Antibiotics - general aspects

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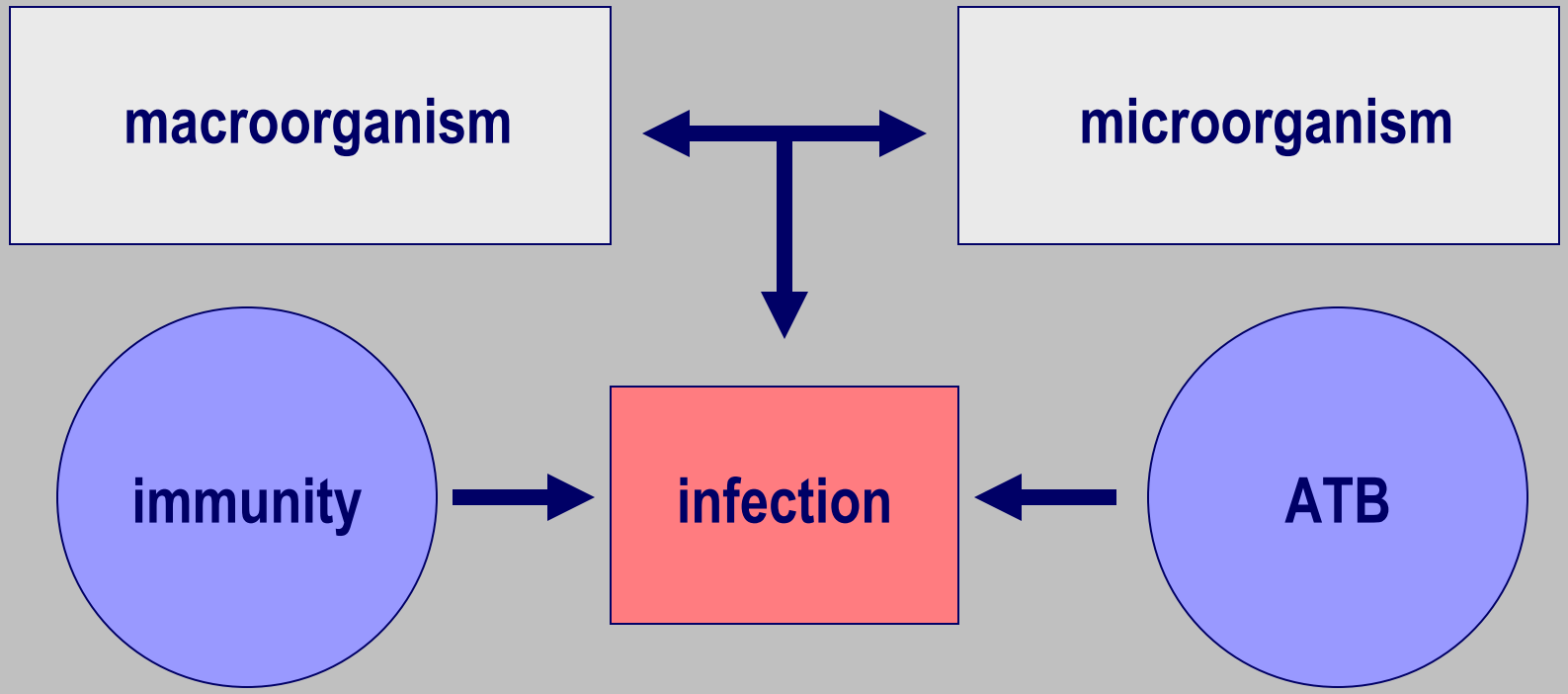
Oddělení klinické mikrobiologie a antibiotická stanice

