MIC-based therapies

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MIC-based therapies

- Arguments pro
  - PK-PD principles of treatment
  - clinical practice guidelines (Belgium)
    - CAP
    - meningitis
  - other clinical indications
- Arguments contra
  - conceptual weaknesses
  - feasibility issues
- Conclusions

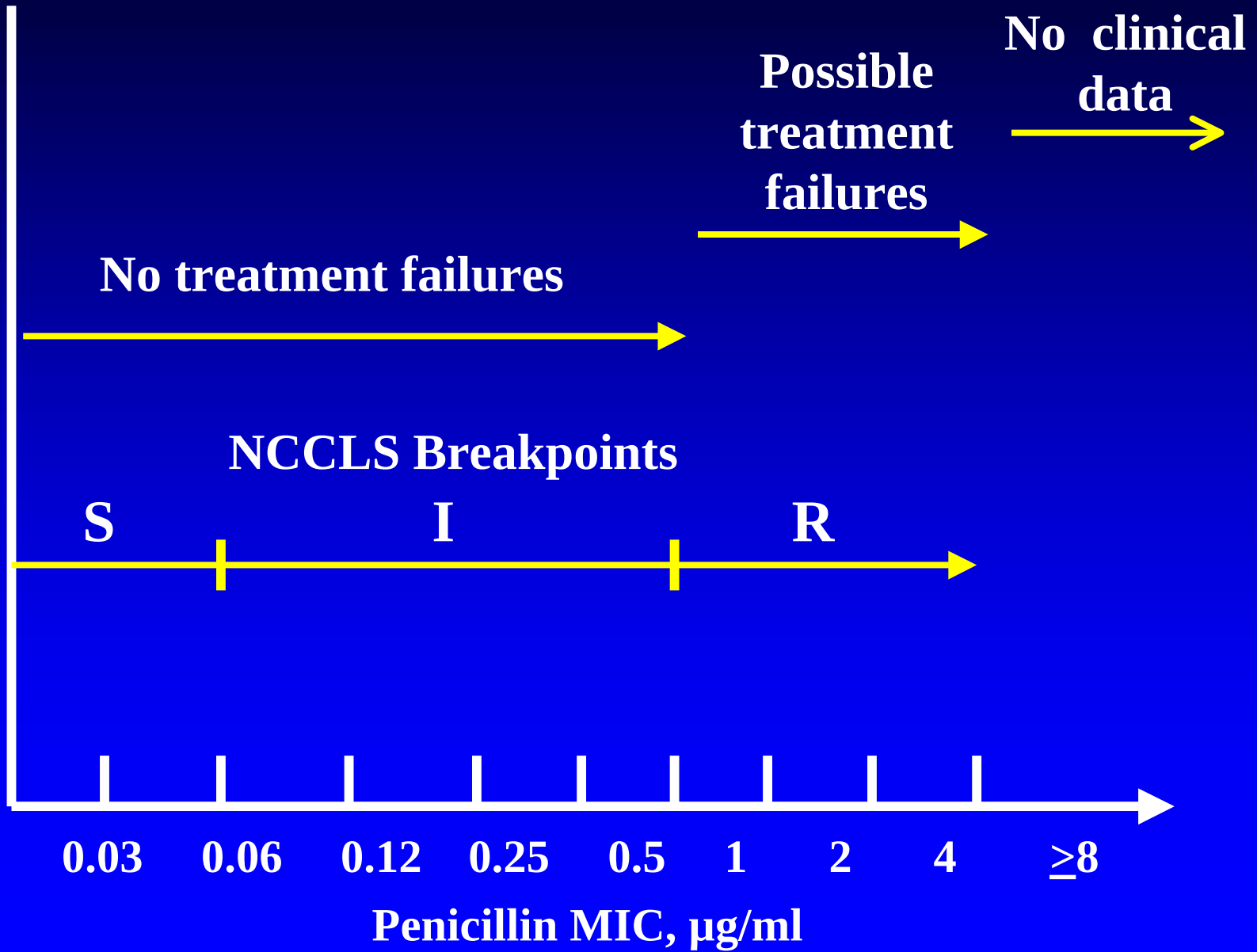
PK-PD principles of treatment

- Parameter of efficacy
  - max bactericidal effect in vitro / in vivo
  - bacteriological eradication
  - clinical cure
- Prevention of resistance
  - bacteriological persistence
  - mutation prevention concentration in vitro

PK-PD principles of treatment

- Time above MIC: beta-lactams
  macrolides
  oxazolidinones
- Peak / MIC: aminoglycosides
  fluoroquinolones
- AUC_{24h}/MIC: fluoroquinolones
  azithromycin and ketolides
  glycopeptides
  streptogramins

