuroxime	2	12 - 15
Cefotetan	1	15 - 18
Ceftazidime	2	12 - 14
Oxacillin	4	4 - 8
Piperacillin	6	16 - 20

Pharmacodynamic Approach for Ceftazidime Treatment of AECB (I)

Background:	Implementation of modern PD in the treatment of AECB
Design:	Prospective randomized multicenter study comparing 3 x 2.0 g CEF i.v. versus 2 x 2.0 g CEF infusion over 2 x 7 hours per day, 2.0 g loading dose on day 1
Patients:	80 patients with AECB, 21 patients had a complete Pk profile in our department

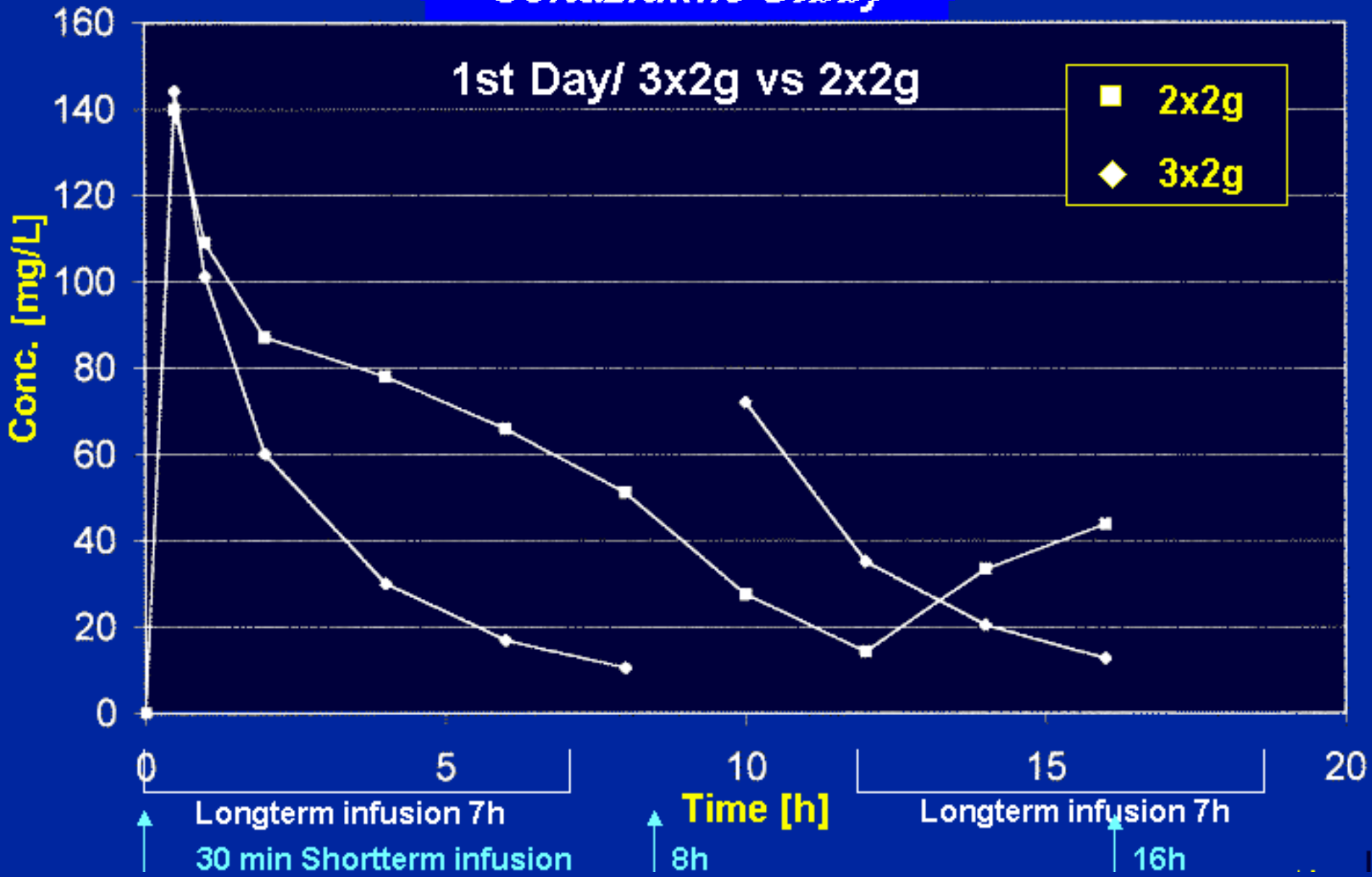
Lück S, Lode H et al. in press 2000

Pharmacodynamic Approach for Ceftazidime Treatment of AECB (II)

