Pharmacokinetics as applied to *in vitro* and animal models

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Topics

- In vitro pharmacodynamic models
  - Post-antibiotic effects (PAE) – effects that continue after antibiotic removal or when antibiotic concentration is subinhibitory
  - Chemostat models – antimicrobial effect in the presence of a varying drug concentration – drug variation simulates variation over time of drug concentration in blood or site of infection
- Value of animal models
  - Differences between virulence of pathogens in humans vs animals
  - Difference in pharmacokinetics between humans and animals, and how these can be modified in animals
- Extrapolation of results of in vitro PD models and animal models to human infections

Chemostat PK/PD models

- In a one-compartment model the antimicrobial agent is added to a central compartment containing medium and antibiotic
- Medium is displaced by pumping in fresh medium at a fixed rate
- This simulates first order pharmacokinetic clearance and half-life and results in an exponential decrease in drug concentration
- Disadvantage of this system is that bacteria are eliminated from the central compartment as well – can be prevented using membrane filter or compensated for mathematically

Ryback et al: Ch 3 in Antimicrobial Pharmacodynamics in Theory and Clinical Prectice, eds Nightingale CH, Murakawa T, Ambrose PG. 2002. Marcel Decker, NY

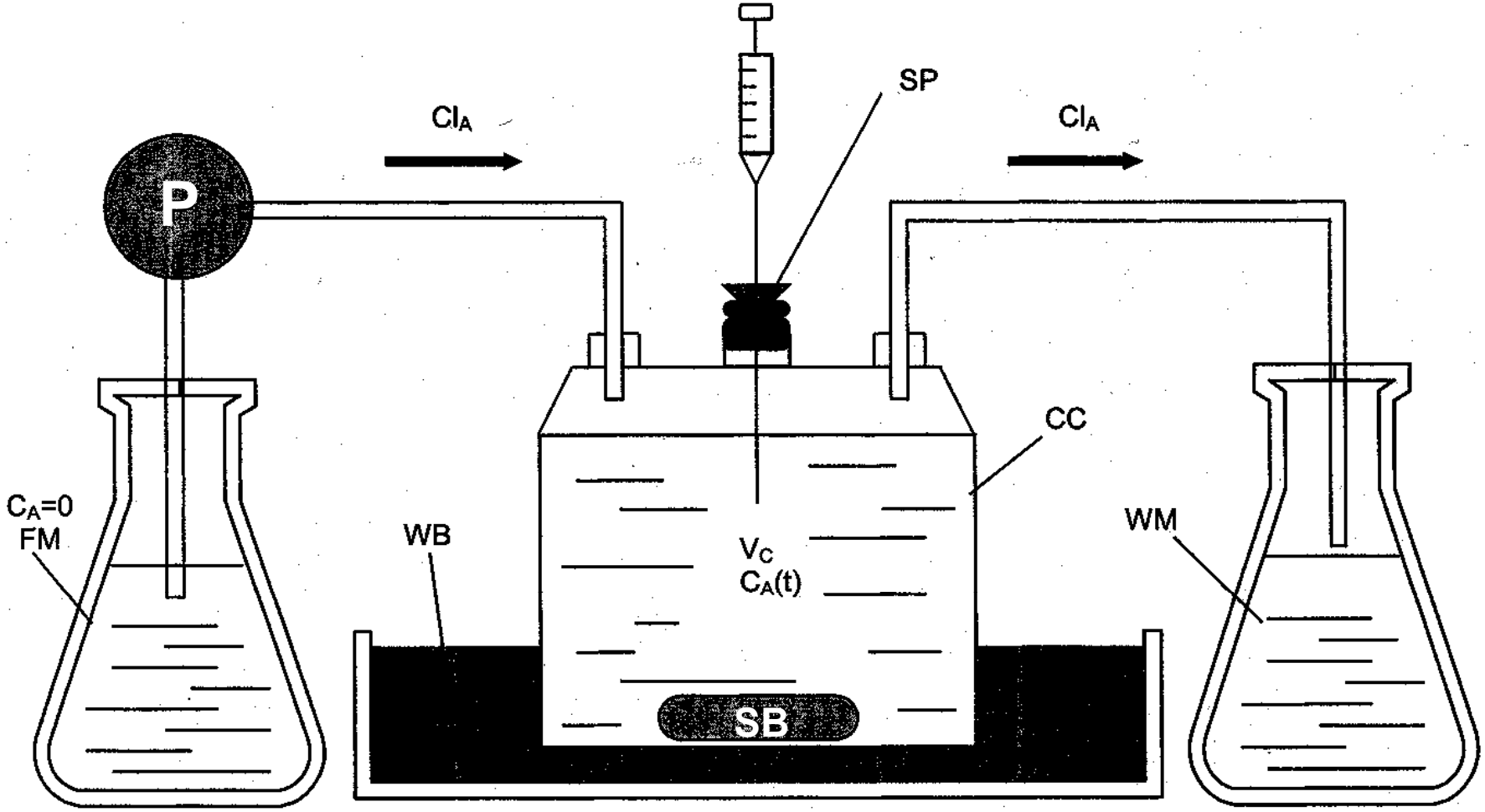
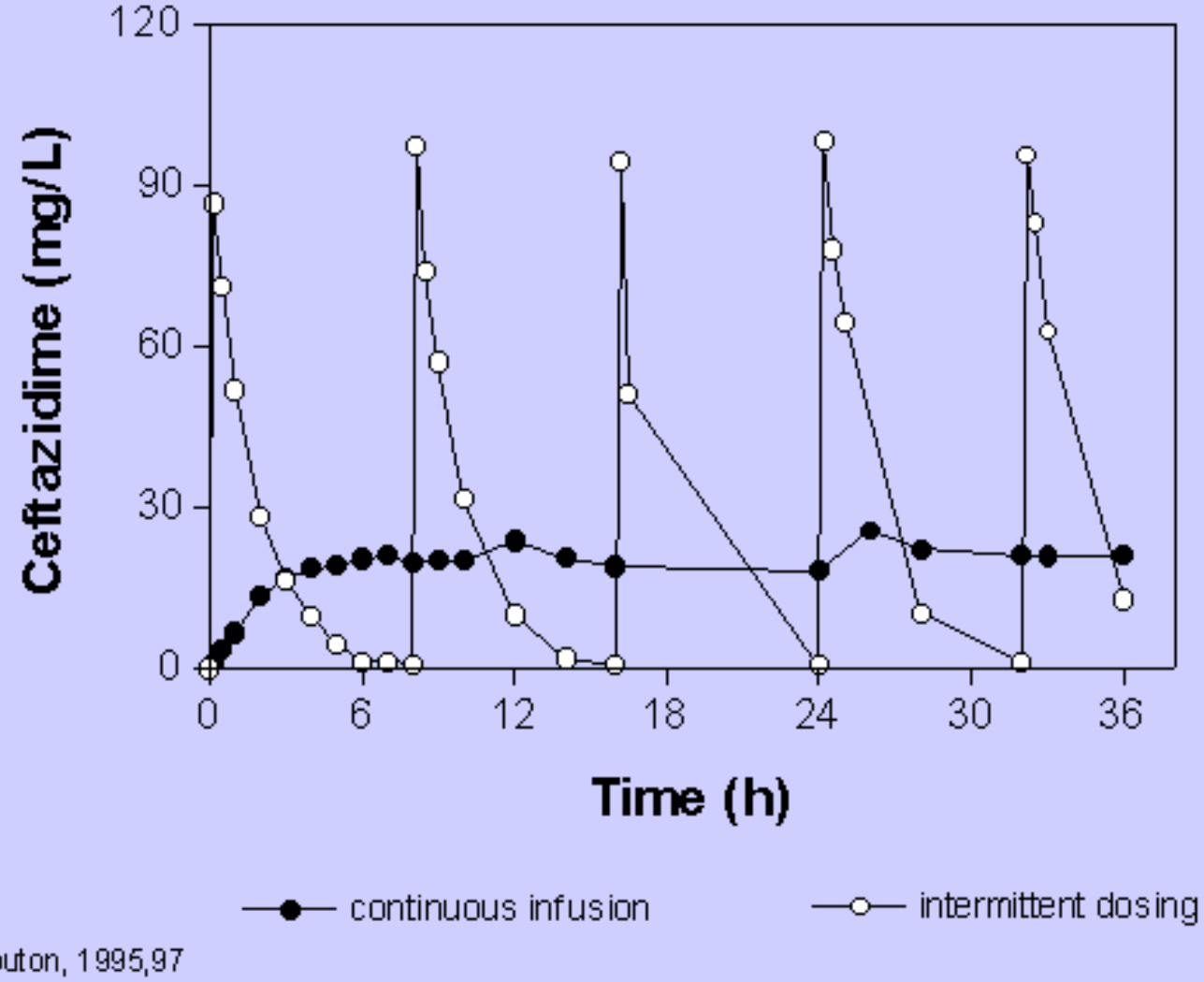


FIGURE 1 One-compartment model. The bacterial inoculum and antibiotic are introduced into the central compartment. C_A = concentration of antibiotic A, CC = central compartment, Cl_A = clearance of antibiotic A, FM = fresh medium, P = peristaltic pump, SP = sampling and injection port, V_C = volume of distribution of antibiotic A, SB = magnetic stir bar, WB = water bath (37.5°C), WM = waste medium.