CAP: Peni-Resistance vs. Clinical Outcome

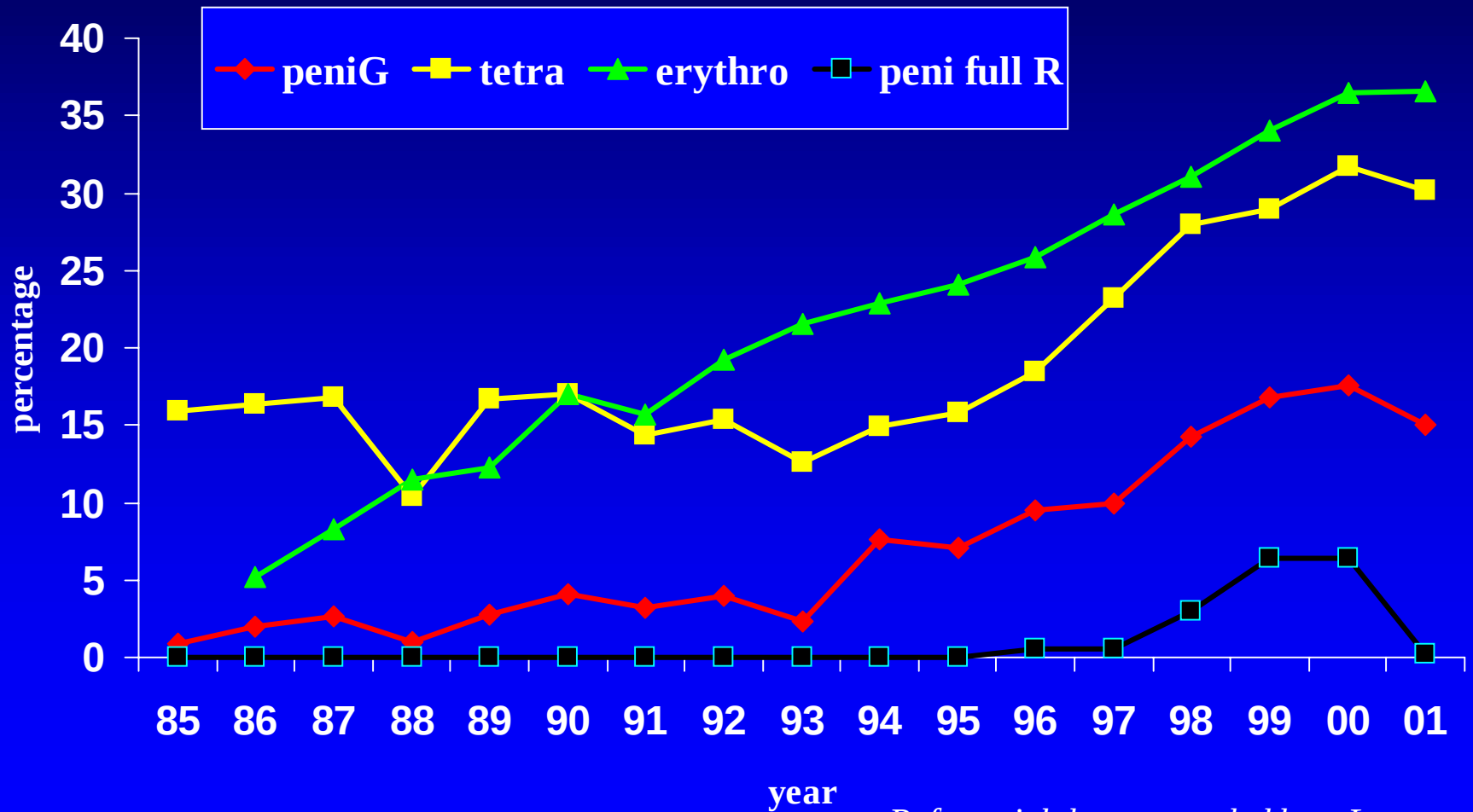


Antibiotic resistance (%) of Streptococcus pneumoniae (Belgium)

	2000 invasive (n=1216)	2001 invasive (n=1427)	2000-2001 mixed (n=341)
penicillin G	17.6	15.0	21.0
I + R	11.6 + 6.0	14.8 + 0.2	10.8 + 10.2
cefotaxime	5.7	0.5	7.3
erythromycin	36.5	36.6	30.3
tetracycline	31.7	30.2	38.5
ofloxacin / ciprofloxacin	0.3	0.1	11.2