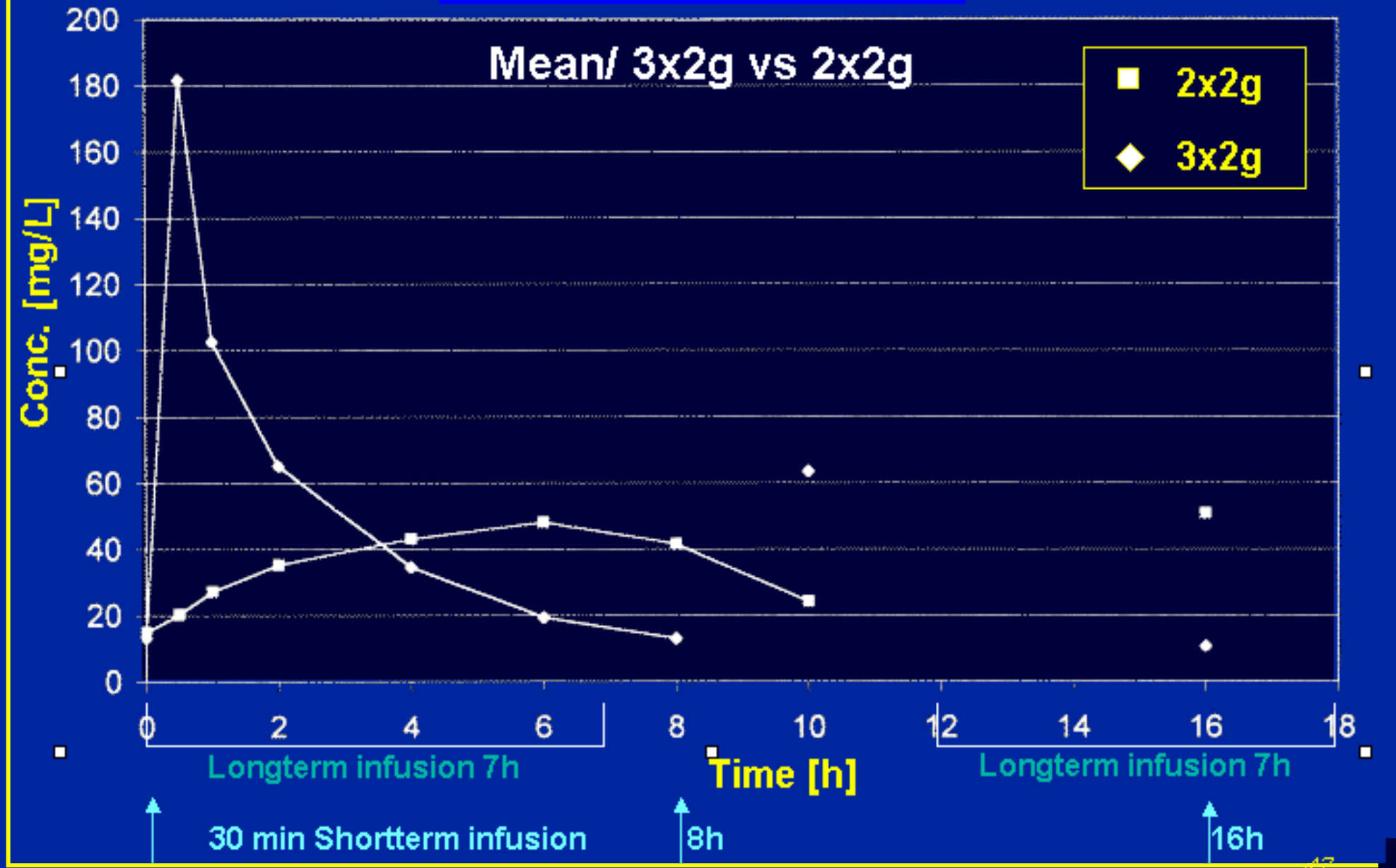
PD-Results:

