# Continuous infusion Pharmacology and Microbiology
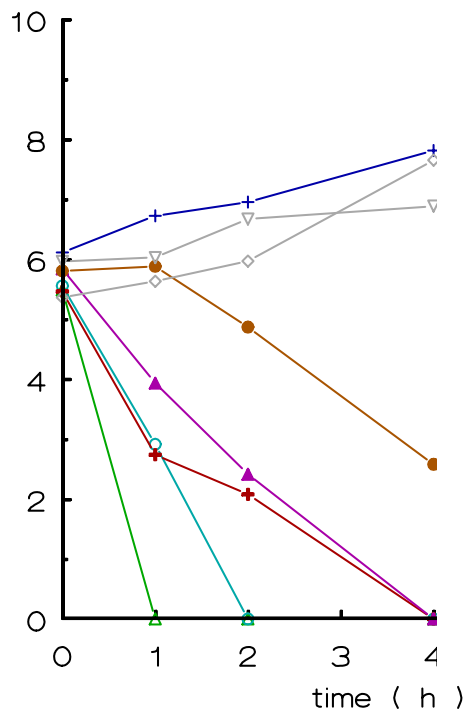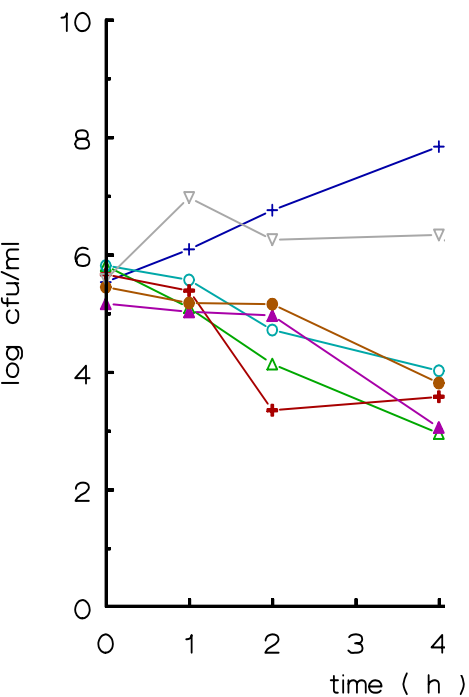


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# Patterns of activity:
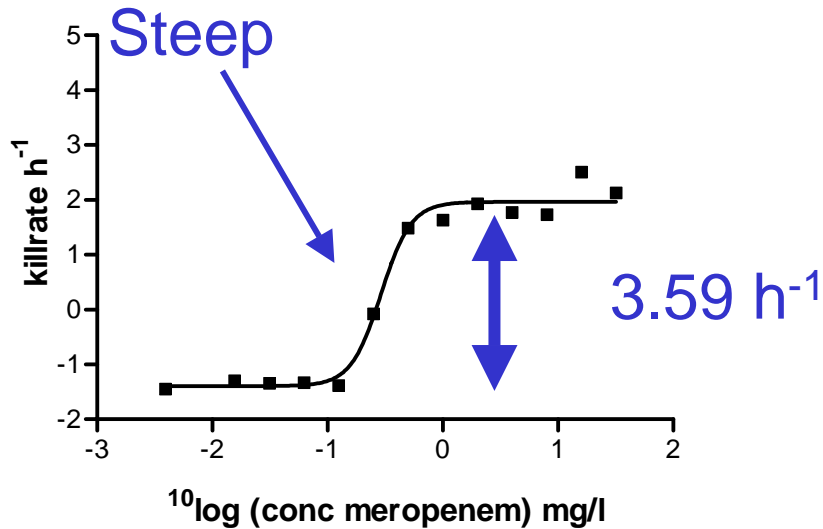# Kill curves of  P. aeruginosa



ceftazidime

tobramycin

Legend:
- — + — controle
- — △ — 32 ∗ MIC
- — ○ — 16 ∗ MIC
- — + — 8 ∗ MIC
- — ▲ — 2 ∗ MIC
- — ● — 1 ∗ MIC
- — ▽ — 0.5 ∗ MIC
- — ◇ — 0.25 ∗ MIC