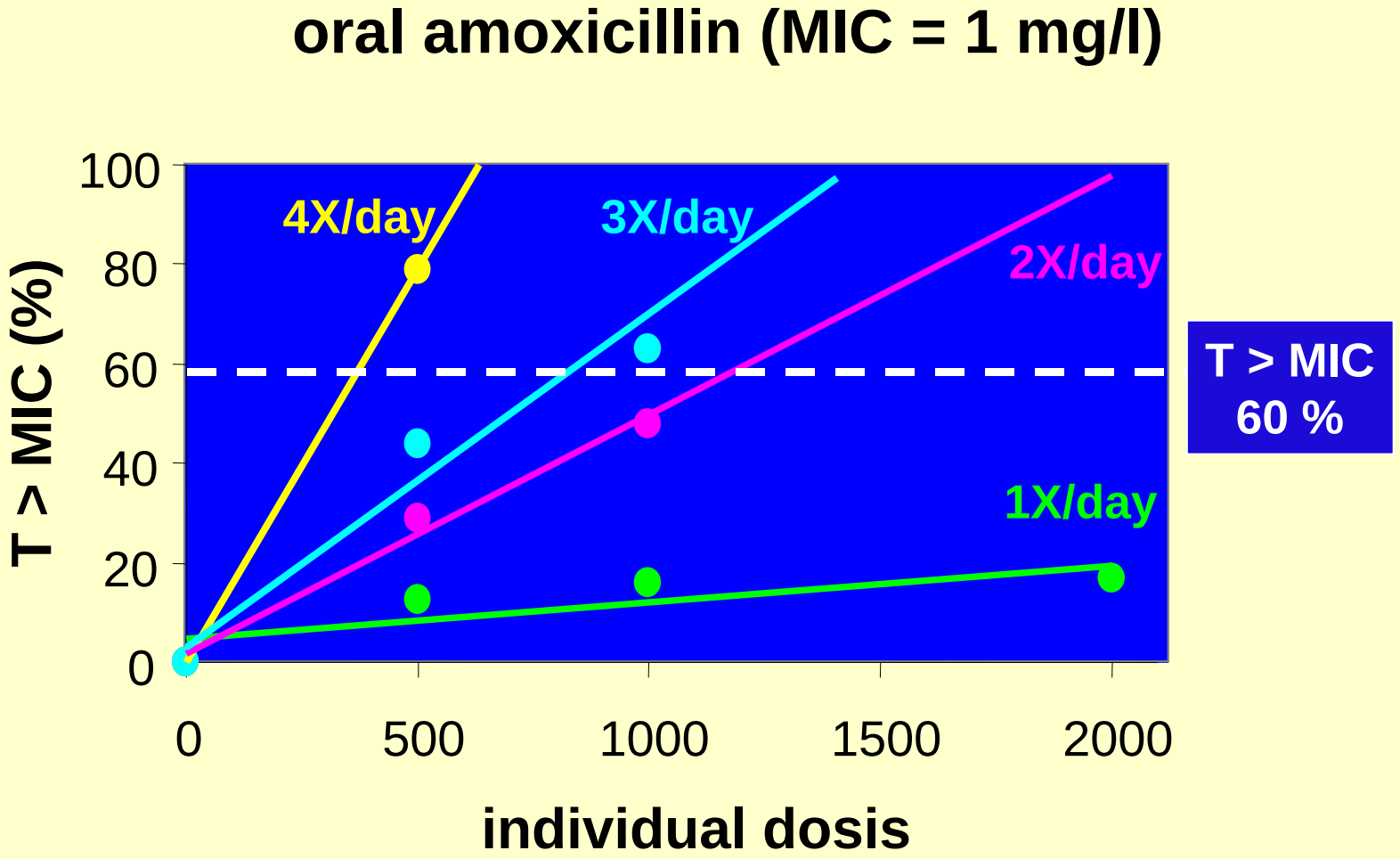
J. Verhaegen. National Reference Laboratory.
R. Vanhoof, et al. ECCMID 2002.

