



**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*

# How we try to improve efficacy, decrease resistance and save money with antibiotics in hospitals ...

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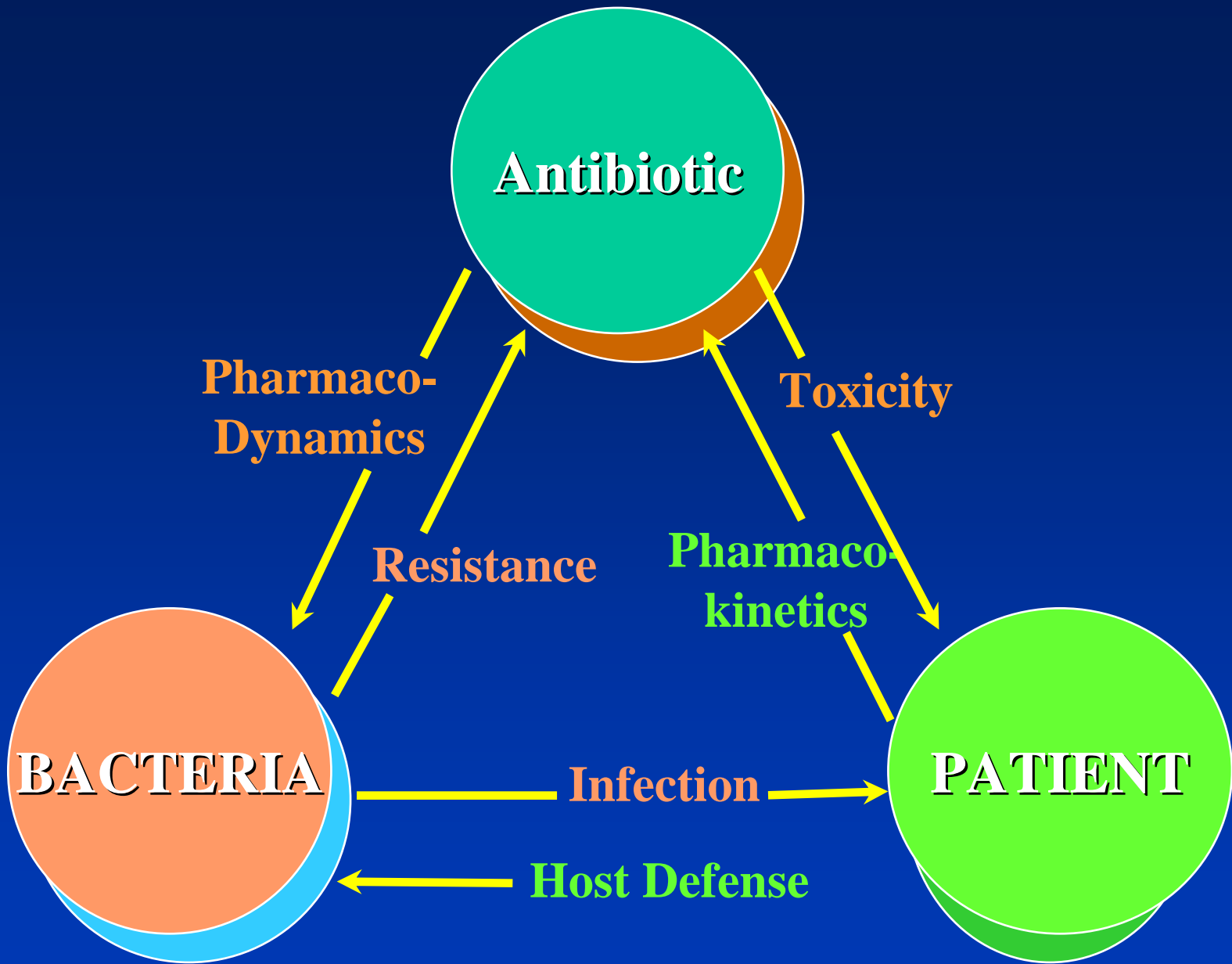
**University at Buffalo**