Nemocnice Na Homolce, Praha

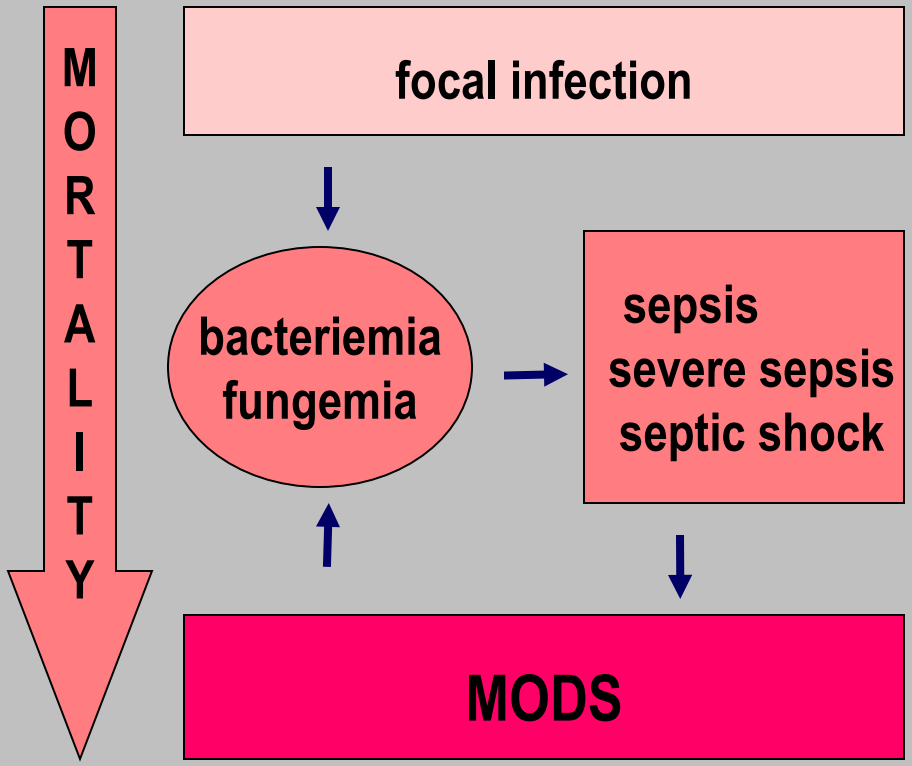
Antibiotics - antimicrobial agents

- antibacterial agents
- antimycotic agents
- antiviral agents
- antiparasitic agents

