Glycopeptides appropriate uses

- **<u>serious</u> infections due to beta-lactam- resistant gram-positive microorganisms**
- **infections due to gram-positive microorganisms in patients with serious allergy to beta-lactam antimicrobials**
- **antibiotic-associated colitis (AAC) non-responding to metronidazole or potentially life-threatening**
- **prophylaxis for endocarditis in patients at high risk**
- **prophylaxis for major surgical procedures**

Comparative efficacy and safety of teicoplanin and vancomycin

Wood, JAC 1996)

Meta-analysis of 11 clinical trials (1276 pts)

Direct comparisons difficult

Teicoplanin as effective as vancomycin

Teicoplanin superior tolerability (?)

Teicoplanin advantages :

- once daily, bolus
- intramuscular
- cost monitoring
(cost more but do less !!!)

3

Can pharmacokinetics/pharmacodynamics help in optimizing glycopeptide treatments ?

- efficacy (primary end-point)
- prevention of emergence of resistance (secondary but crucial endpoint)

4

Glycopeptides PK/PD:
which is the important parameter ?

- slowly cidal
- time-dependent killing
- long half-life

⇨ **AUC / MIC ratio**

But, what is this ?

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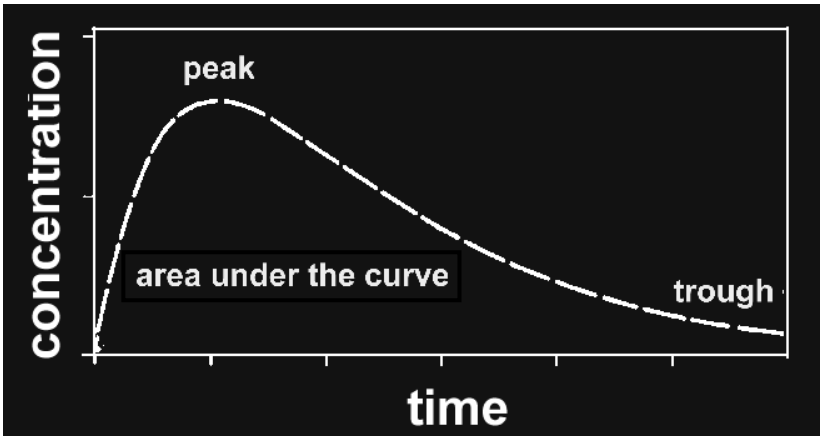
Area under the curve (AUC)



⇨ **dependent on the total dose and half-life**

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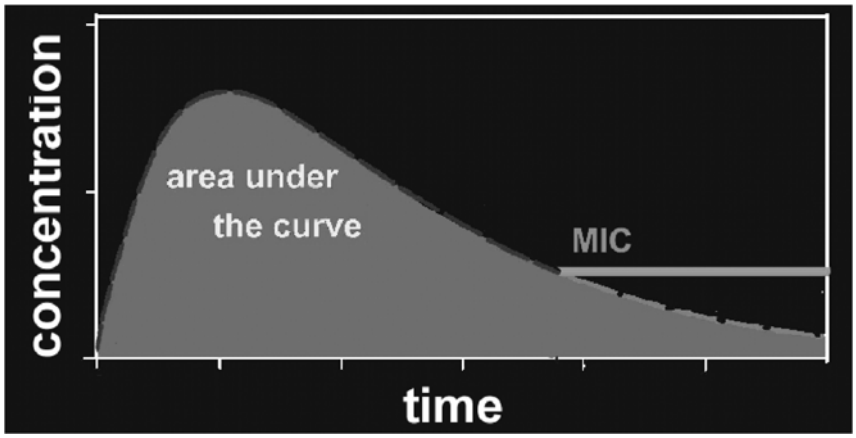
AUC / MIC ratio