Median MIC of pathogens	- 1.65 (range: 0.05 - 8 mg/l)
Median serum maximum concentration during continuous infusion	- 48 (range: 30 - 139 mg/l)
Median serum trough concentration during continuous infusion	- 13.9 (range: 5.2 - 43 mg/l)
Median AUC/24 hr during continuous infusion	- 836 (range: 438 - 1838 mg*h/l)
Median AUC/24 hr with intermittent infusion	- 1066 (range: 812 - 1502 mg*h/l)
AUC/MiC ratio during continuous infusion	- 105 (MIC: 8 mg/l)

Ceftazidime Study

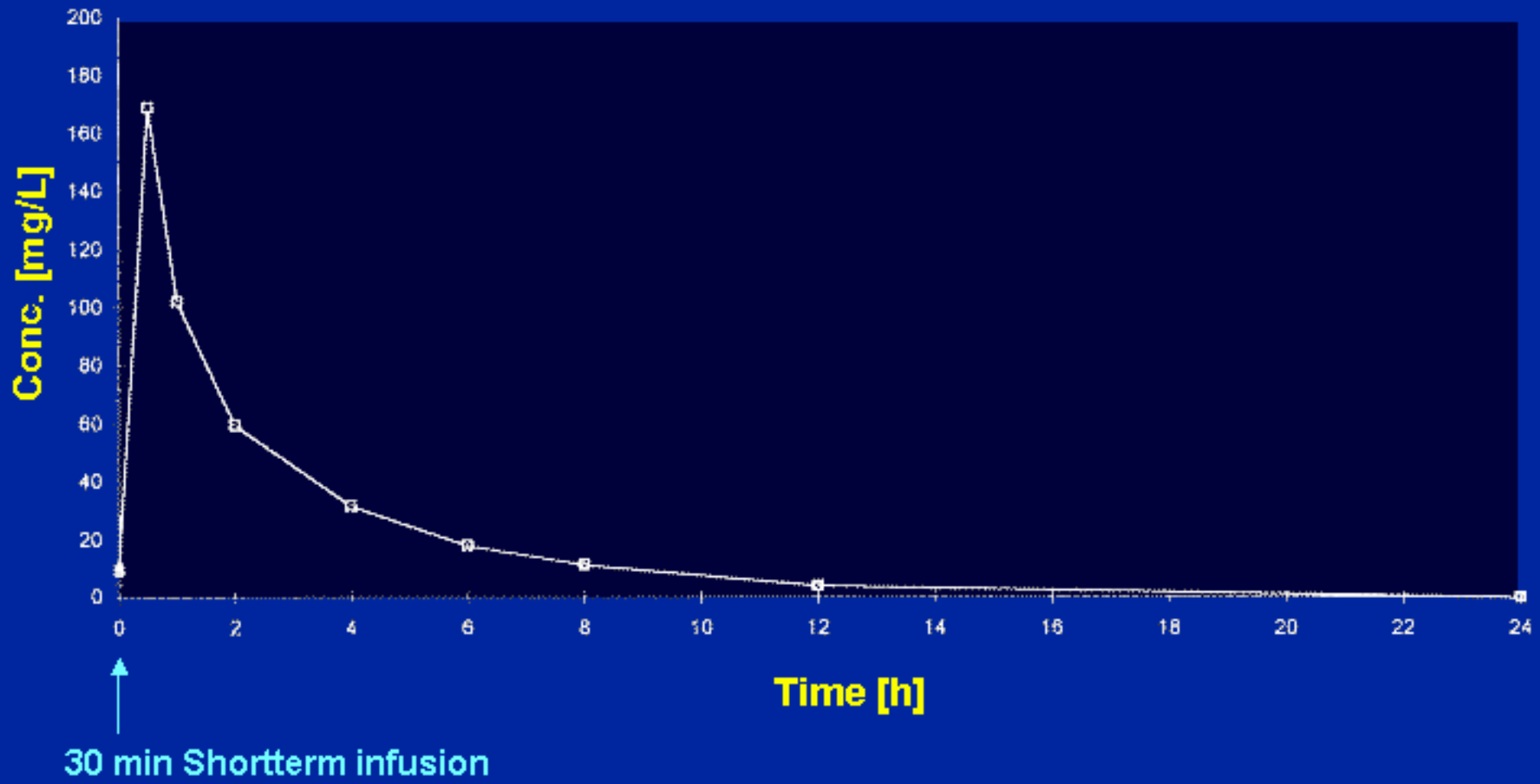