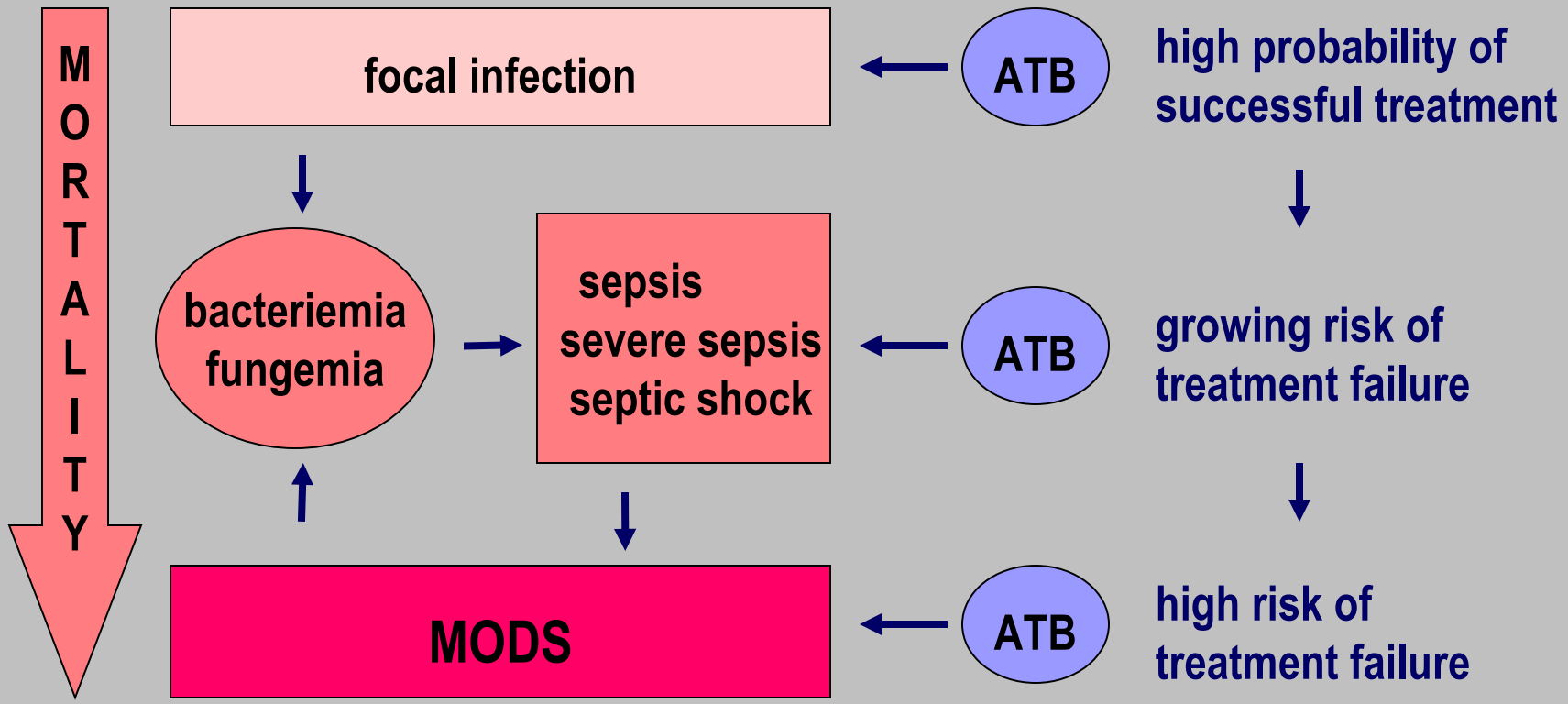
Antiinfective effect of antibiotics



Antiinfective effect of antibiotics



Antiinfective effect of antibiotics



Antibiotics

- **Antimicrobial activity**
- Pharmacokinetics
- Pharmacodynamics and dosing
- Clinical use
- Clinical and epidemiological safety
- Antibiotic policies

Antimicrobial action and clinical efficacy

- **anti-microbial action**
  - **activity *in vitro* (MIC, MBC)**

- **clinical efficacy**
  - **activity *in vivo*, influence on clinical symptoms of infection** (duration and intensity, prognosis of infectious disease)
  - **extremely complicated parameter** (availability of effective drug concentration in place of infection, virulence and quantity of pathogen, condition of antimicrobial defense mechanisms and immune system, localisation of pathogenic process, presence of foreign bodies, …)
  - **self-limited infections, serious (life threatening) infections**

Evaluation of anti-microbial treatment efficacy

- **clinical outcome (clinical cure)**
  - **elimination of clinical symptoms**
- **microbiological outcome (microbiological cure)**
  - **elimination of pathogen (eradication)**

Anti-microbial activity of antibiotics
MIC and MBC

- **MIC - minimum inhibitory concentration**
  - the lowest concentration, which is able to eliminate microbial growth
- **MBC - minimum bactericidal concentration**
  - the lowest concentration, which is able to kill the micro-organism

Minimum inhibitory and bactericidal concentration

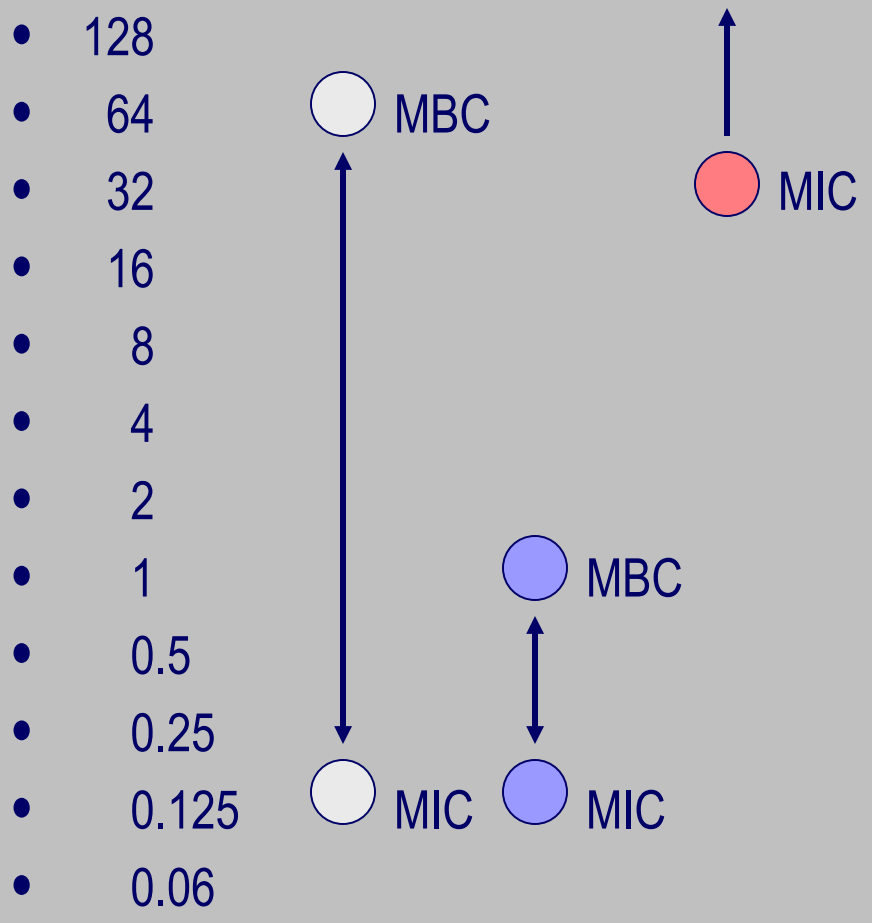
- 128
- 64
- 32
- 16
- 8
- 4
- 2
- 1
- 0.5
- 0.25
- 0.125
- 0.06