Evolution of *S. pneumoniae* resistance in Belgium

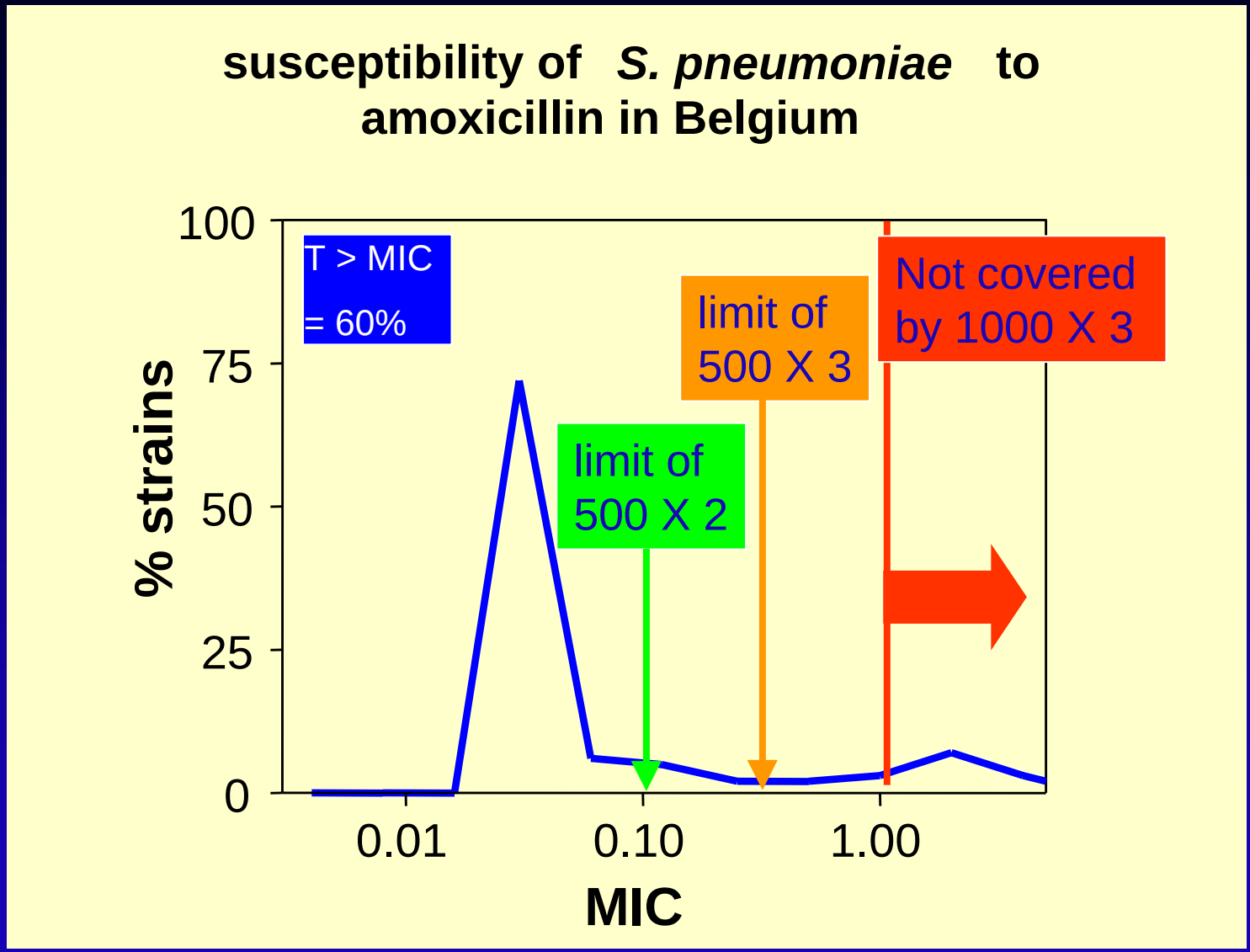


Referentielabo pneumokokken, Leuven

Optimizing dosage for beta-lactams

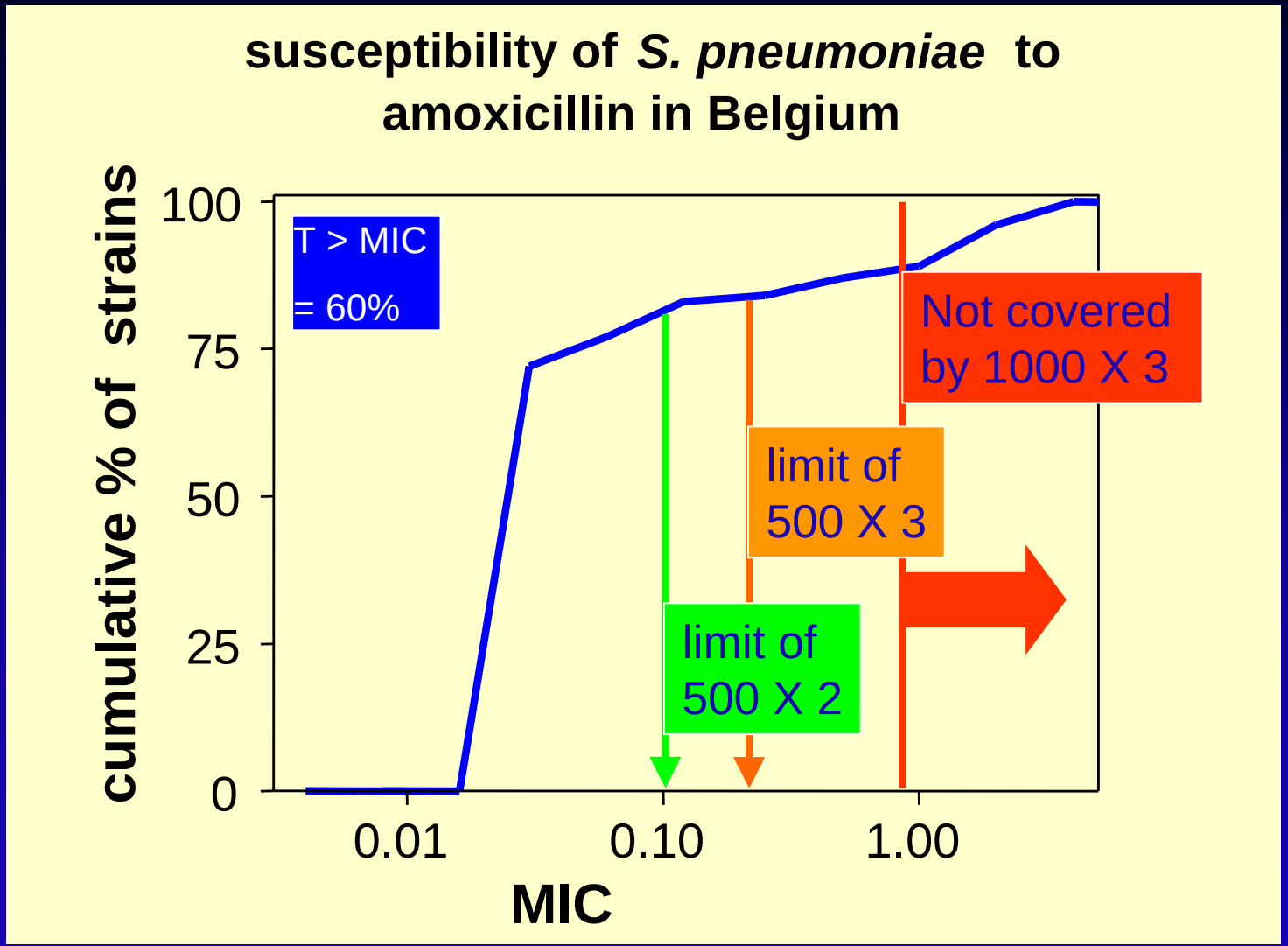