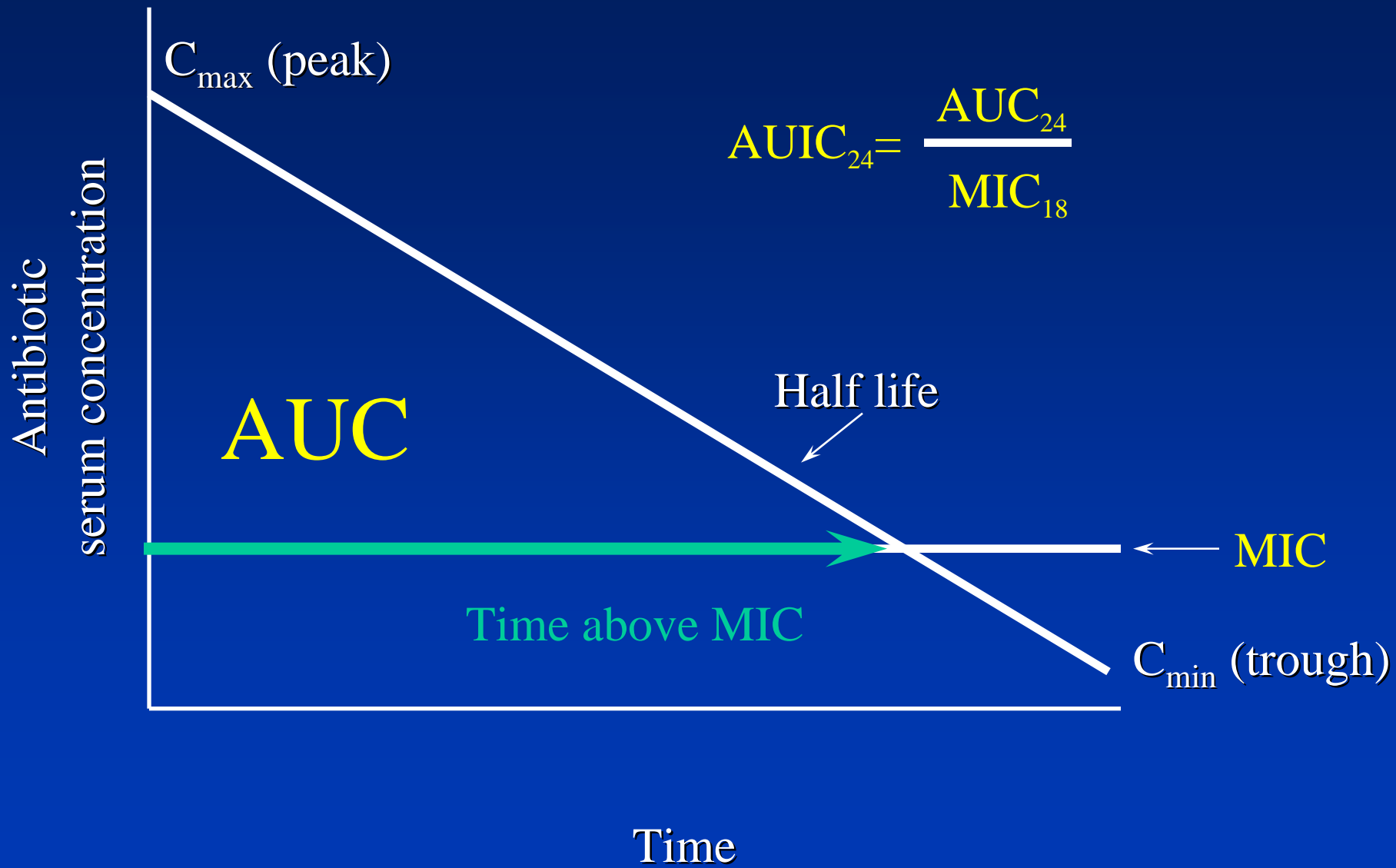
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Presented at UCL on Thursday February 28th <sub>1</sub>