# T$_{>MIC}$ related      AUC related

**meropenem**

Steep

**tobramycin**

Shallow

3.59 h$^{-1}$

13.4 h$^{-1}$
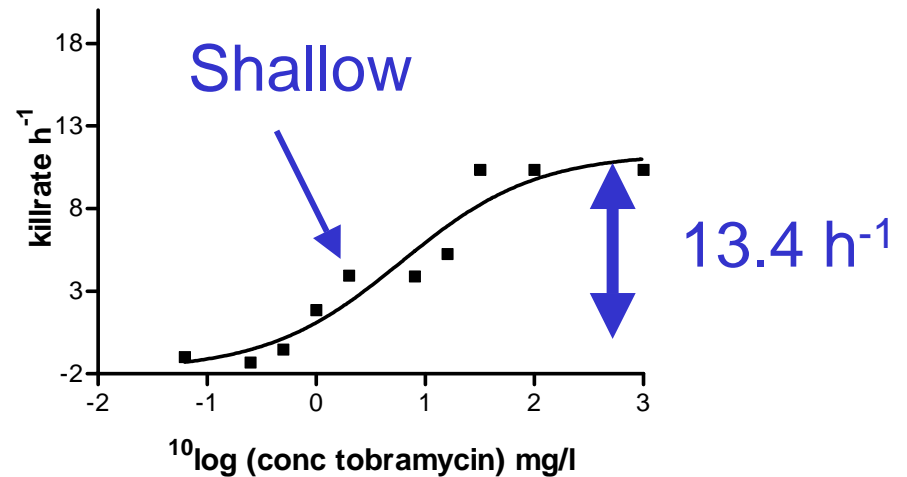
γ **high :  steep slope**
            **'concentration independent'**
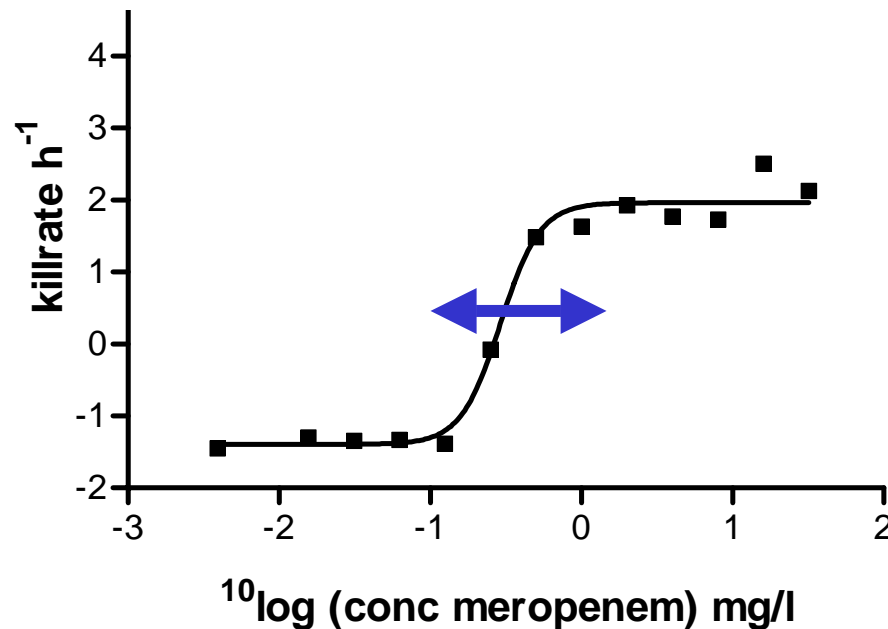
γ **low:    shallow slope**
            **'concentration dependent'**

Hill equation

$$E = E\max . \frac{C^{\gamma}}{C^{\gamma} + EC^{\gamma}_{50}}$$

# The difference in concentration between Max effect en no effect is small

# Aim for concentrations at max effect

Although the concentration effect relationships indicates antimicrobial effect is reached above a certain concentration , this concentration needs to be related to the MIC