Ryback et al: Ch 3 in Antimicrobial Pharmacodynamics in Theory and Clinical Prectice

Chemostat model – drug concentrations achieved



Mouton, 1995,97

Chemostat model example

- To simulate QD dosing in humans, an initial bolus of cefdinir was injected into the chemostat at time zero (achieving a peak concentration of 3 mg/liter), whereas for BID dosing, boluses were instilled at time zero and at h 12 (achieving a peak concentration of 1.6 mg/liter).

- Targeted concentrations were derived from reported data on human cefdinir pharmacokinetics. Although 60 to 70% of cefdinir is protein bound, we chose to simulate total serum concentrations in the model, as the significance of protein-binding values below 85 to 90% and the effect on tissue penetration and clinical impact are unclear .

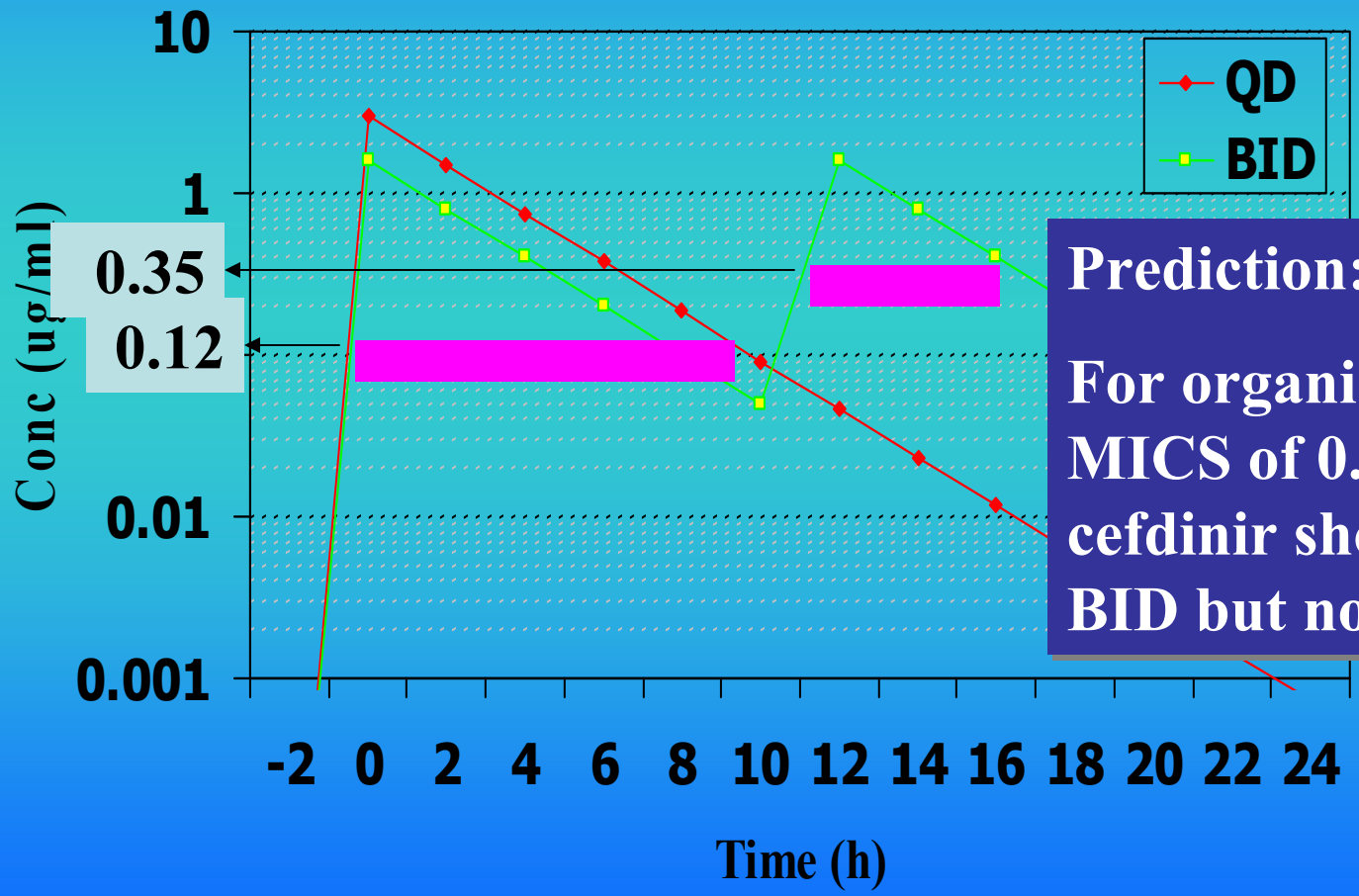
- By pumping of antibiotic-free medium into the system at a rate of 1.7 ml/min with a peristaltic pump, an equal volume of antibiotic-containing medium was displaced.