# Model Antibiotics for Human PK/PD trials:

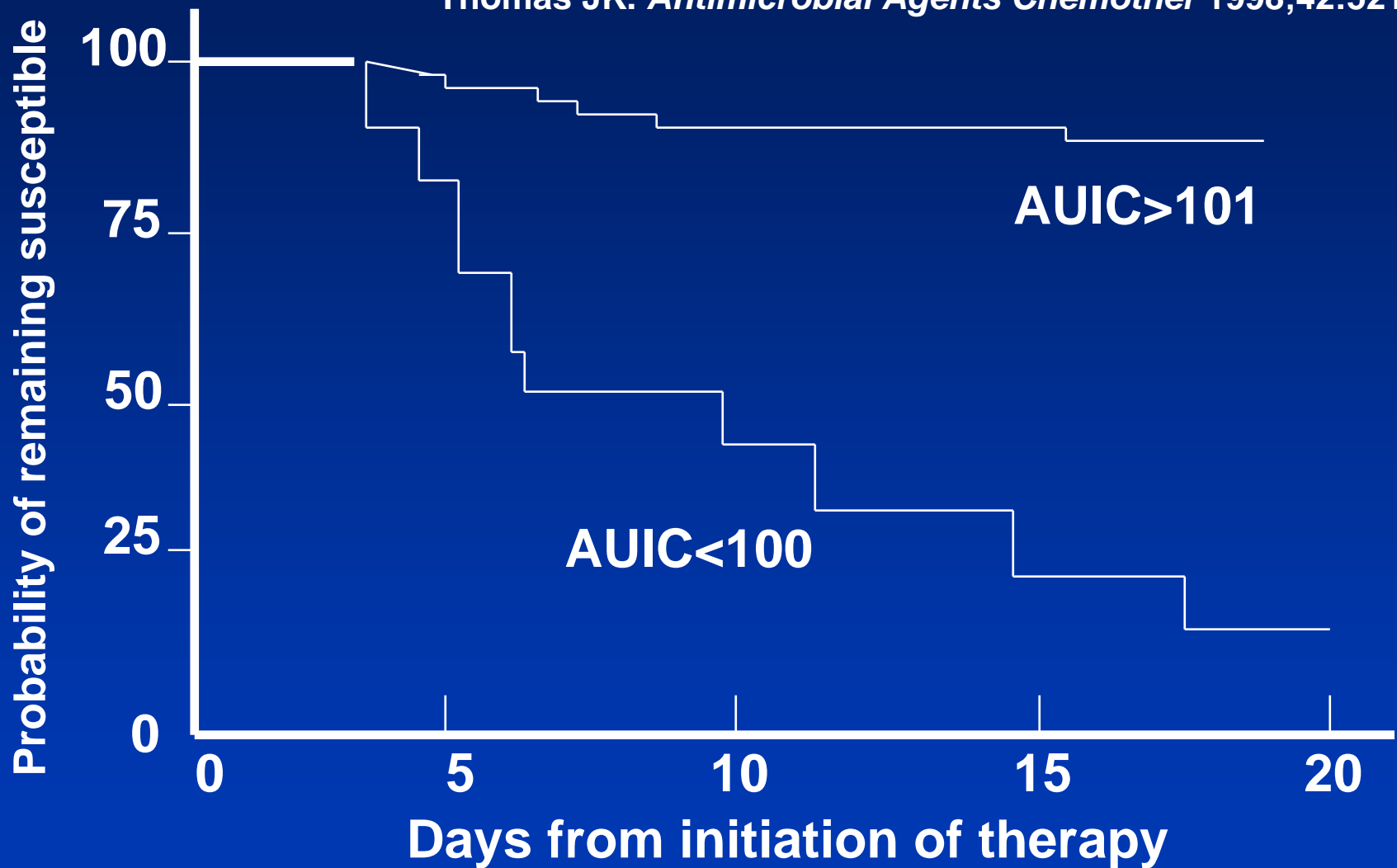
- Ciprofloxacin
- Grepafloxacin
- Tobramycin
- Piperacillin
- Ceftazidime
- Azithromycin
- Linezolid
- Cefmenoxime
- Cefepime
- Aztreonam
- Synercid
- Imipenem
- Telithromycin
- Vancomycin