# Relationship between Stationary Concentration and MIC of meropenem
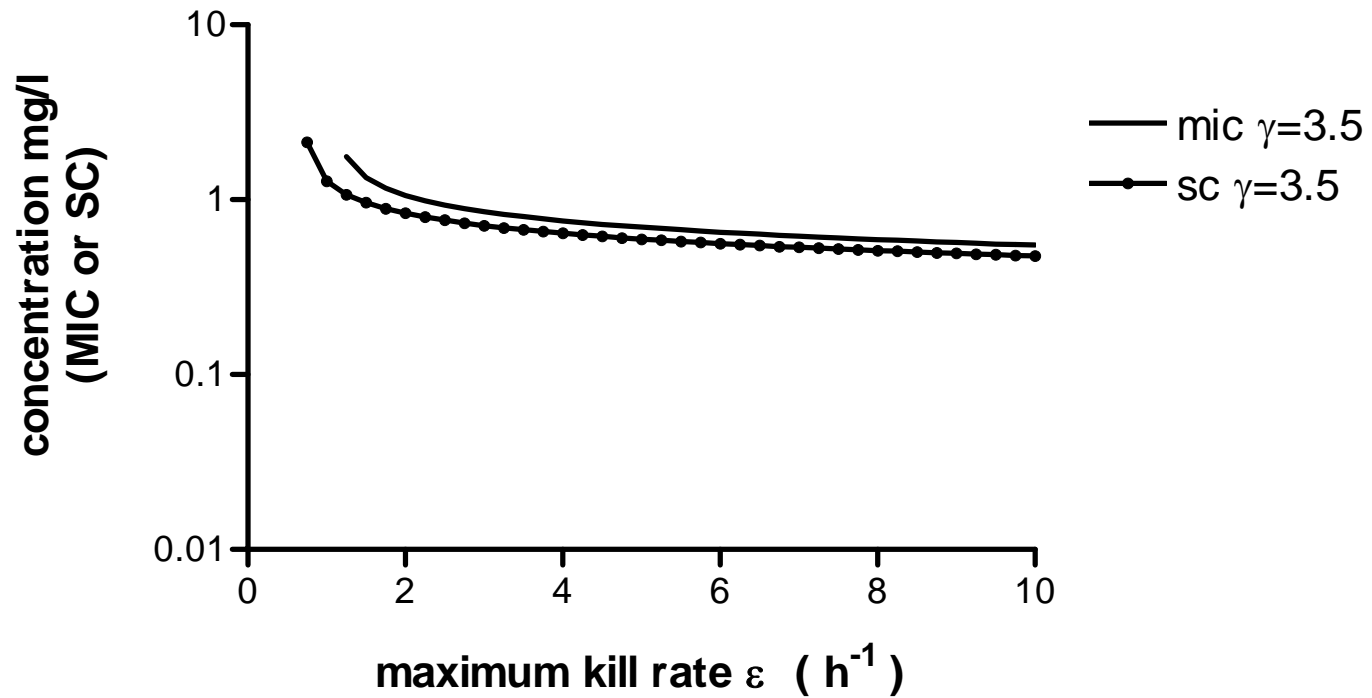


*Fig 2*

Using continuous infusion and maintaining a concentration above the SC or MIC should result in optimal treatment effect
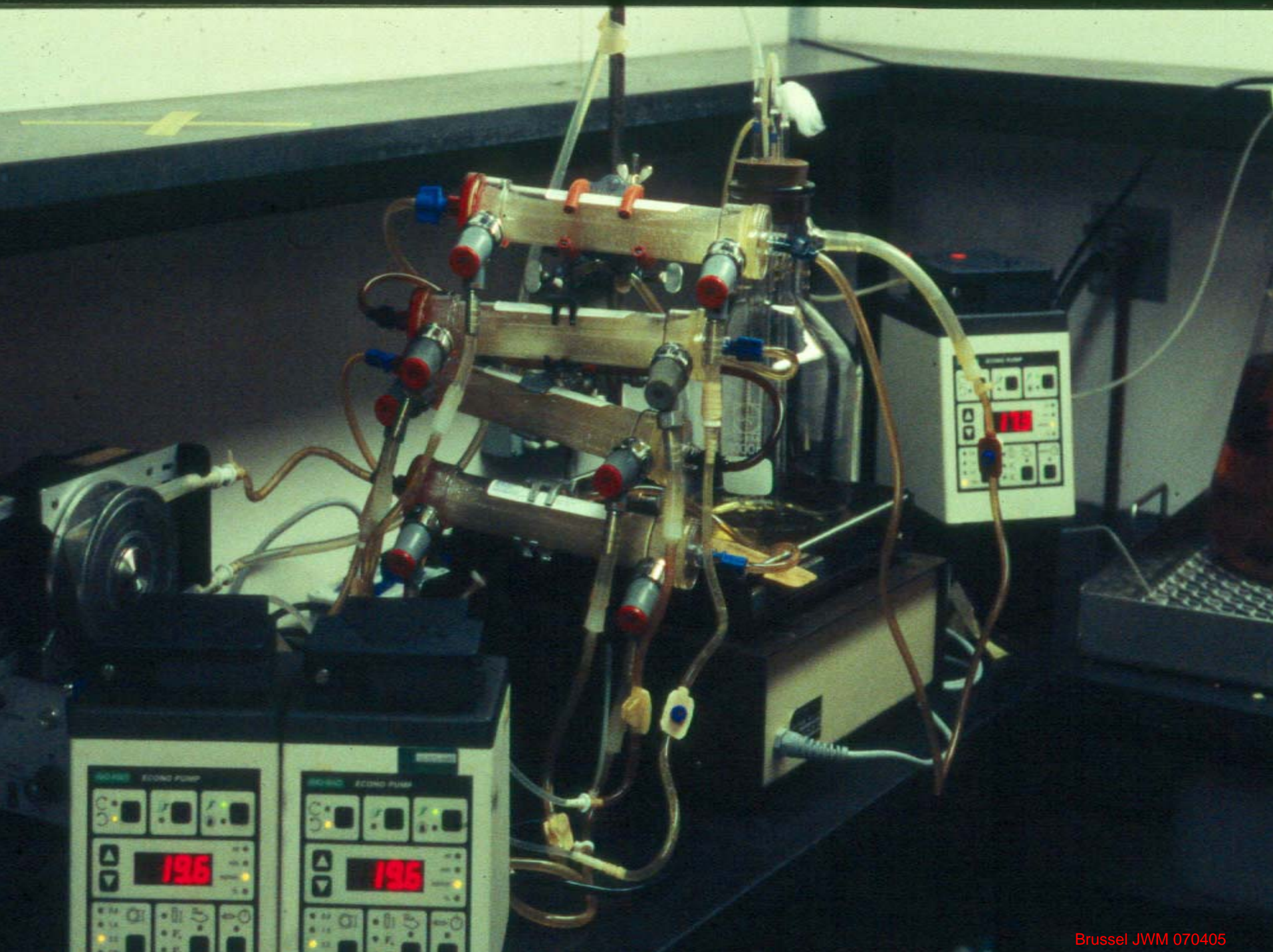
TABLE 2. Changes in bacterial concentrations during treatment with intermittent and continuous dosing regimens of ceftazidime[a]

