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*

Correct Dosing of Antibiotics: Impact of Clinical Pharmacy

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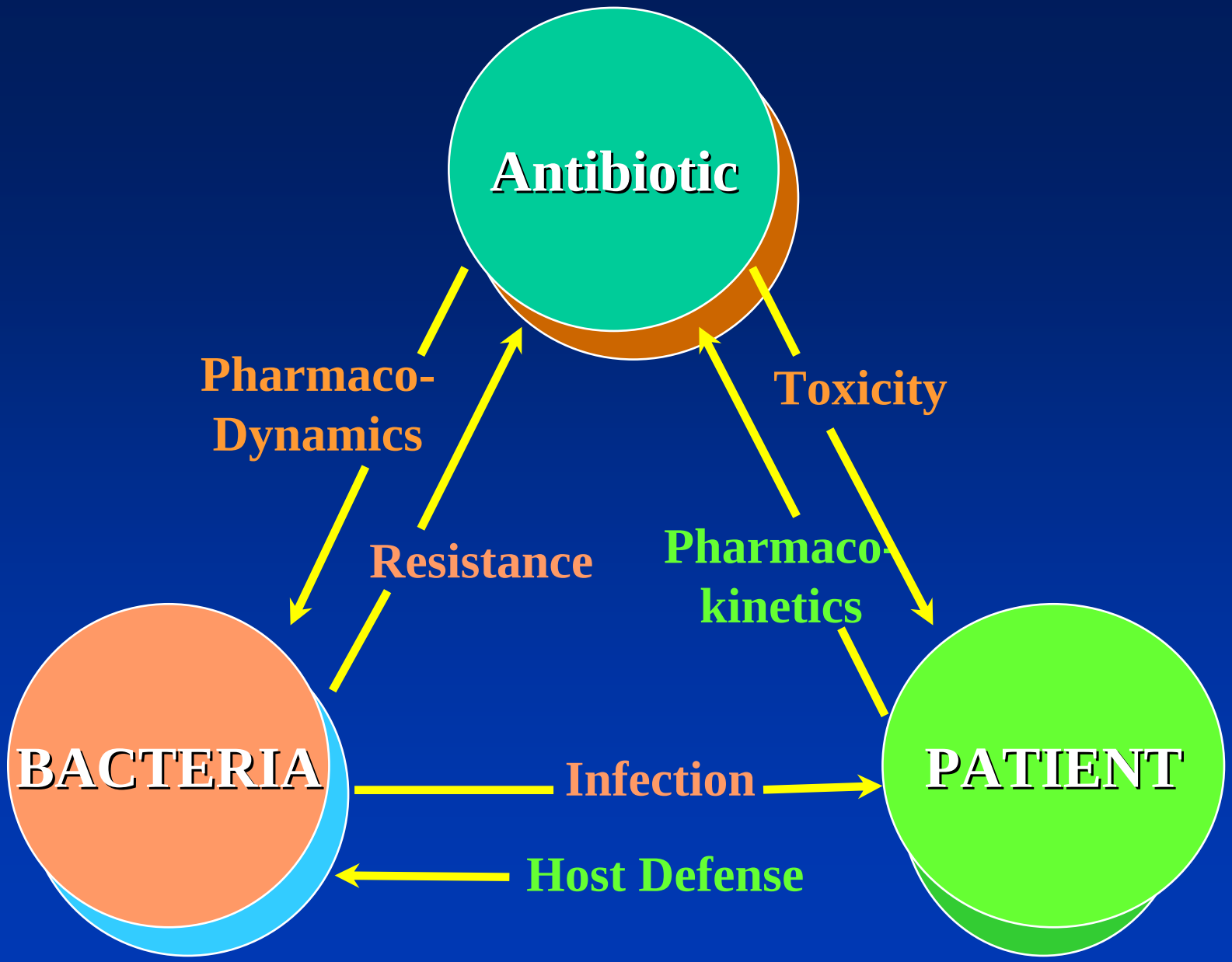
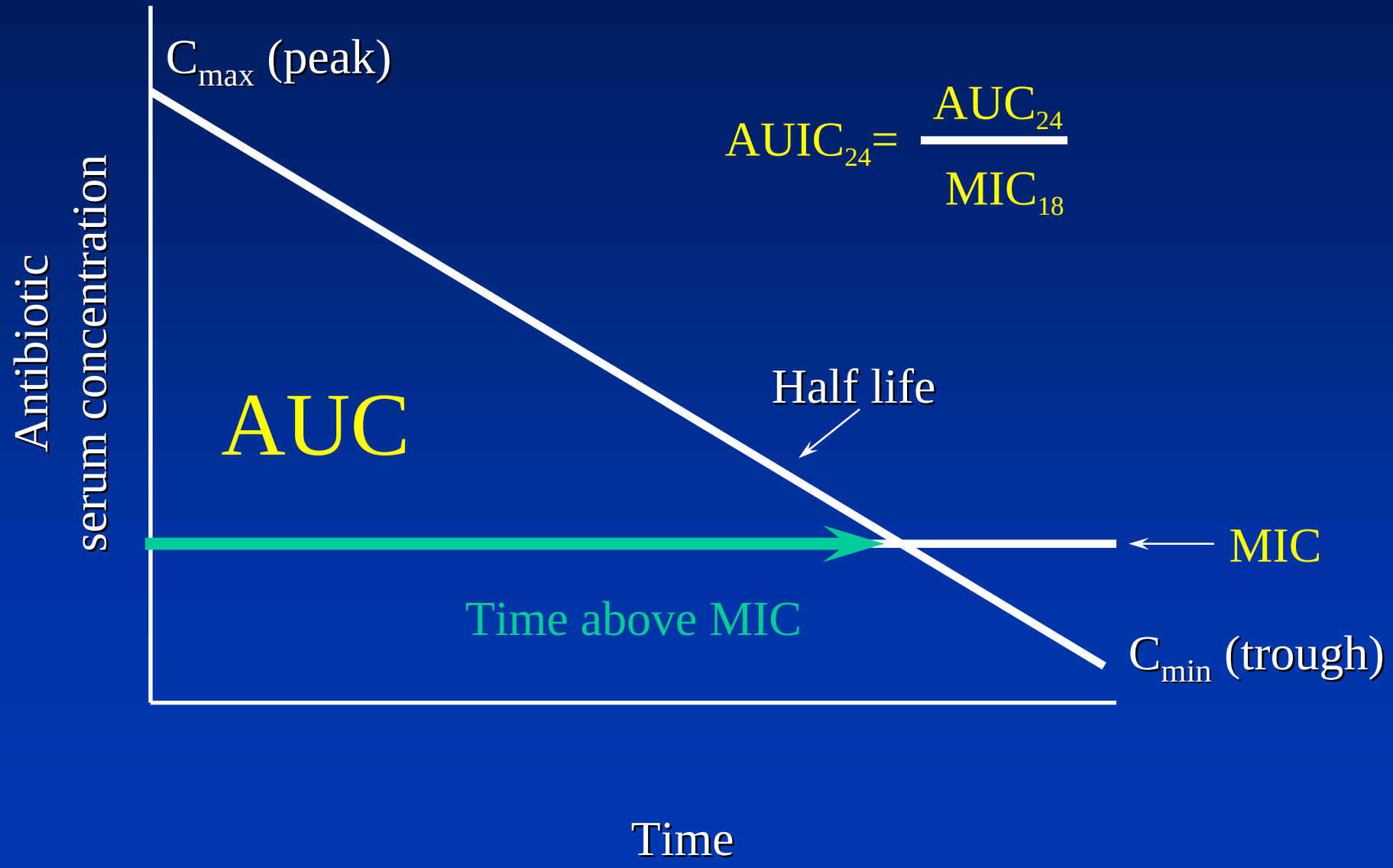
Presented at the KU-Leuven on Tuesday February 26th