Amoxicillin dosage and resistance



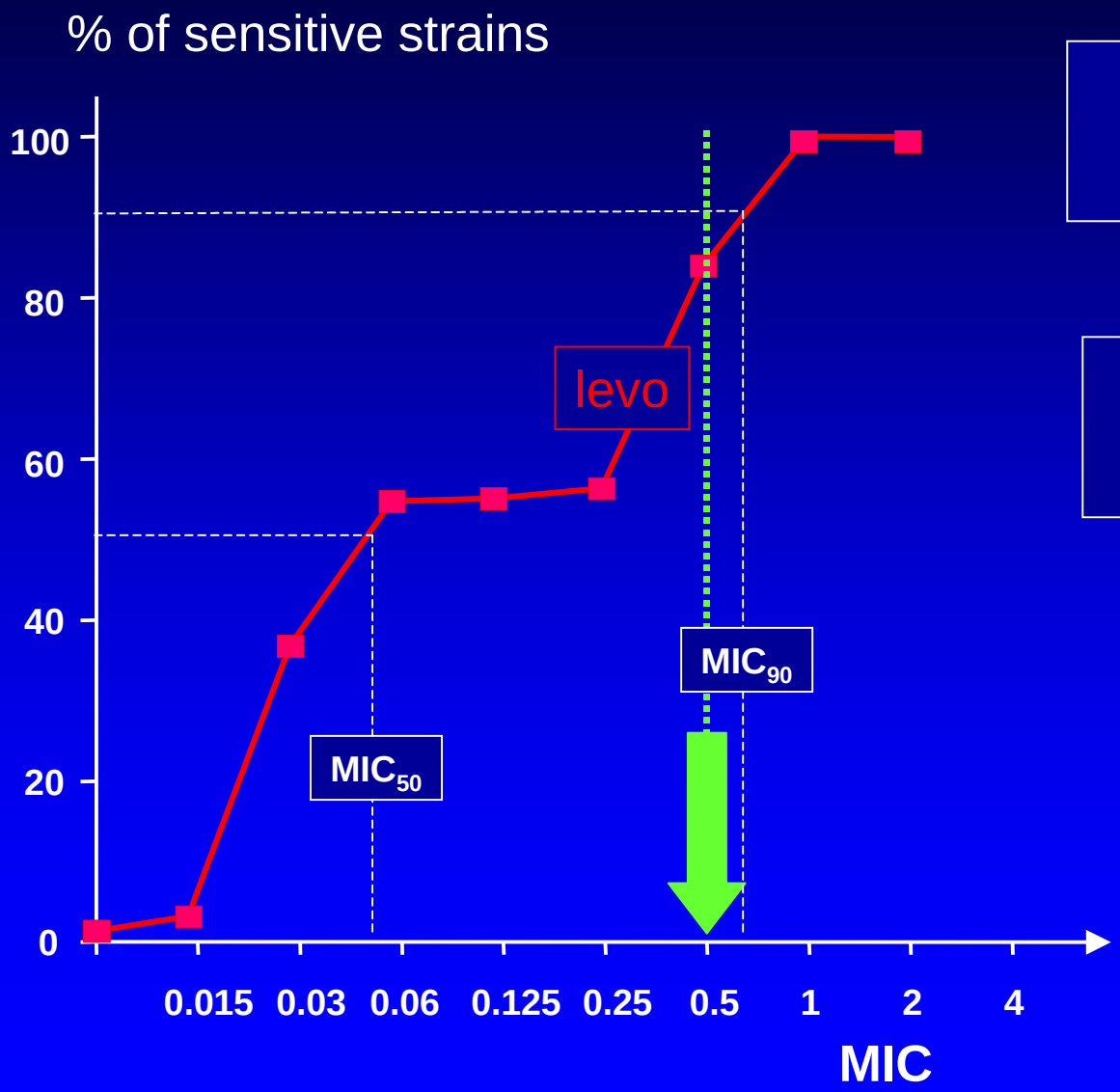
MIC data: J. Verhaegen et al., 2001.

Amoxicillin dosage and resistance



MIC data: J. Verhaegen et al., 2001.