# 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

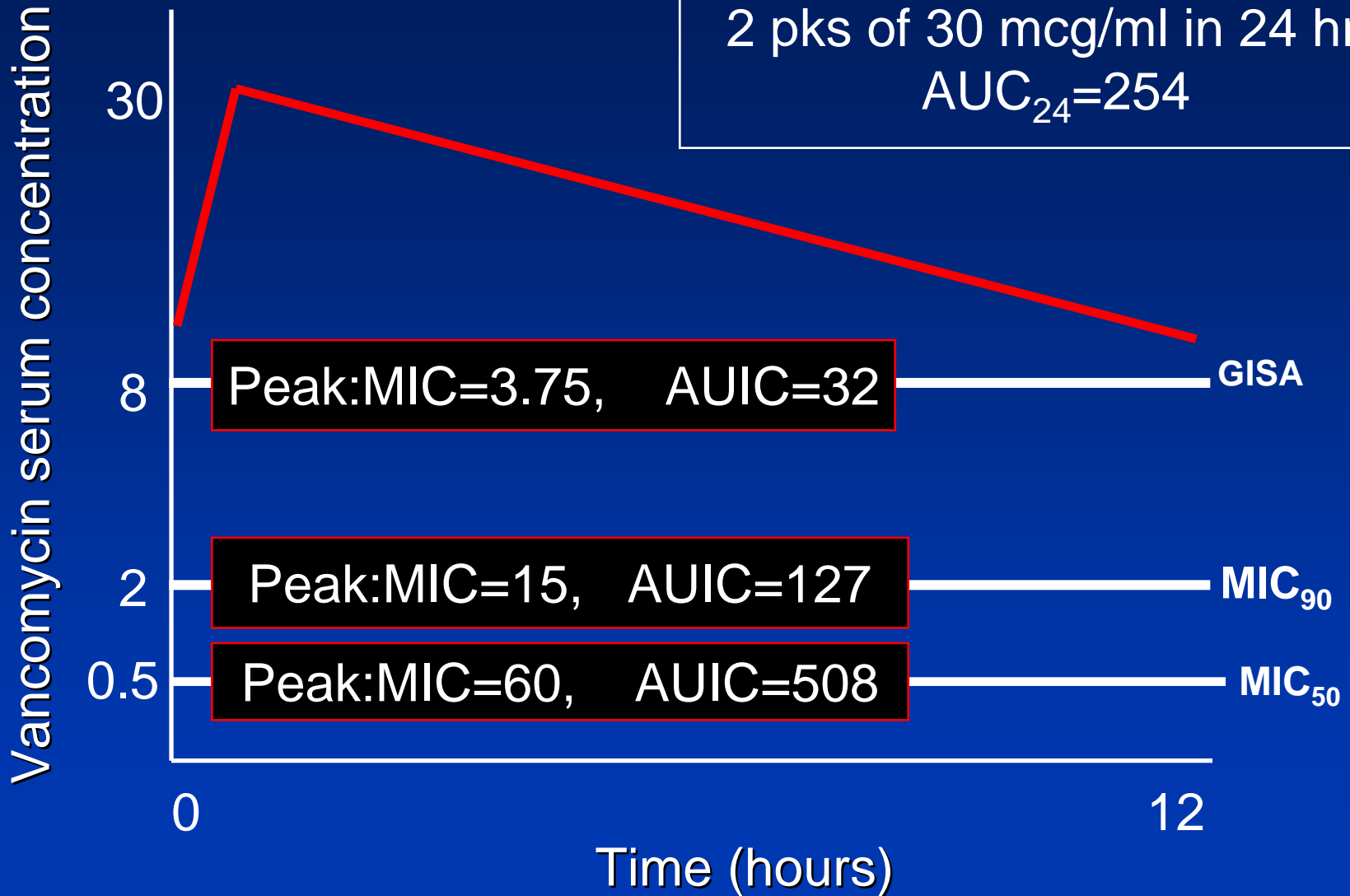
Thomas JK. *Antimicrobial Agents Chemother* 1998;42:521–527.



# 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”

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



# Vancomycin: AUCs 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 AUC and time above MIC
- Dosing controls the blood levels in most patients, so any low AUCs 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...