⇨ **dependent on the total dose, half-life and MIC**

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AUC *vs* peak and trough

<u>In a given schedule</u>,

- **peak** and **trough** levels, and
- **AUC**

are <u>directly</u> correlated

- to one another
- to the dose
- to the inverse of the clearance

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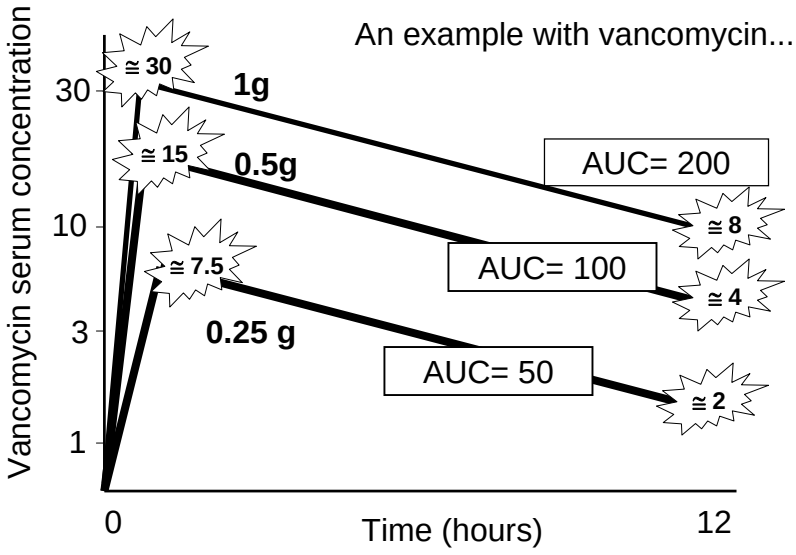
Peak, trough, and AUC are interelated...



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Glycopeptides dosing recommendations at the Cliniques Saint-Luc

Vancomycin

start with 1 g / 12 h and then:

- ➔ peak (t_0) 25-35 mg/L
- ➔ trough 5-10 mg/L
- ➔ AUC ≅ 200 mg/L x h^{-1}
  AUC_{24h} ≅ 400 mg/L x h^{-1}

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Vancomycin Outcomes *vs* MIC and AUC/MICs

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

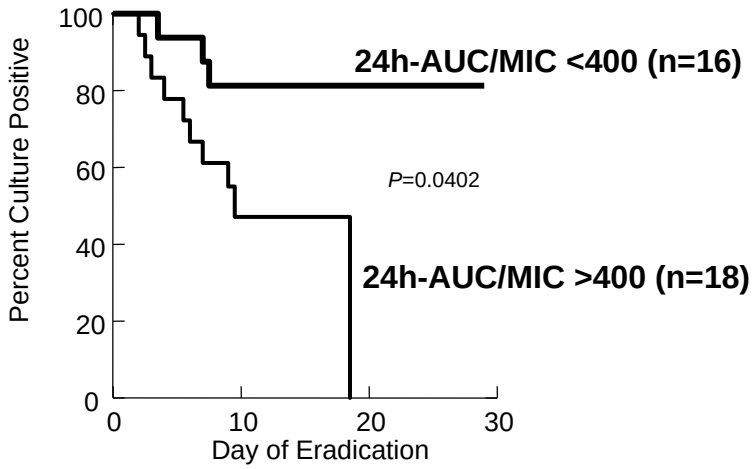
[a] $p < 0.001$
[b] $p < 0.005$

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

Vancomycin 1g every 12h (normal adult)
PK/PD parameters for 1g every 12h

MIC	Peak/MIC	24h-AUC/MIC	
1	30	400	
2	15	200	
4	7.5	100	
8	3.75	50	

Vancomycin "time to eradication" in MRSA Infections



Moise, Forrest & Schentag. Submitted, 2000.

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Vancomycin /Teicoplanin PK/PD parameters taking into account protein binding

	protein binding (%)	half life (h)	24h-AUC * total mg/L xh^{-1}	24h-AUC * "free" ** mg/L xh^{-1}	MIC max * mg/L
vancomycin (1g / 12h)	10- 50 %	6	400	≅ 200	≅ 1- 2
teicoplanin (6 mg/kg in 24h)	90	> 40	560	≅ 56	≅ 0.5

* values directly proportional to the dose

** *in vitro* and animal PK/PD studies of most antibiotics show that only free drug is active

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Teicoplanin recommanded levels

- **common indications : trough > 10 mg/l**
  ⇨ **6 mg / (kg x d)**
- **for *S. aureus* septicemia, *S. aureus* endocarditis, osteoarthritis, …**
  trough > 20 mg/l ⇨ 12 mg / (kg x d)
- **if every other day ⇨ 18 mg / kg every 48 h**

Conclusions (1/3) ...

- **Both vancomycin and teicoplanin should be used restrictively !!**
- **If needed, both should be administered correctly**
- **Monitoring is beneficial if associated with a full PK analysis**
  - **avoidance/correction in errors of administration**
  - **decreased incidence of side effects**
  - **increased efficacy**

True monitoring is never a single determination !!