- This resulted in the simulation of a monoexponential pharmacokinetic process that was adjusted to attain the desired cefdinir half-life of 2 h.

Ross et al. AAC 2001, 45:2936-8

Comparison of Once-Daily versus Twice-Daily Administration of Cefdinir – concentrations achieved in chemostat

Standard dosing – 600 mg/d or 14 mg/kg/d



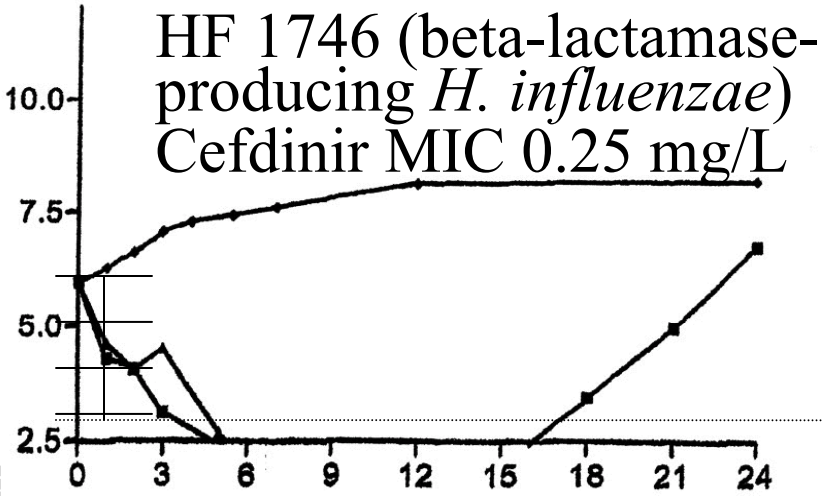
Prediction:

For organisms with MICS of 0.25 mg/L, cefdinir should work BID but not QD

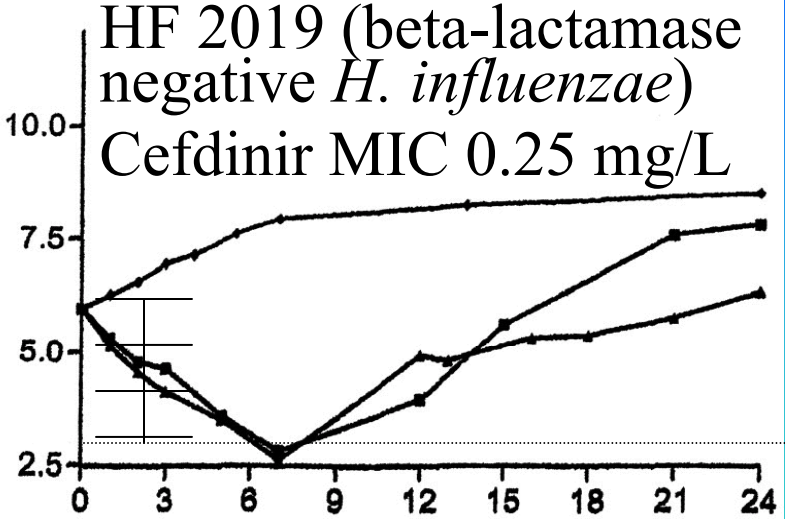
Adapted from Ross et al. AAC 2001, 45:2936-8

Activity of cefdinir in chemostat at dose of 600 mg QD (●) and 300 mg BID (🚌)
Growth controls are represented by the symbol ▲