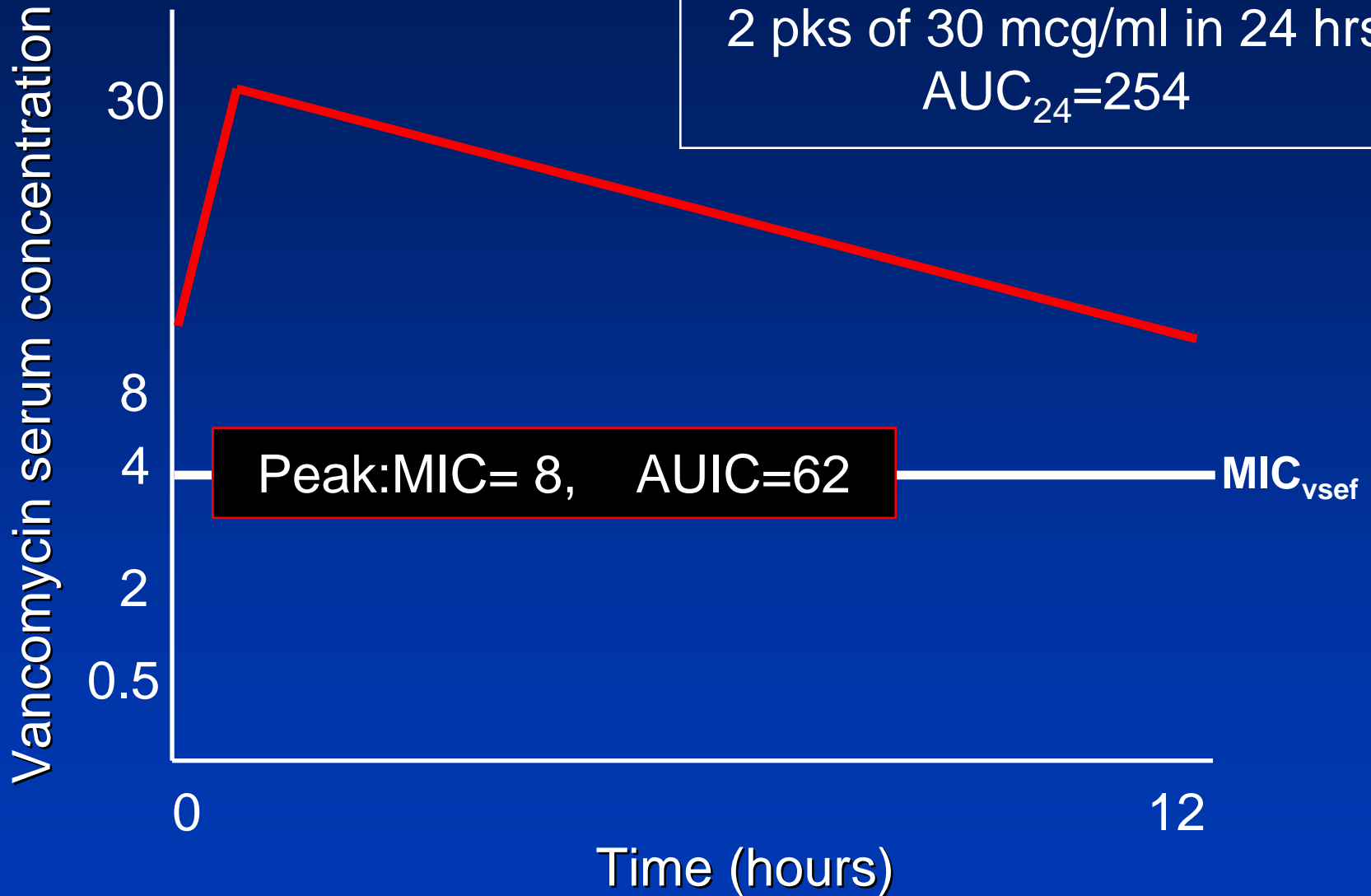
# Vancomycin Outcomes vs AUCs

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

<sup>a</sup>  $p < 0.001$

<sup>b</sup>  $p < 0.005$

Vancomycin 1 gm q 12hr:  
2 pks of 30 mcg/ml in 24 hrs  
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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 ( $AUC_{24} \sim 500$ ) for MIC=4.0
    - Quadruple the dose ( $AUC_{24} \sim 1000$ ) 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 AUCs 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 $\leq$ 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 $\leq$ 0.5

# Patient 2:

## Healthcare Resources Used

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

<sup>a</sup> Values expressed are means.