| Strain (MIC, mg/liter) | Interval (h) | Change in bacterial concn[b] | | |
|---|---|---|---|---|
| | | Intermittent | Continuous | Difference |
| ATCC 27853 (1) | 8 | 3.3 | 3.7 | 0.4 |
| | 32 | 0.7 | 2.9 | 2.2[c] |
| CF4 (4) | 8 | 3.3 | 3.6 | 0.3 |
| | 32 | 1.1 | 3.9 | 2.8[d] |
| CF16 (16) | 8 | 2.8 | 1.3 | −1.5 |
| | 32 | −2.9 | −3.2 | −0.3 |

[a] Changes between 0 and 8 h (after one dosing interval) and 0 and 32 h (after 4 dosing intervals).

[b] Given as change in $\log_{10}$ CFU per milliliter between $t = 0$ h and $t = 8$ h or $t = 32$ h (geometric mean of at least two experiments).

[c] $P < 0.05$ for the strains not producing β-lactamase.

[d] $P < 0.05$.

Mouton & Den Hollander AAC 1994 38:931

# Efficacy of Continuous vs Intermittent infusion

|  |  | PD50 mg/kg/day | |
|---|---|---|---|
|  |  | intermittent | continuous |
| normal | 5h | 0.35 | 0.36 |
|  | 34h | 3.5 | 1.08 |
| neutropenic | 5h | 24.4 | 1.52 |

Roosendaal et al. 1986, AAC 30:403; Roosendaal et al. 1985, JID 152:373

# Efficacy in Relation to MIC

CI ceftazidime, *K. pneumoniae* rat pneumonia 5h after infection

| Scheme | | Dose mg/kg/day | Concentration mg/L | Conc/MIC |
|---|---|---|---|---|
| PD100 | normal | 0.94 | 0.06 | 0.3 |
| | leukopenic | 3.75 | 0.38 | 1.9 |
| PD50 | normal | 0.36 | 0.04 | 0.2 |
| | leukopenic | 1.52 | 0.17 | 0.85 |