PK-PD levofloxacin and S. *pneumoniae* in Belgium



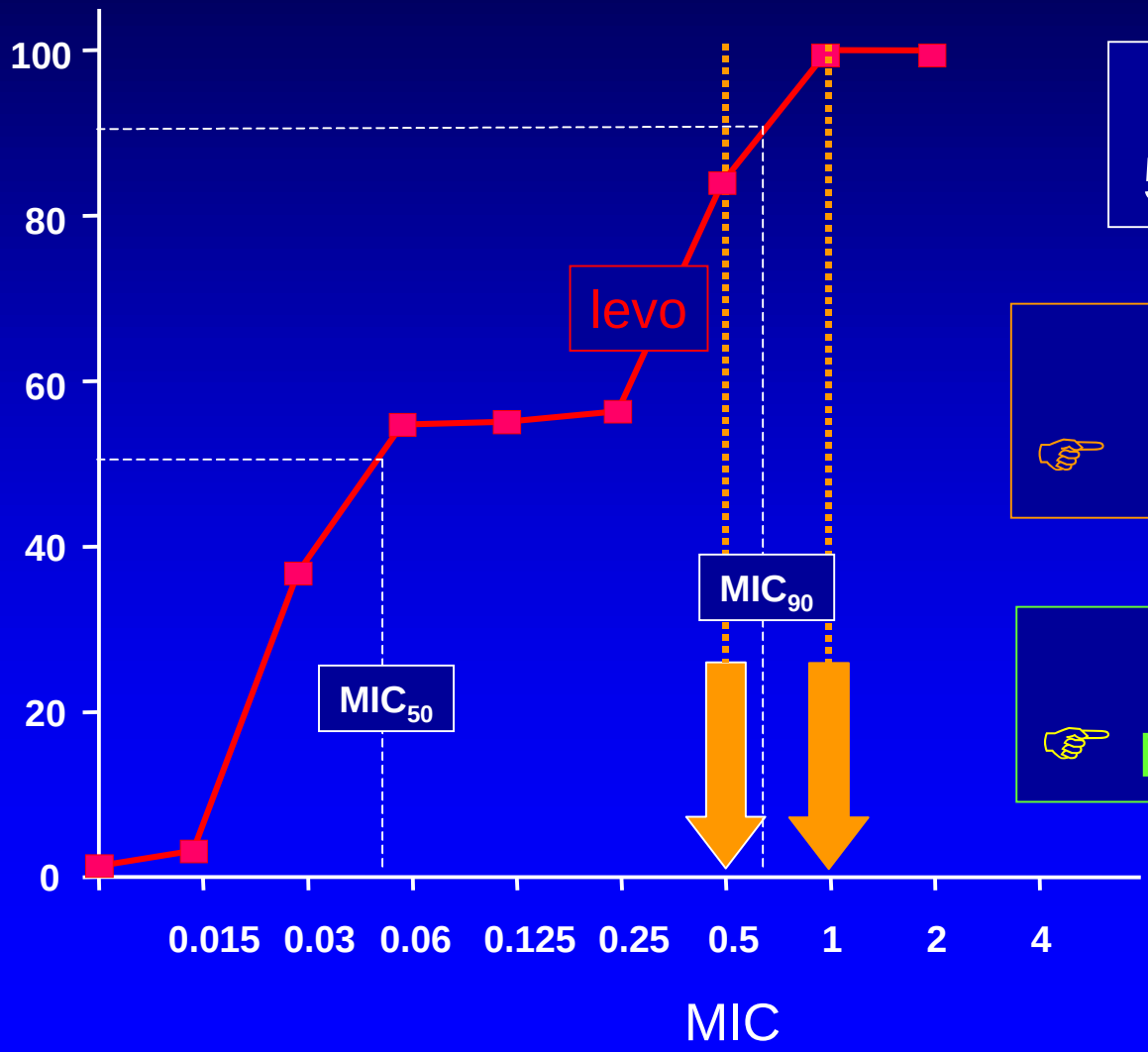
Levofloxacin
500 mg once-a-day

AUC = 47 (mg/l)xh
peak = 5 mg/l

☞ MIC_{max} = 0.5

MIC data: J. Verhaegen et al., 2001.

PK-PD levofloxacin and *S. pneumoniae* in Belgium



IDAB recommendation:

Levofloxacin
500 mg TWICE daily

AUC = 94 (mg/l)xh

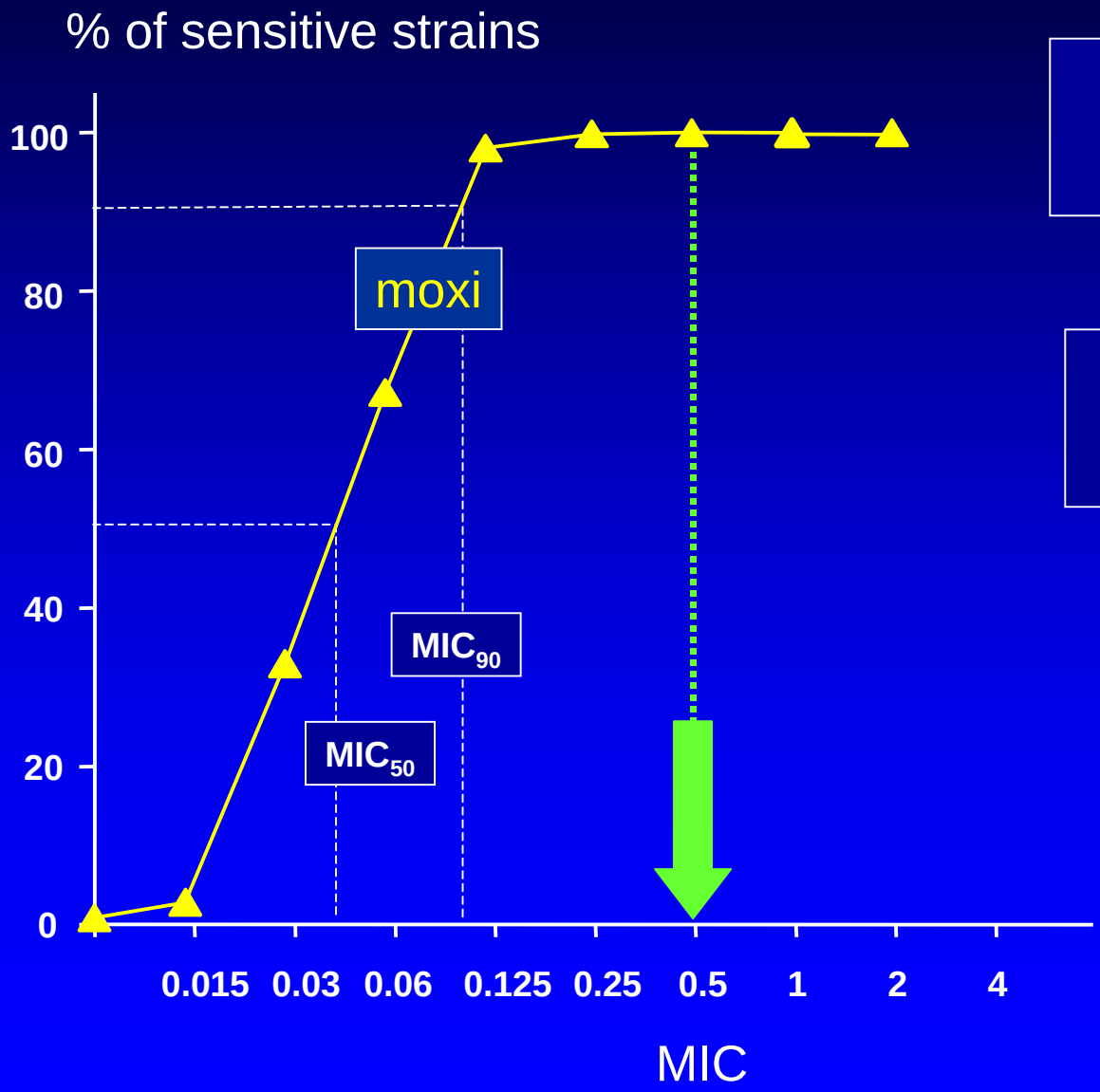
☞ MIC_{max} = 1.0 for AUC/MIC

peak = 5 mg/l

☞ MIC_{max} = 0.5 for peak/MIC

MIC data: J. Verhaegen et al., 2001.

PK-PD moxifloxacin and *S. pneumoniae* in Belgium



Moxifloxacin
400 mg once-a-day

AUC = 48 (mg/l)xh
peak = 4.5 mg/l

☞ MIC_{max} = 0.5

MIC data: J. Verhaegen et al., 2001.

Interpretive criteria for susceptibility testing (MIC:mg/L)

	Susceptible	Intermediate	Resistant
N. meningitidis [1]			
penicillin	≤ 0.06	0.12-1	≥ 2
cefotax / ceftriax	≤ 0.25	0.5-1	≥ 2
S. pneumoniae [2]			
penicillin	≤ 0.06	0.12-1	≥ 2
cefotax / ceftriax			
non-meningitis	≤ 1	2	≥ 4
meningitis	≤ 0.5	1	≥ 2

(1): IDAB 2000. AAC 1992; 36: 1028.

(2): NCCLS 2002.

N. meningitidis: susceptibility data Belgium 1998 (n = 220)

	MIC_{90} (mg/L)	susceptible (%)
penicillin G	0.032	97.7*
rifampin	0.125	100
ciprofloxacin	0.004	100

* *5 strains with MIC > 0.064 mg/L; highest MIC 0.25 mg/L (intermediate)*

S. pneumoniae cerebrospinal fluid isolates
Belgium 1997-2000 (n=237)

	Intermediate (%)	Resistant (%)
penicillin G	11.8	2.1
cefotaxime	4.6	0.4
meropenem	1.3	0.0
vancomycin	0.0	0.0
levofloxacin	0.0	0.4

ICAAC 2001.

Acta Clin Belg (in press).

S. pneumoniae cerebrospinal fluid isolates
Belgium 1997-2000 (n = 237)

- highest MIC for penicillin : 2 mg/L (5 strains)
- highest MIC for cefotaxime : 2 mg/L (1 strain)
- highest MIC for meropenem : 0.5 mg/L (3 strains)
- highest MIC for levofloxacin : 12 mg/L (1 strain)

(MIC for moxifloxacin: 1 mg/L)

Acta Clin Belg (in press).

Pharmacokinetics in bacterial meningitis

- CSF / serum concentration values are highly variable
- peak levels in serum and CSF do not coincide
- concentration-time curves in serum and CSF do not run parallel
- elimination half-life is increased in CSF

Infect Dis Clin North Am 1999; 13: 595.

Pharmacodynamics of beta-lactam antibiotics in bacterial meningitis

- CSF levels must exceed MIC by 10-30 fold to obtain maximal bactericidal activity in experimental animal models
- Time > MIC is the only parameter that independently correlates with bacterial killing in experimental pneumococcal meningitis
- Time > MIC needs to be 75-100 % to obtain maximal killing (sterilization at 24 hours)
- Time > MIC of 50 % results in 50 % of the maximal killing rate (sterilization at 72 hours)

Infect Dis Clin North Am 1999; 13: 595.

Clinical relevance of antibiotic resistance in bacterial meningitis

N. meningitidis

- intermediate resistance not associated with clinical failure if treatment with high dose of penicillin

S. pneumoniae

- treatment failure and death reported due to penicillin intermediate and resistant pneumococci, treated with penicillin G
- clinical and bacteriological failures reported when using cefotaxime or ceftriaxone for cephalosporin intermediate or resistant PRSP

Clin Microbiol Rev 1998; 11: 628.