HF 1746 (beta-lactamase-producing *H. influenzae*) Cefdinir MIC 0.25 mg/L

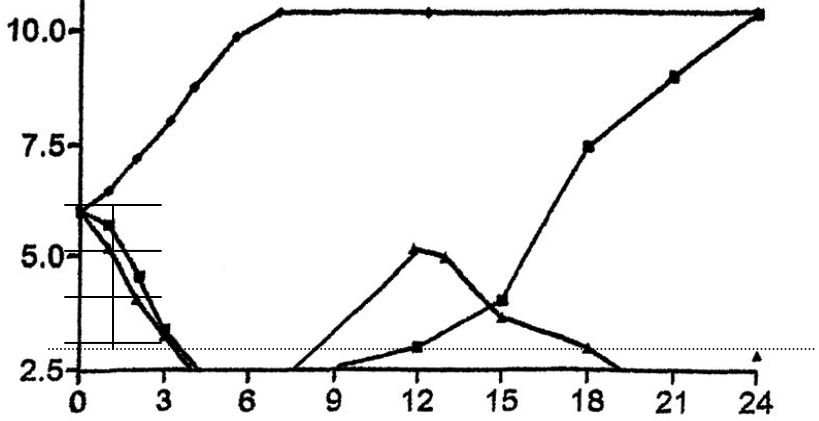


HF 2019 (beta-lactamase negative *H. influenzae*) Cefdinir MIC 0.25 mg/L

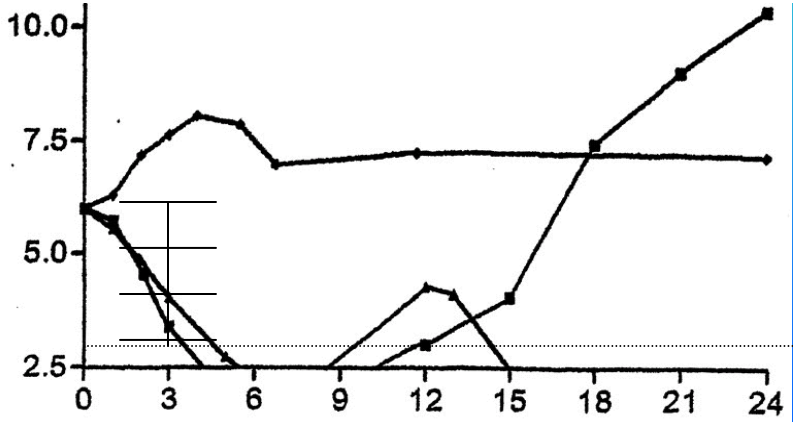


Log_{10} cfu/ml

SP30 (penicillin-sensitive *S. pneumoniae*) penicillin MIC <0.06 mg/liter (C). Cefdinir MIC 0.25 mg/L



S-53 (penicillin-intermediate *S. pneumoniae*) penicillin MIC 0.25 mg/liter (D). Cefdinir MIC 0.5 mg/L