Applied Pharmacokinetics and Pharmacodynamics: 4th Edition, 2006


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

Model Antibiotics for Human PK/PD trials:

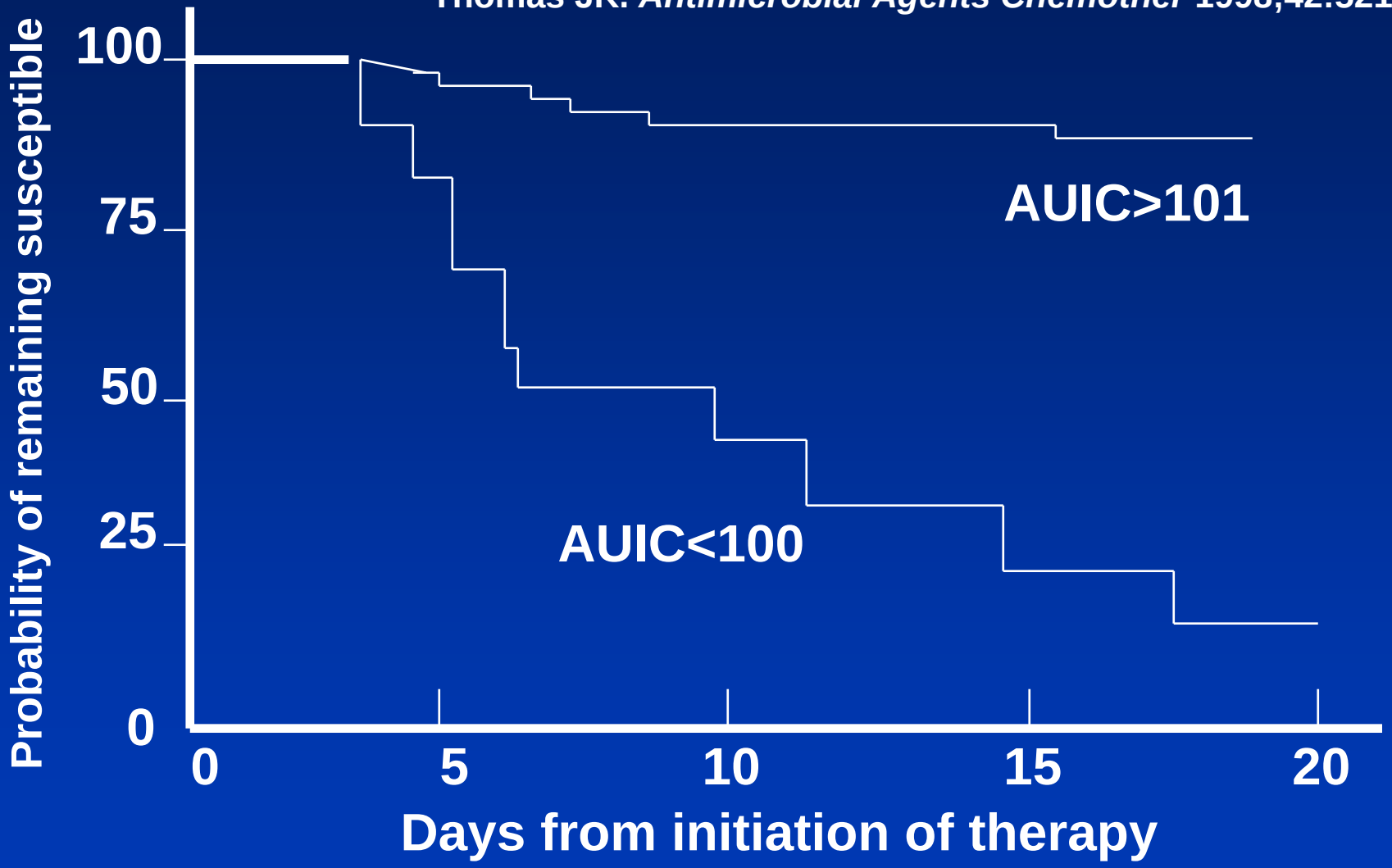
- **Ciprofloxacin**
- **Grepafloxacin**
- **Tobramycin**
- **Piperacillin**
- **Ceftazidime**
- **Azithromycin**
- **Linezolid**
- **Cefmenoxime**
- **Cefepime**
- **Aztreonam**
- **Synercid**
- **Imipenem**
- **Telithromycin**
- **Vancomycin**

Advantages of Antibiotics

- **You can readily isolate, grow and study the "receptor" for an antibiotic**
  - **Fortunate, because susceptibility varies tremendously between "receptors"**
- **Correlations between in vivo Pharmacokinetics and in vivo Pharmacodynamics are feasible; This also includes Resistance**