Ceftazidime Study



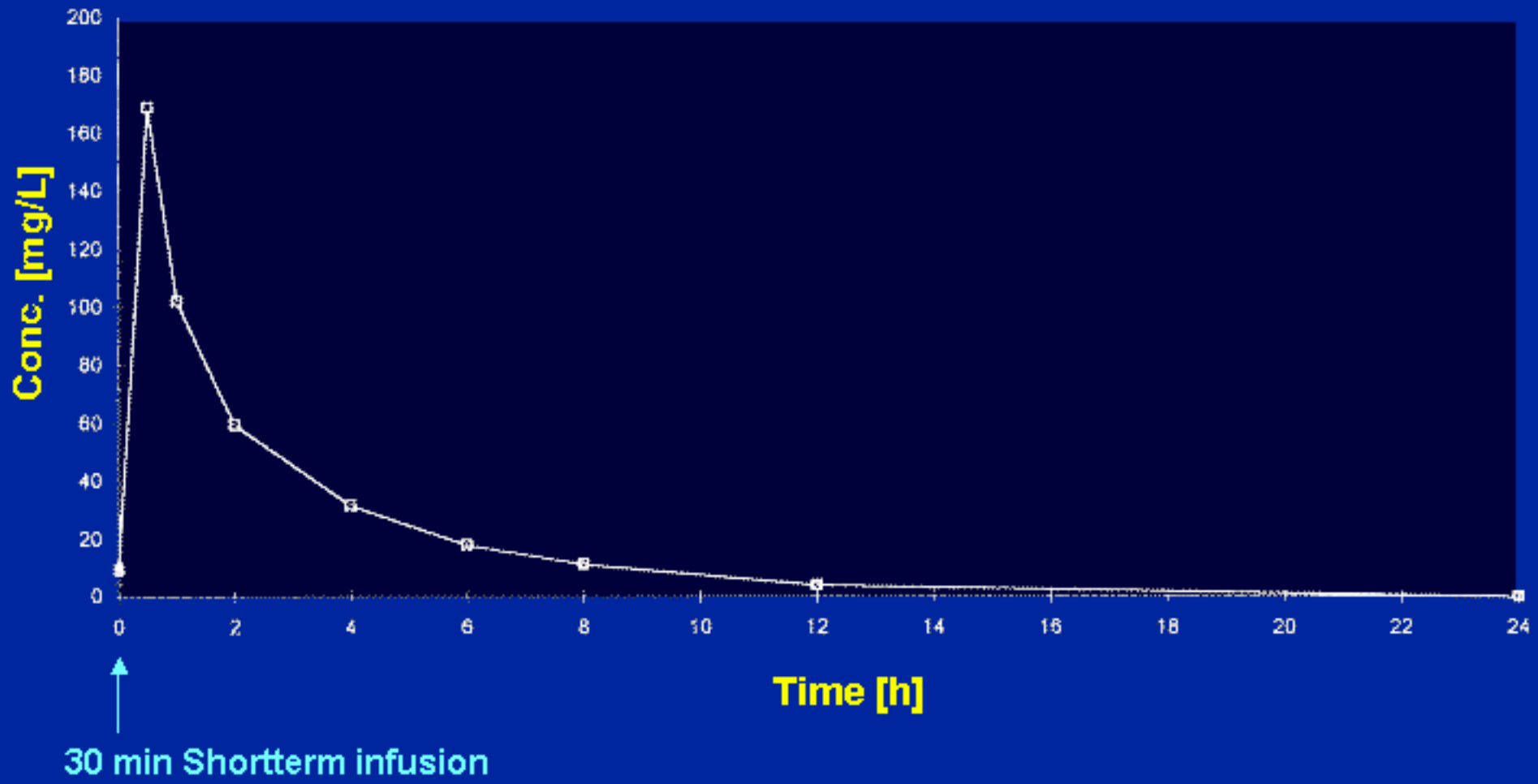
Ceftazidime Study

Mean values/End 3x2g



Ceftazidime Study

Mean values/End 3x2g



Pharmacodynamic Approach for Ceftazidime Treatment of AECB (III)

Clinical results: All 21 patients clinically cured or improved All bacteria which were eradicated are presumed eradicted

Conclusions: The PD approach in treatment of AECB with ceftazidime 2 x 2.0 g as continuous infusion over 2 x 7 hours daily is as effective, safe and less expressive than conventional therapy