Ross et al. AAC 2001, 45:2936-8

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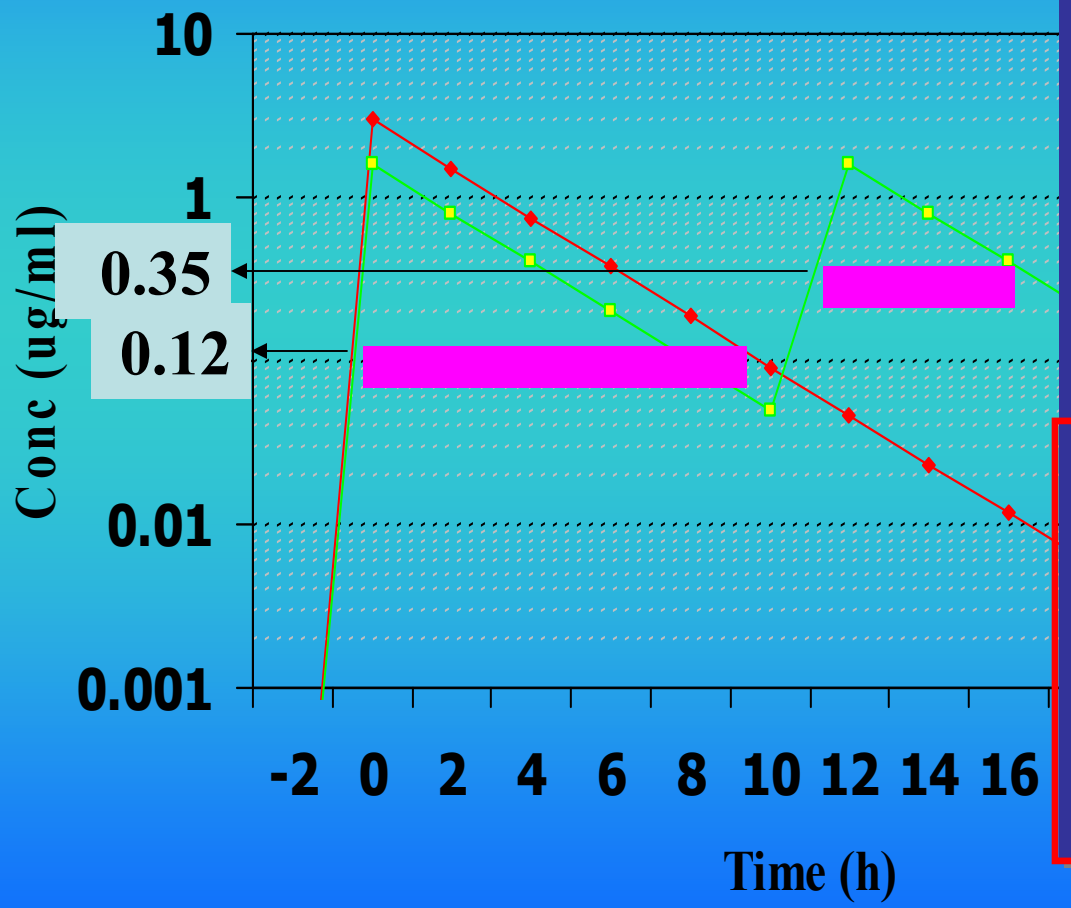

Prediction:

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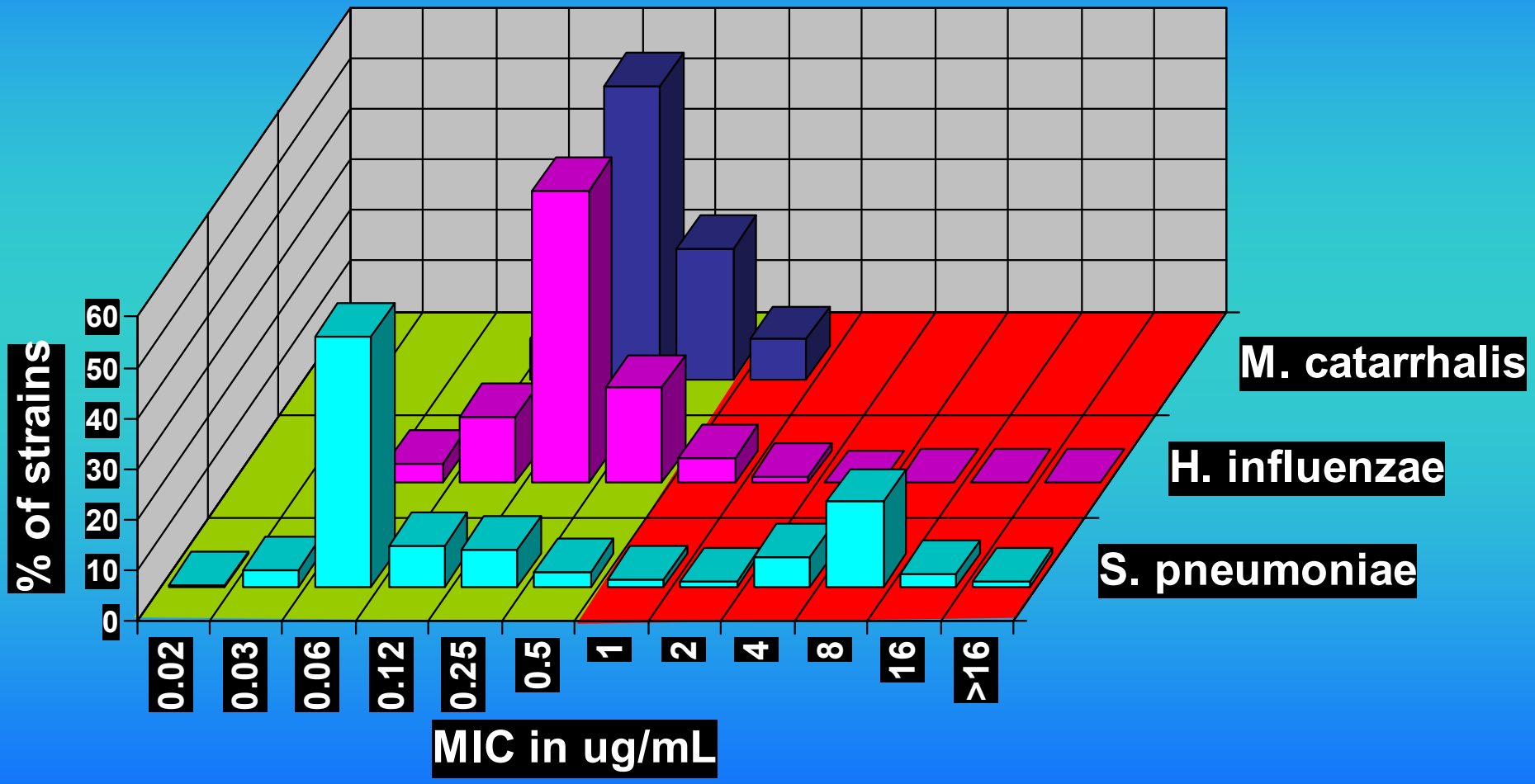
Findings:

Cefdinir was bactericidal for 3 of 4 isolates BID and for 0/4 isolates QD

Adapted from Ross et al. AAC 2001, 45:2936-8

Cefdinir

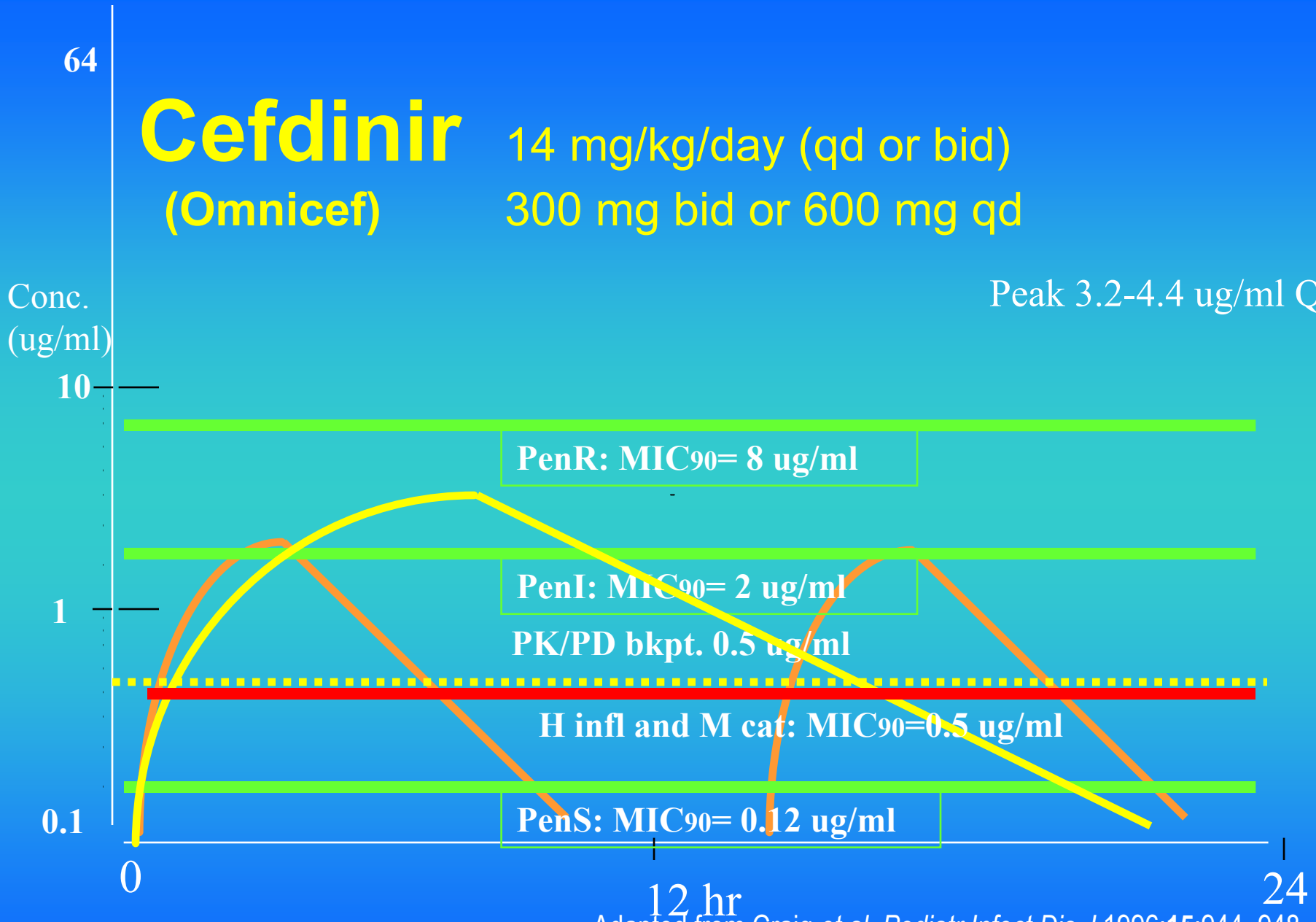


Alexander Project USA 2000: S. pneumoniae (n=1362), H. influenzae (n=634), M. catarrhalis 2000 (n=206)

Cefdinir
(Omnicef)

14 mg/kg/day (qd or bid)
300 mg bid or 600 mg qd

Peak 3.2-4.4 ug/ml QD



Adapted from Craig *et al. Pediatr Infect Dis J* 1996;**15**:944–948
and Jacobs *et al. Antimicrob Agents Chemother* 1999,**43**:1901–1908

Animal PK/PD models

Half-Lives in Mice and Humans

Drug	Half-life in Minutes	
	Mice	Humans
Penicillin G	5	30
Imipenem	8	60
Cefazolin	15	108
Gentamicin	18	150
Ciprofloxacin	32	240
Erythromycin	35	180
Minocycline	120	1080

WA Craig, 2002

Pharmacokinetics of Ciprofloxacin in Animals

Species	Dose	Cmax	T1/2	AUC
Mouse	5	1.5	0.52	1.8
Rat	5	1.2	1.2	2.2
Dog	5	1.5	3.0	4.8
Man	7	2.7	4.4	11

WA Craig, 2002

Ways to Reduce Clearance and Prolong Half-life

- Probenecid - reduces tubular secretion of beta-lactam antibiotics
- Renal impairment - can be induced in mice and rats by administering uranyl nitrate. Slows elimination of renally excreted drugs
- Increase protein binding of drugs eliminated primarily by glomerular filtration

WA Craig, 2002

Serum Protein Binding of Antimicrobials in Animals

Drug	Mice	Human
Cefonacid	78%	97%
Ceftiaxone	76%	95%
Cefditoren	87%	88%
Telithromycin	88%	60%

WA Craig, 2002

Other Factors to Consider with Pharmacokinetics in Animal Models

- Infection can significantly alter pharmaco-kinetics in animals. Usually get higher concentrations and larger AUCs
- Penetration of antimicrobials into fibrin can vary remarkably
- Drug conscentrations is extracellular fluid of tissues related to ratio of the surface area for diffusion and the volume of fluid.