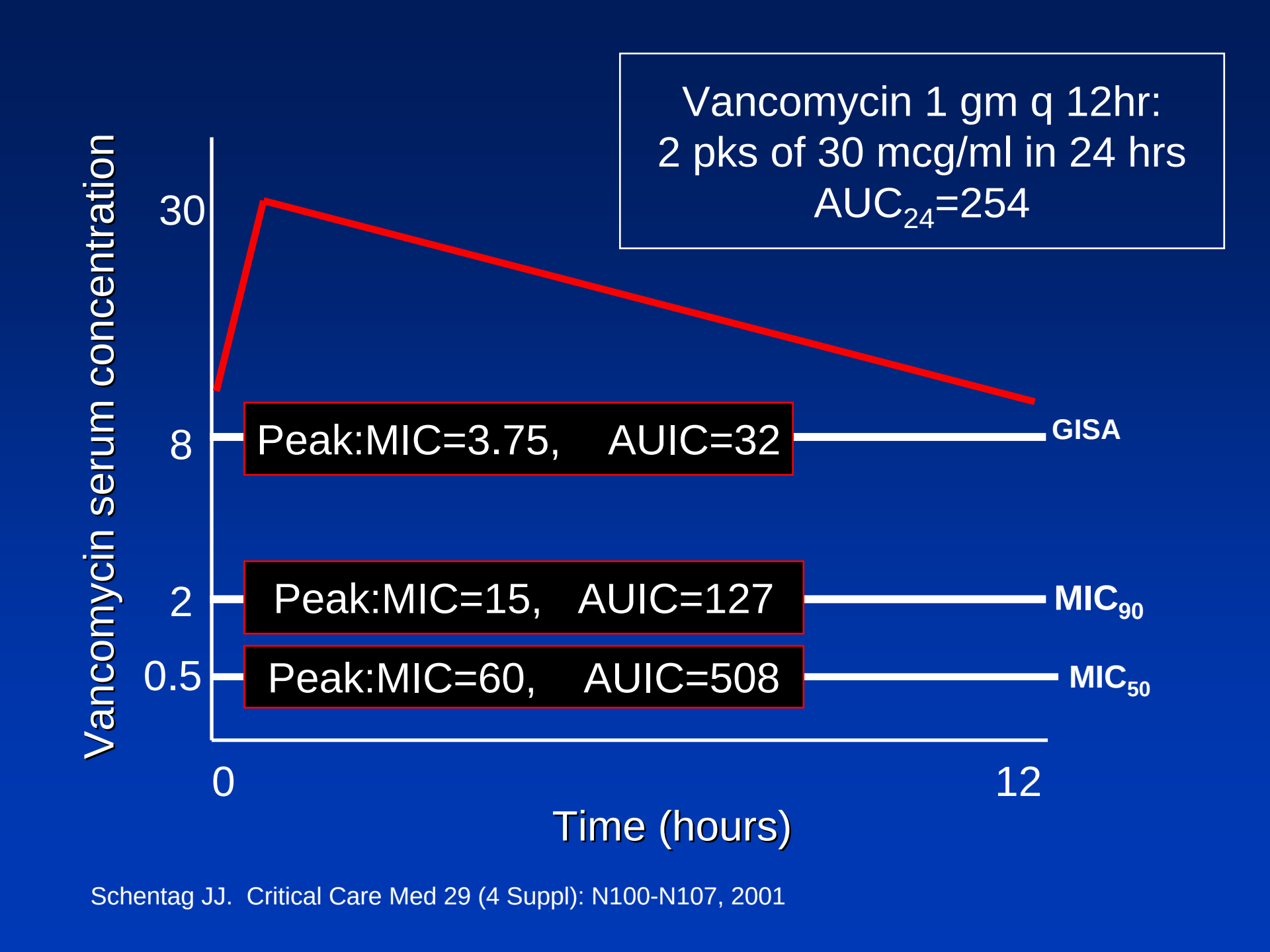
AUIC vs Resistance

Thomas JK. *Antimicrobial Agents Chemother* 1998;42:521–527.



Vancomycin – Role in Therapy

- Up until ~ 1990, it was the undisputed drug of choice for gram positives such as staphylococci and enterococci, and was always perceived as effective.
- Purpose of Serum Conc. Monitoring was to avoid toxicity; rigid range of concentration defined as peak ~ 30 mcg/ml and trough ~ 10 mcg/ml
- Problems followed increasing use
  - 1991: E. faecium became VREF
  - 1995-1998: Arrival of VISA and Declining success *vs*. MRSA, even when “susceptible”