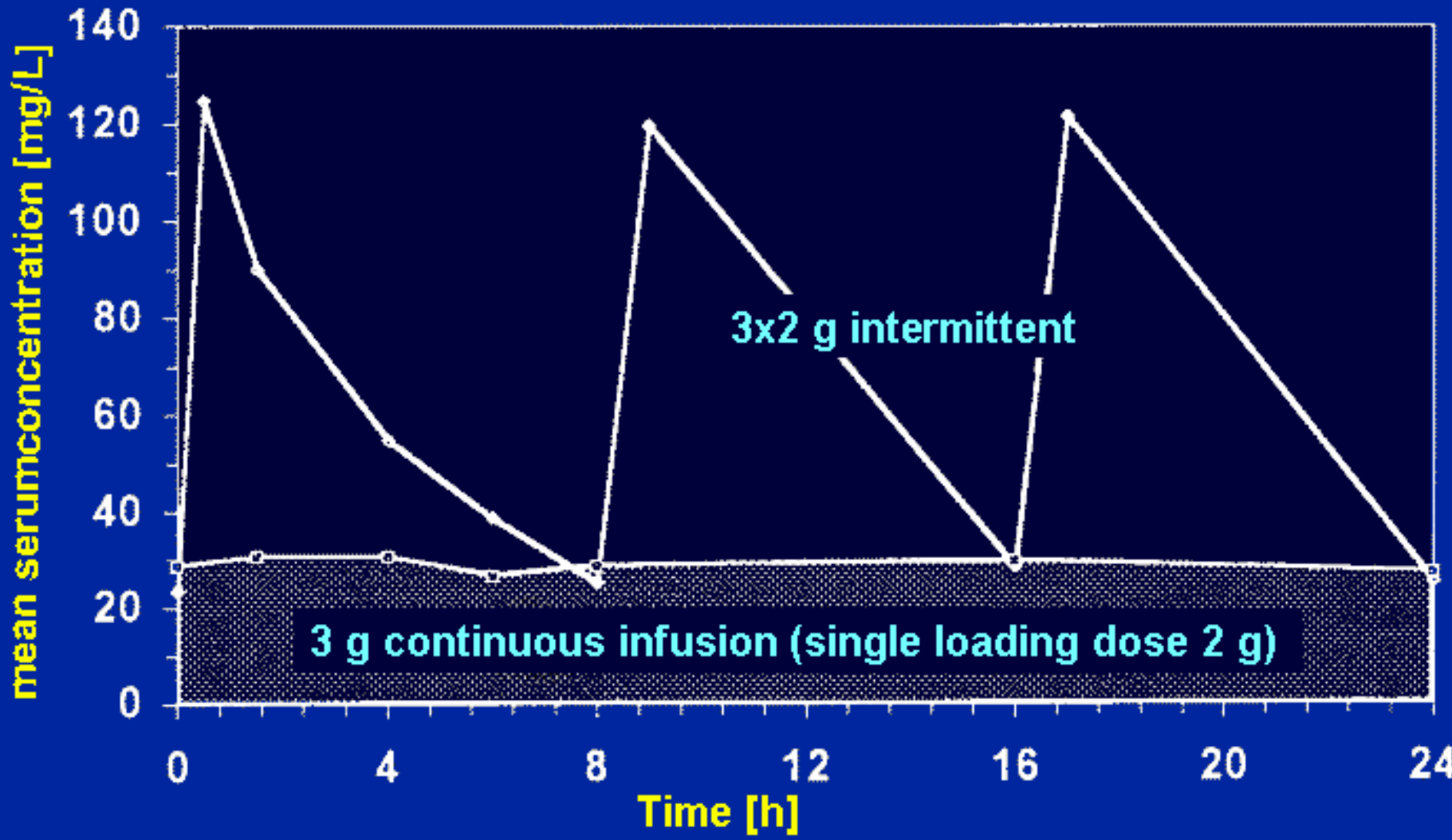
Implementation of PD Approach in Clinical Practice

Summary

1. New data support the role of continuous infusion administration for the β-lactam antibiotics
2. This approach optimizes the PD profile of these agents, thereby maximizing the potential for good clinical outcomes at reduced costs
3. Dosing in continuous infusion should be orientated on MIC of the pathogen, adequate anticipated serum concentrations and Pk of the individual antibiotic

Continuous Infusion of Ceftazidime

Randomized crossover study with 12 critically ill patients



Mod. after Benko AS *et al. Antimicrob Ag Chemother* 1996; 40(3):691-695