Roosendaal et al. 1986, AAC 30:403

# Efficacy in Relation to MIC
## continuous infusion ceftazidime, K. pneumoniae rat pneumonia

| Scheme | Condition | Infection duration | Dose mg/kg/day | Concentration mg/L | Conc/MIC |
|---|---|---|---|---|---|
| PD100 | normal | 5h | 0.94 | 0.06 | 0.3 |
| | | 34h | 15 | 1.52 | 7.6 |
| | leukopenic | 5h | 3.75 | 0.38 | 1.9 |
| PD50 | normal | 5h | 0.36 | 0.04 | 0.2 |
| | | 34h | 1.08 | 0.12 | 0.60 |
| | leukopenic | 5h | 1.52 | 0.17 | 0.85 |

Roosendaal et al. 1986, AAC 30:403; Roosendaal et al. 1985, JID 152:373

# Target Concentration
## continuous infusion

- Maximum effect time-kill at 4 x MIC

- Maximum effect in vitro model 4 x MIC (Mouton et al 1994)

- Effect in endocarditis model 4 x MIC (Xiong et al 1994)

- Effect in pneumonia model dependent on severity of infection    (Roosendaal et al 1985,86)

Ceftazidime concentrations ICU patients

Normogram Continuous

Mouton & Vinks, JAC 1996

Brussel JWM 070405
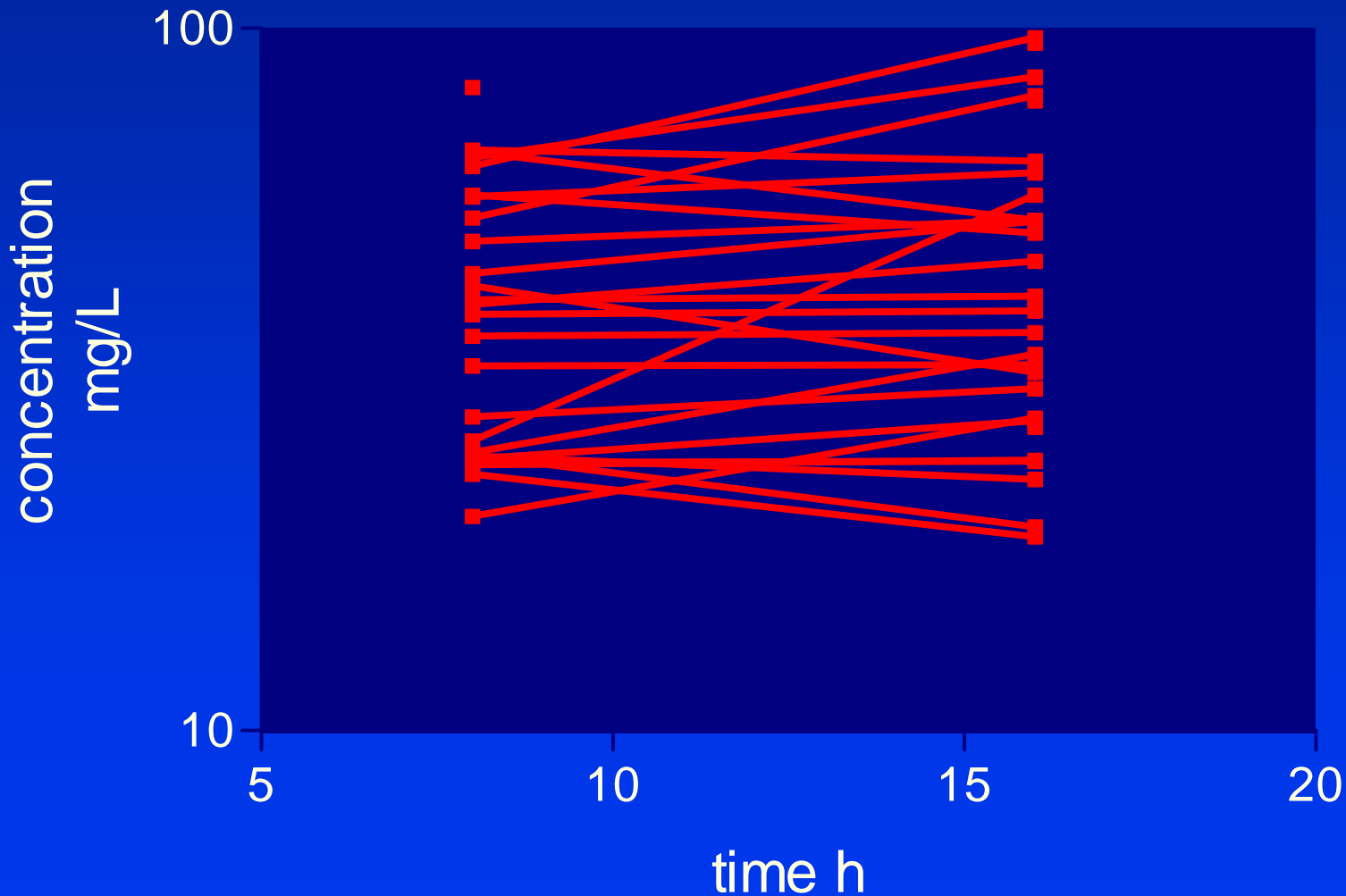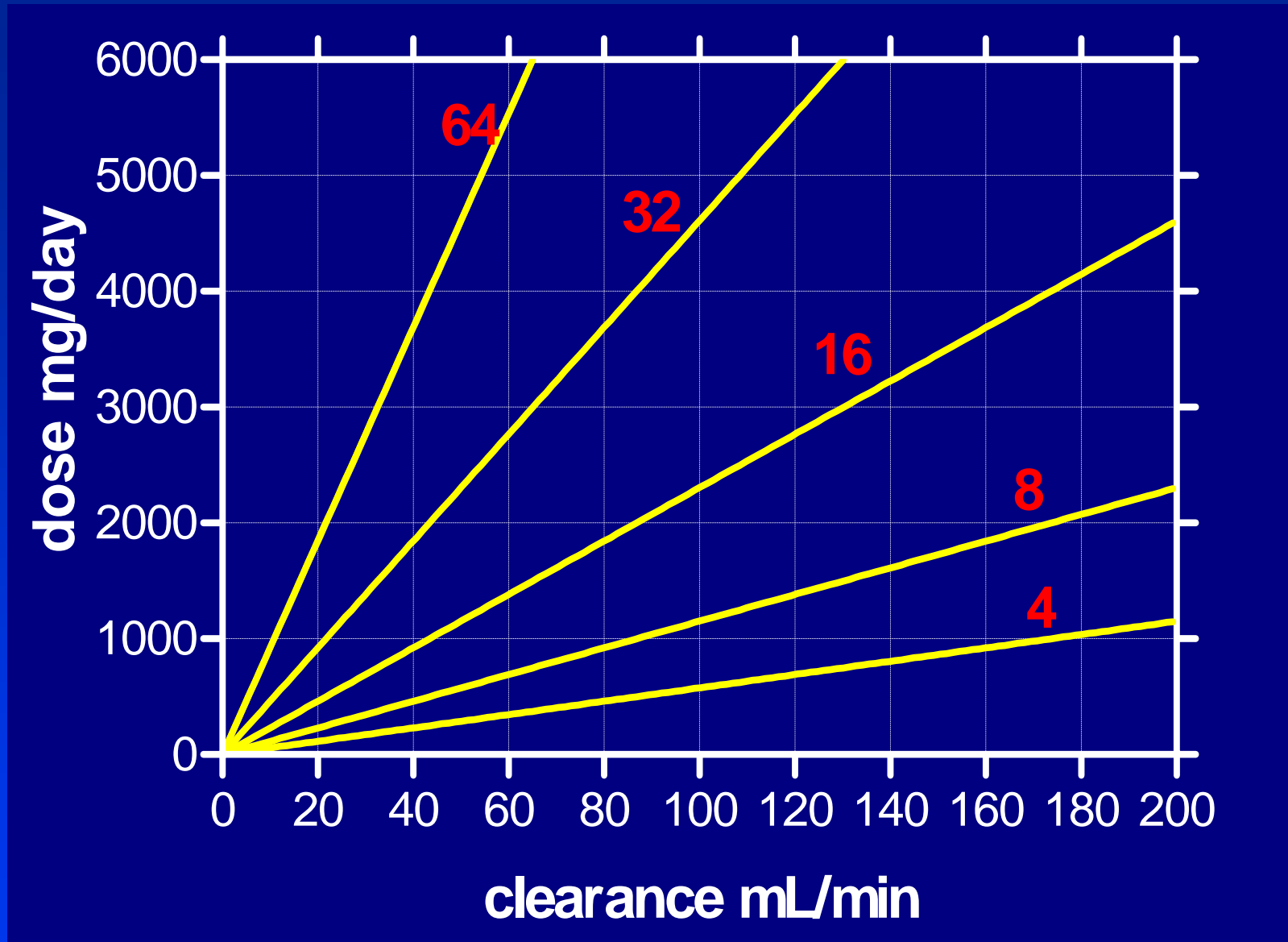
# Continuous infusion of beta-lactams seems to be more effective