Schentag JJ. Critical Care Med 29 (4 Suppl): N100-N107, 2001

Vancomycin: AUICs *vs* Time > MIC?

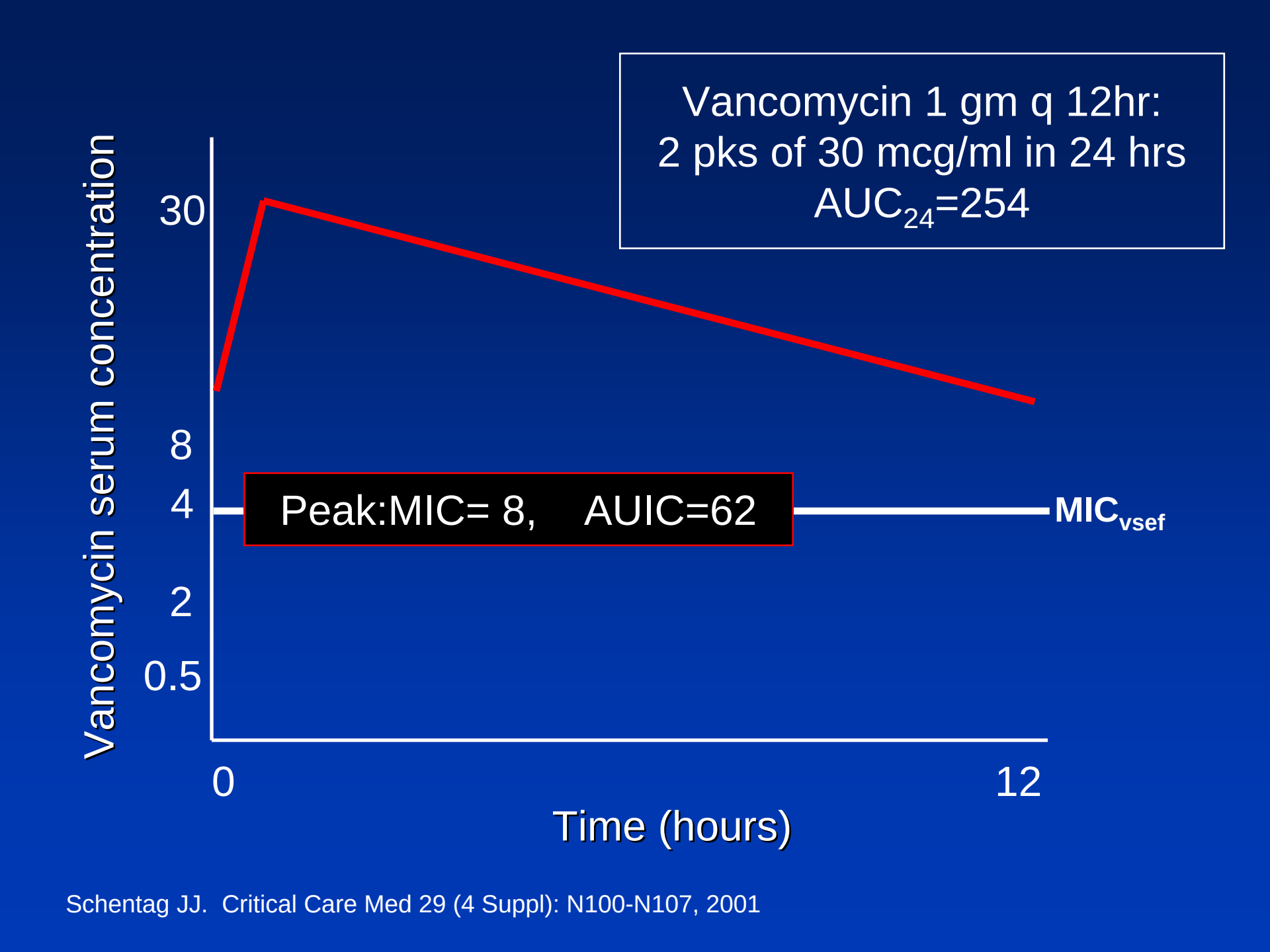
- Vancomycin is slowly cidal, and demonstrates time-dependent killing and a long half-life. With these properties, there ought to be good correlation between AUIC and time above MIC
- Dosing controls the blood levels in most patients, so any low AUICs or short time>MICs would be the result of high organism MICs
- Correlation study in 84 patients at MFH
  - This was 1993, and the goal was to understand VREF development in bacteremia patients…