Clinical practice guideline for bacterial meningitis (Belgium)

- always perform MIC testing on CSF isolates
- since pneumococcal resistance to 3rd generation cephalosporins remains rare and low level, addition of vancomycin to the empirical therapy not (yet) necessary
- concern about penetration BBB when using adjuvant dexamethasone in case of less susceptible pneumococci

Acta Clin Belg 2001; 56: 225.

IDAB symposium, September 2002.

MIC-based therapies: Infective Endocarditis

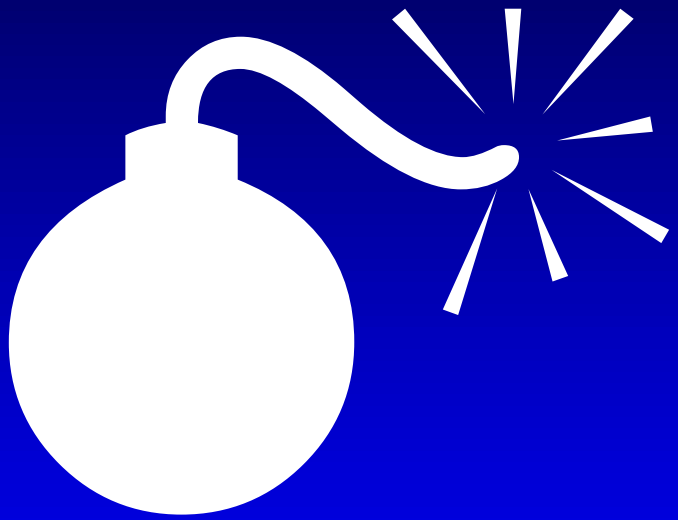
- viridans streptococci or S. bovis
  - penicillin MIC $\leq$ 0.1 mg/L
  - penicillin MIC > 0.1 mg/L but $\leq$ 0.5 mg/L
  - penicillin MIC > 0.5 mg/L
- enterococci:
  - low or high level resistance to gentamicin

AHA guidelines.
JAMA 1995; 274: 1706 / Circulation 1998; 98: 2936.

MIC-based therapies: other indications

- viridans streptococci bacteremia in neutropenic patients: (penicillin; 3rd gen cephalosporins)
- glycopeptide-resistant enterococci bacteremia: (ampicillin; vancomycin; teicoplanin; linezolid)
- Pseudomonas or enterobacteriaceae CSF infection (postoperative):(3rd gen cephalosporins; ceftazidime; cefepime; meropenem)

IDAB Guide to Extended Antimicrobial Susceptibility Testing 2000.



MIC-based therapies: Conceptual weaknesses (1)

- MIC is artificial in vitro test
  - standard bacterial concentration
  - stable antibiotic concentration
  - incubation time / temperature / environment
- PK variability among individual patients
  - absorption / distribution volumes in sepsis patients
  - drug-drug interactions
  - fixed dose irrespective of body weight and gender
  - dose reduction according to renal function starts at GFR < 50 ml/min.

MIC-based therapies: Conceptual weaknesses (2)

- PK data
  - derived from studies in healthy adults; not measured in individual patients
  - total or free serumconcentration
  - serumconcentration or concentration at infection site (CSF / ELF / …)
- MIC data
  - susceptibility testing on one CFU only
  - different breakpoints in US/UK/NL/FR/GER/SP…

MIC-based therapies: Conceptual weaknesses (3)

- PK-PD characteristics
  - modelling based upon MIC_{90} and mean serumconcentrations
  - relevance of mutation prevention concentration not established

(Craig. CID 2001; 33 (suppl 3): S233)

  - PK-PD magnitudes to reduce risk of FQ resistance in pneumococci not established

(Craig. CID 2001; 33 (suppl 3): S233)

MIC-based therapies: Conceptual weaknesses (4)

- PK-PD characteristics
  - environmental conditions at site of infection may influence both PK and PD
  - sum of AUIC values predictive of killing rates in patients with antibiotics in combination; or

    (Shentag. CID 1998; 27: 40)

    type-specific PK-PD indices explain most of the variation for antibiotic combination and summing AUIC is poor predictor of antibacterial activity

    (Mouton. AAC 1999; 43: 2473)
  - optimal dosing schemes based upon PK-PD limited by toxicity and feasibility issues

MIC-based therapies: Feasibility issues

- MIC on all “relevant” isolates
  - work load
  - cost
- No relevant isolate (negative culture results)
- Multiple relevant isolates (mixed infections)
- No measurement of individual PK-data

MIC-based therapies: Conclusions

- PK-PD characteristics are a useful tool
  - to provide an explanation for clinical observations
  - to establish more effective dosing regimens
  - to establish breakpoints
  - to propose dosing regimens for clinical trials with new antibiotics
  - to design studies with new treatment modalities

MIC-based therapies: Conclusions

- PK-PD modelling
  - cannot replace clinical trials (efficacy; toxicity)
  - cannot replace clinical experience
  - does not consider other factors involved in clinical failure or cure
  - does not consider other factors involved in emergence of antibiotic resistance

MIC-based therapies: Conclusions

- MIC-based therapies for individual patients
  - not for routine daily practice
  - reserved for specific indications
    - severe and difficult-to-treat infections
      - empirical regimens
      - directed therapy
    - specific drug-microbe combinations
      - directed therapy