- Good correlation in interstitial fluids with those in serum. Lower peak levels and higher trough levels in fluid collections

WA Craig, 2002

Correlation of Pharmacodynamic Parameters with Efficacy

- Use neutropenic murine thigh-and lung-infection models
- Evaluate 20-30 different dosing regimens (5 different total doses given at 4-6 different dosing intervals)
- Measure efficacy from change in Log_{10} CFU per thigh or lung at the end of 24 hours of therapy
- Correlate efficacy with various pharmacodynamic parameters (Time above MIC, peak/MIC, 24-Hr AUC/MIC)

WA Craig, 2002

Animal Models for Susceptibility Breakpoint Determinations

- Simulate human pharmacokinetics in animals (induce renal impairment with uranyl nitrate)
- Infect groups of animals with organisms with varying MICs
- Treat the animals for at least 24 hours with dosage regimen used to treat human infections
- Find the MIC value that separates bacterial killing from bacterial growth

WA Craig, 2002

PK/PD Parameters

- Is the magnitude of the parameter required for efficacy the same in different animal species?

  YES

- Does the magnitude of the parameter vary with:
  1. the dosing regimen? NO
  2. different drugs within the same class? NO
  3. different organisms ? Minimal
  4. different sites of infection (e.g. blood, lung, peritoneum, soft tissue)? NO

WA Craig, 2002

Conclusions

- Serum clearance of most antimicrobials is faster in animals than in man
- Serum protein binding is usually less in animals than in man
- The higher doses required for studies in animal models may result in non-linear kinetics
- Sensitive drug assays should be used to identify deep tissue compartments that could prolong activity against very susceptible organisms

WA Craig, 2002