Vancomycin Outcomes vs AUICs

	Outcome		
	Satisfactory	Unsatisfactory	Indeterminate
MIC >1.0 µg/ml	1	4[a]	0
MIC <1.0 µg/ml	74	2	3
AUIC <125	4	4[b]	0
AUIC >125 (76)	71	2	3
Total Patients (84)	75	6	3

[a] $p < 0.001$
[b] $p < 0.005$

Hyatt, et al. *Clin Pharmacokinet*. 1995;28:143-160.



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Enterococcus faecium (VSEF-VREF)

- Dangers of the inadvertent high MIC organism like *E. faecium*, with a fixed-AUC drug like vancomycin
- We lost the use of vancomycin for *E. faecium* by 1998
- Large increases in vancomycin dosing could have delayed this loss.
  - Target AUIC is 125 for VSEF (Hyatt et al. Clin PK 1995;28:143)
    - Double the dose (AUC_{24} ~ 500) for MIC=4.0
    - Quadruple the dose (AUC_{24} ~ 1000) for MIC=8
      - Peaks of ~150, troughs of 110….
- Alternatives for MIC > 8.0 mcg/ml:
  - Quinupristin/Dalfopristin (September 20, 1999)
  - Linezolid (April 18, 2000)

…….What about S. aureus, esp. MRSA?

MRSA: Issues With "Appropriately Dosed" Vancomycin?

- MRSA MICs are usually 0.5 to 1.0 mcg/ml
  - Slow killing of organisms in vitro and in vivo
- MRSA MBCs are increasingly 4-32 mcg/ml
  - Staphylococci that are not yet VISA or VRSA, but no longer responding to vancomycin at AUICs of 125-250
- Clinical Evidence of Problems with Vancomycin?; Failures even before VISAs with MICs ~ 2-4 mcg/ml

Patient 2 and Patient 3

- Patient 2
  - 78-year-old male
  - Developed MRSA pneumonia day 107, treated with vancomycin
  - Initial infection × 15 days
  - 2nd infection × 15 days
  - 3rd infection × 8 days
  - 4th infection × 7 days
    - MRSA now colonized
  - Vanco MIC≤0.5
- Patient 3
  - 71-year-old female
  - Admitted from NH with MRSA pneumonia, treated with vancomycin
  - Initial infection × 10 days
  - 2nd infection × 5 days
  - Patient expired, day 20
    - MRSA not eradicated
  - Vanco MIC≤0.5

Patient 2: Healthcare Resources Used

Event	Vanco AUIC[a]	Vanco levels[b]	Total ($)	$/day
Initial infection (1/13/98-1/27/98)	394	Rdm >20	29,055	1,937
2nd infection (2/2/98-2/16/98)	195	ND	38,588	2,573
3rd infection (2/21/98-2/28/98)	266	ND	16,385	2,048
4th infection (3/18/98-3/24/98)	736	Tr>20	23,375	3,339

[a] Values expressed are means.
[b] Rdm = random; ND = not done; Tr = trough.

Why Is Vancomycin Failing?

- Slowly or poorly cidal, hetero-resistance?
- MBC >> MIC for these vancomycin exposed organisms?
- Increasingly larger fractions of the organism population reach the definition of tolerance
- Vancomycin PK/PD target of 125 is too low for this drug; For MRSA, we may need AUICs of 400 or even more?