<sup>b</sup> Rdm = random; ND = not done; Tr = trough.

# Why Is Vancomycin Failing?

- Slowly or poorly cidal, hetero-resistance?
- $MBC \gg MIC$  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 AUCs of 400 or even more?

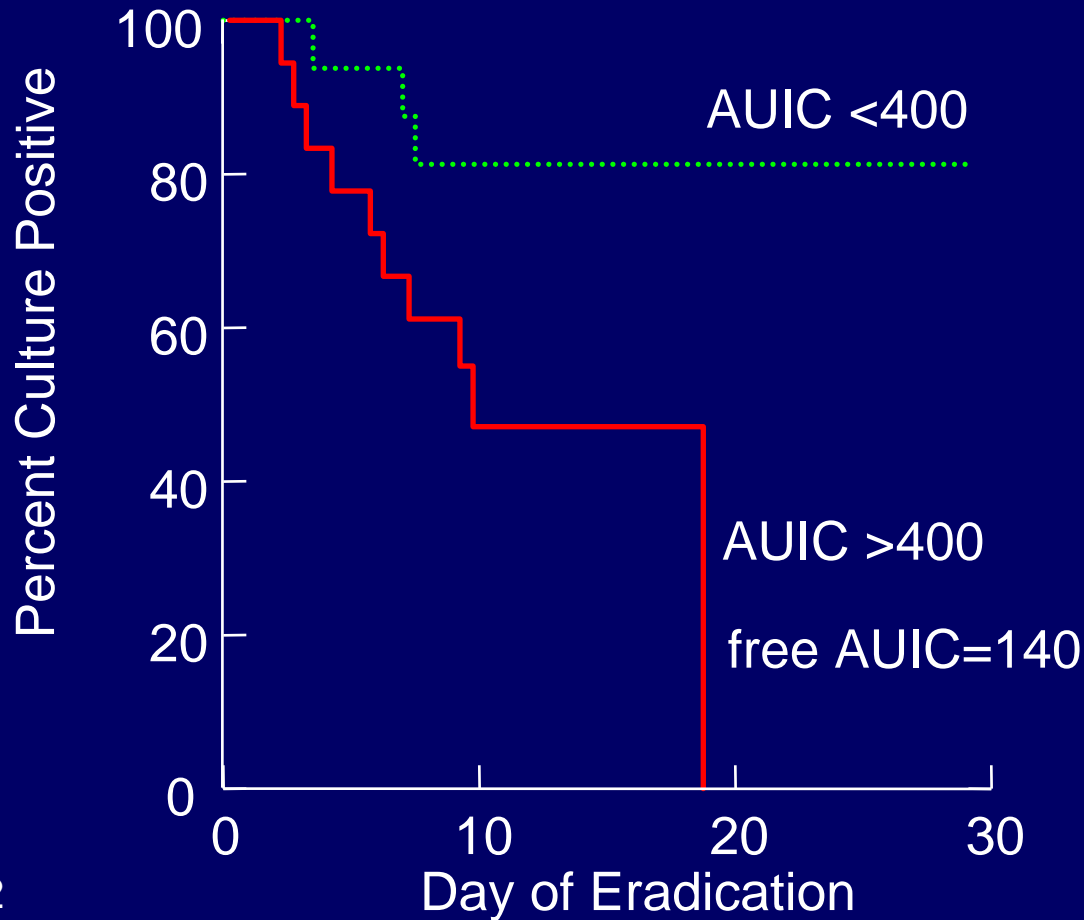
# ***PK/PD study in S. aureus LRTI***

- 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  $AUIC < 400$**





# Comparison of Vancomycin days to eradication for MRSA Infections



# 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**