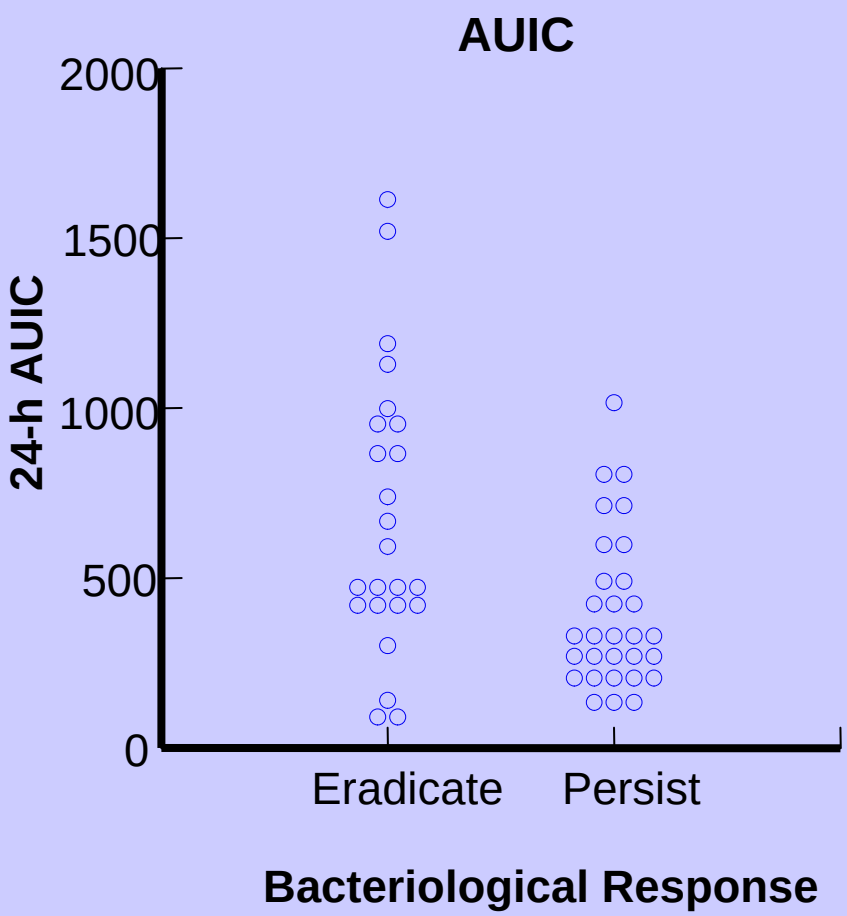
PK/PD study in S. aureus LRTI

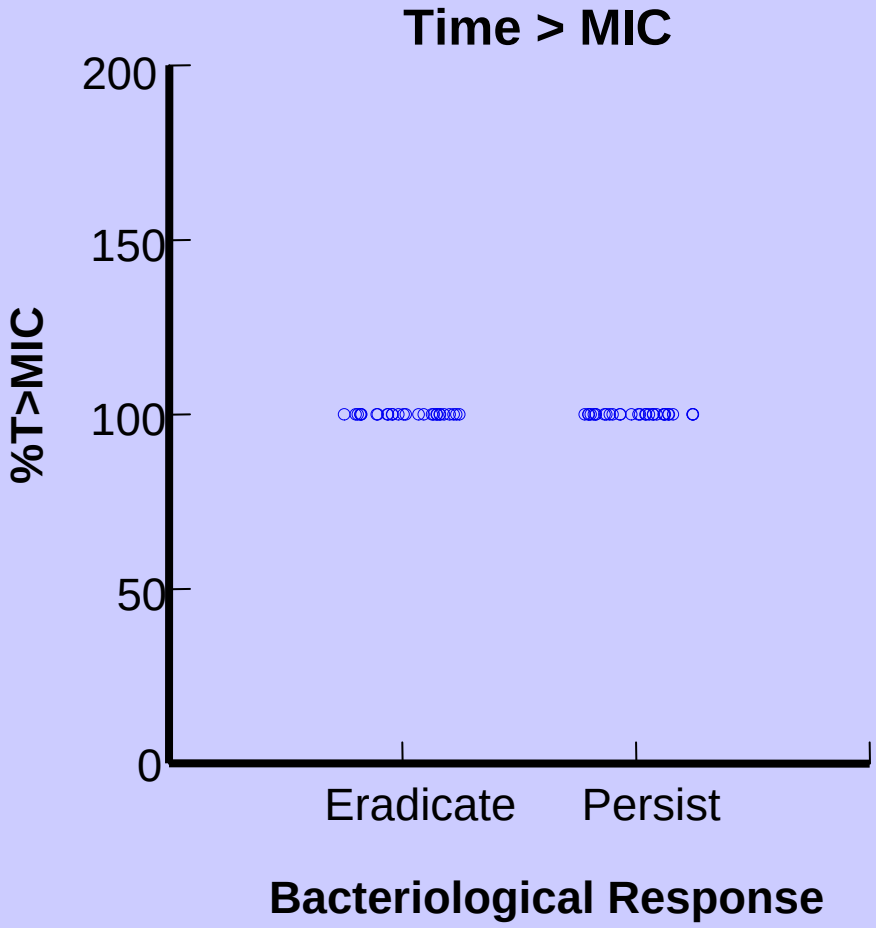
- 108 patients in 1998 that qualified for PK/PD and LRTI out of a total of 160 pts at MFH that year (Mean Age=74, 67% on Ventilator at baseline); Main reason for exclusion was insufficient proof of LRTI
- All patients had PK/PD as $AUIC_{24}$; for endpoints we could often derive time to bacterial eradication (via daily cultures) and time to clinical cure (via daily scoring). We also collected the usual cure-failure micro and clinical data typical of registration trials.
- Clinical success was 59% overall; 54% for MRSA, 71% for MSSA
  - **Oxacillin vs MSSA was 100% effective**
  - **Failure overall was associated (LR analysis) with MRSA, low albumin, low CCr, multi-lobe involvement and AUIC <400**

Moise, Forrest, Schentag et al. Clinical Pharmacokinetics 2004; 43: 925-942

AUIC vs T>MIC and Microbiological Response

Moise, Forrest, Schentag et al. Clinical Pharmacokinetics 2004; 43: 925-942





AUIC vs T > MIC and Clinical Response

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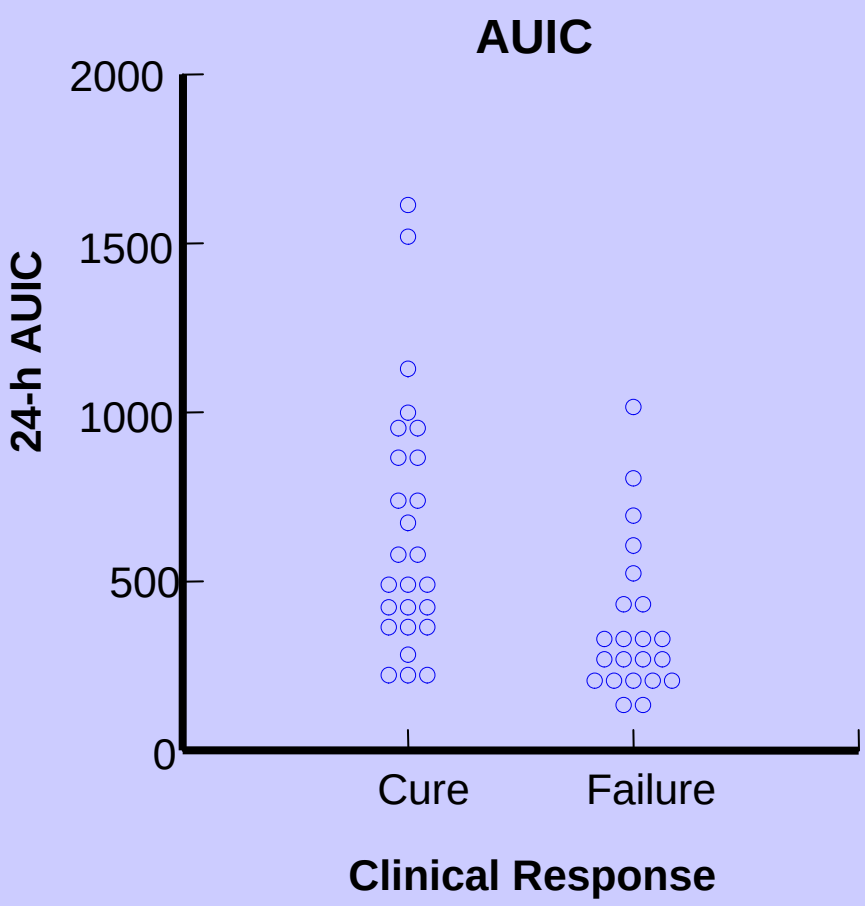
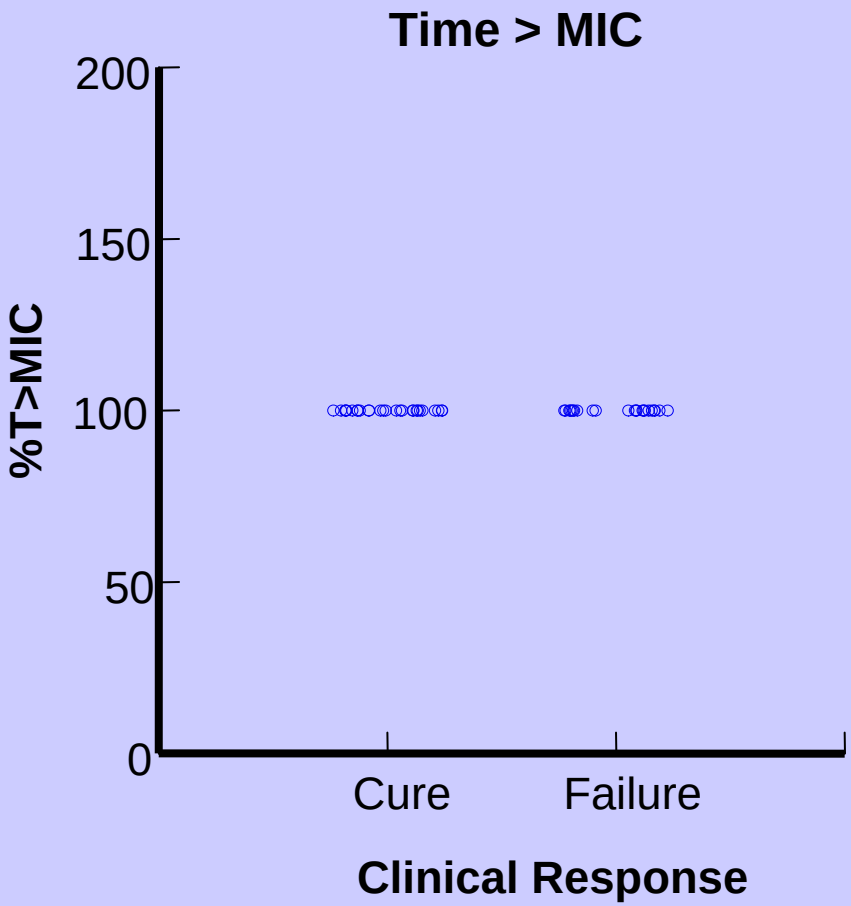
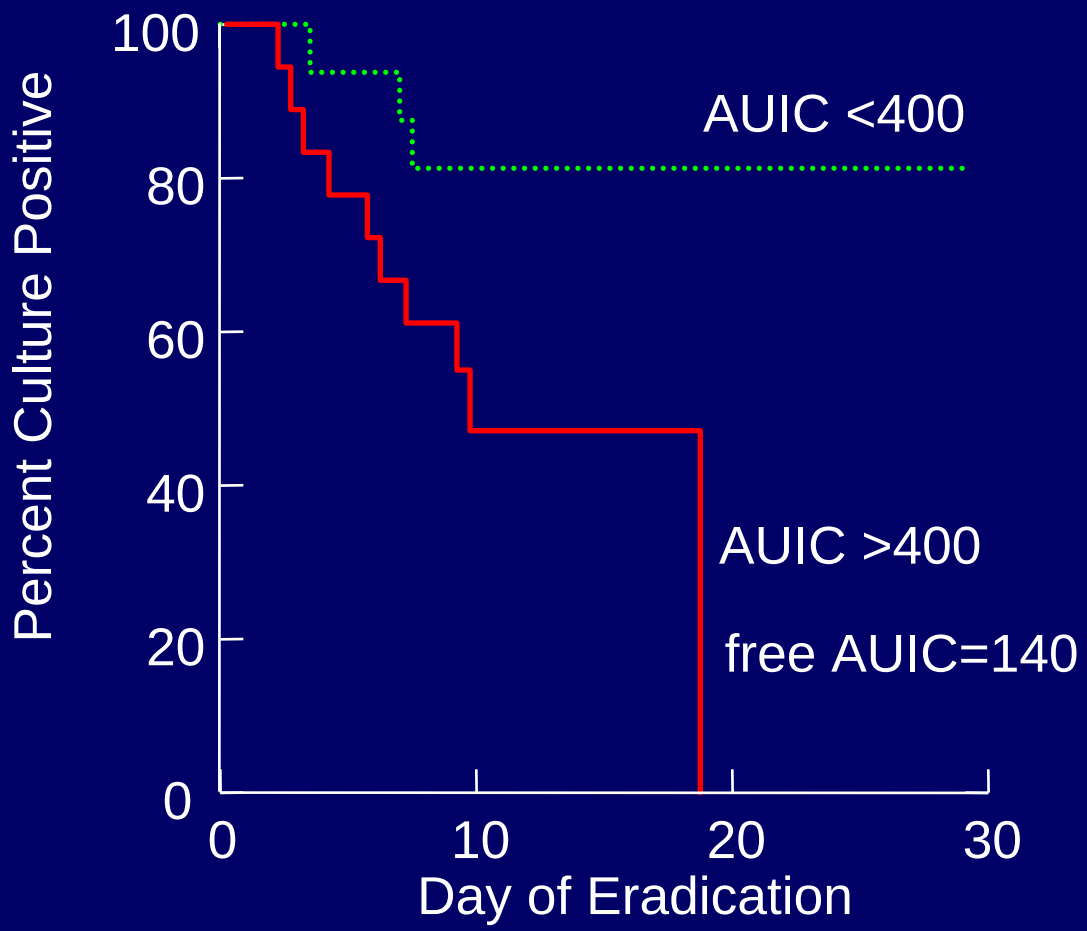




Comparison of Vancomycin days to eradication for MRSA Infections



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Moise & Schentag. **Clinical Pharmacokinetics 2004; 43: 925-942**

Strategies for MRSA failing Vancomycin after 5 d. Treatment

- In the Vancomycin failure patient with MIC ~ 2.0:
  - Raise the vancomycin dose; target peaks of 50 mcg/ml and troughs of 20 mcg/ml, AUCs > 500
  - Vancomycin at conventional doses (troughs ~ 10) in Combination therapy: Target Synergy
    - Rifampin (resistance after 2-3 days TX)
      - Data of Burnie et al.
    - Aminoglycosides (combo is very nephro-toxic)
    - Oxacillin (U-shaped dose response – failures)
    - Linezolid (antagonistic or indifferent in vitro)
    - Synercid (synergistic in vitro, esp. at high inoculum)