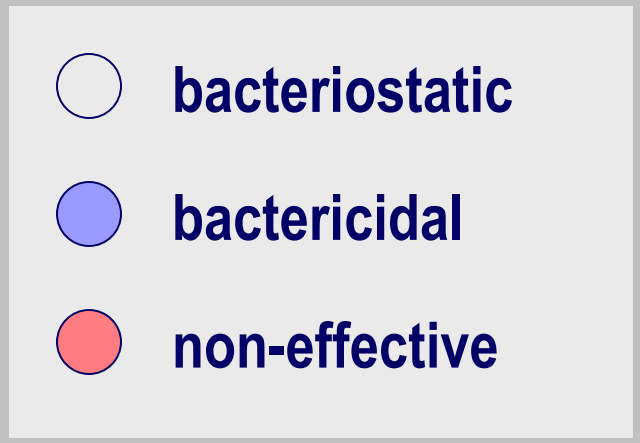
determination of MIC (MBC) in series of dilutions (mg/l)

the first dilution without observed microbial growth define value of MIC (MBC)

Antimicrobial action of antibiotics

bactericidal and bacteriostatic effect





Mechanisms of action

- **inhibition of cell wall synthesis**
  - **betalactams, glykopeptides, ...**
- **inhibition of proteosynthesis**
  - **aminoglykosides, macrolides, lincosamides, tetracyclines,...**
- **influence on microbial DNA (inhibition of DNA gyrase)**
  - **quinolones,...**
- **inhibition of folic acid metabolism**
  - **sulfonamides**

Susceptibility and resistance to antibiotics

microbiological definition of resistance

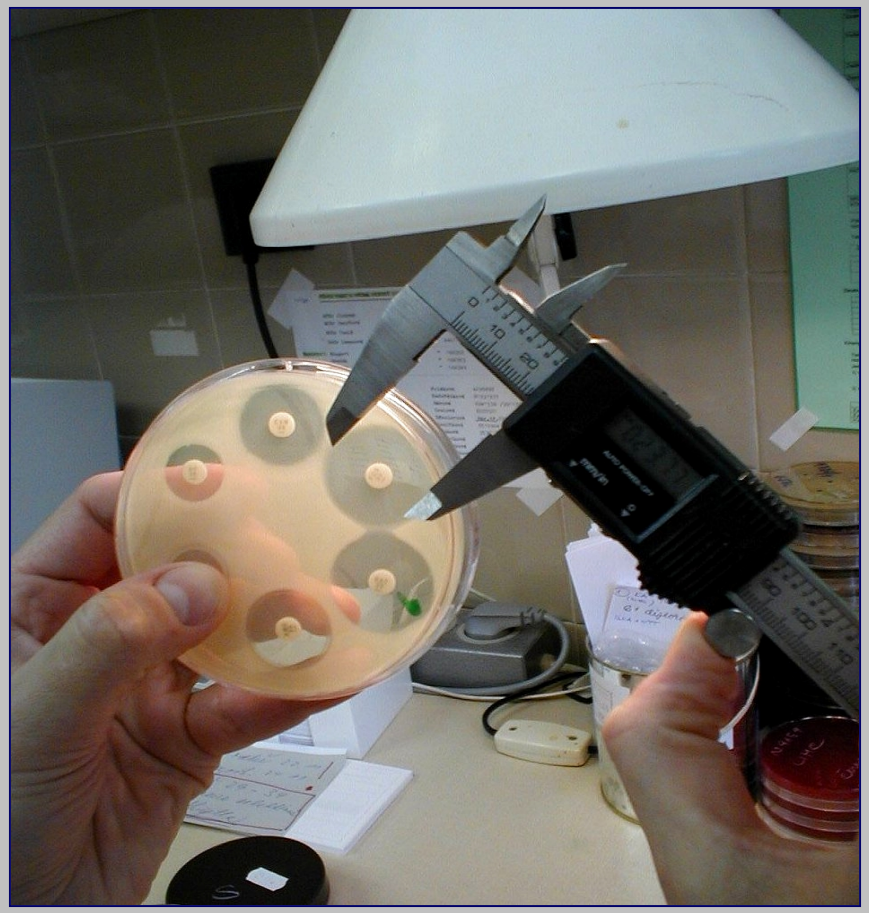
- presence of genetically encoded molecular mechanism, which is able to decrease antimicrobial activity of particular antibiotic
  (enzyme inactivation, change of target structure, block of penetration to the target structure, active efflux, …)

Susceptibility and resistance to antibiotics

clinical definition of resistance

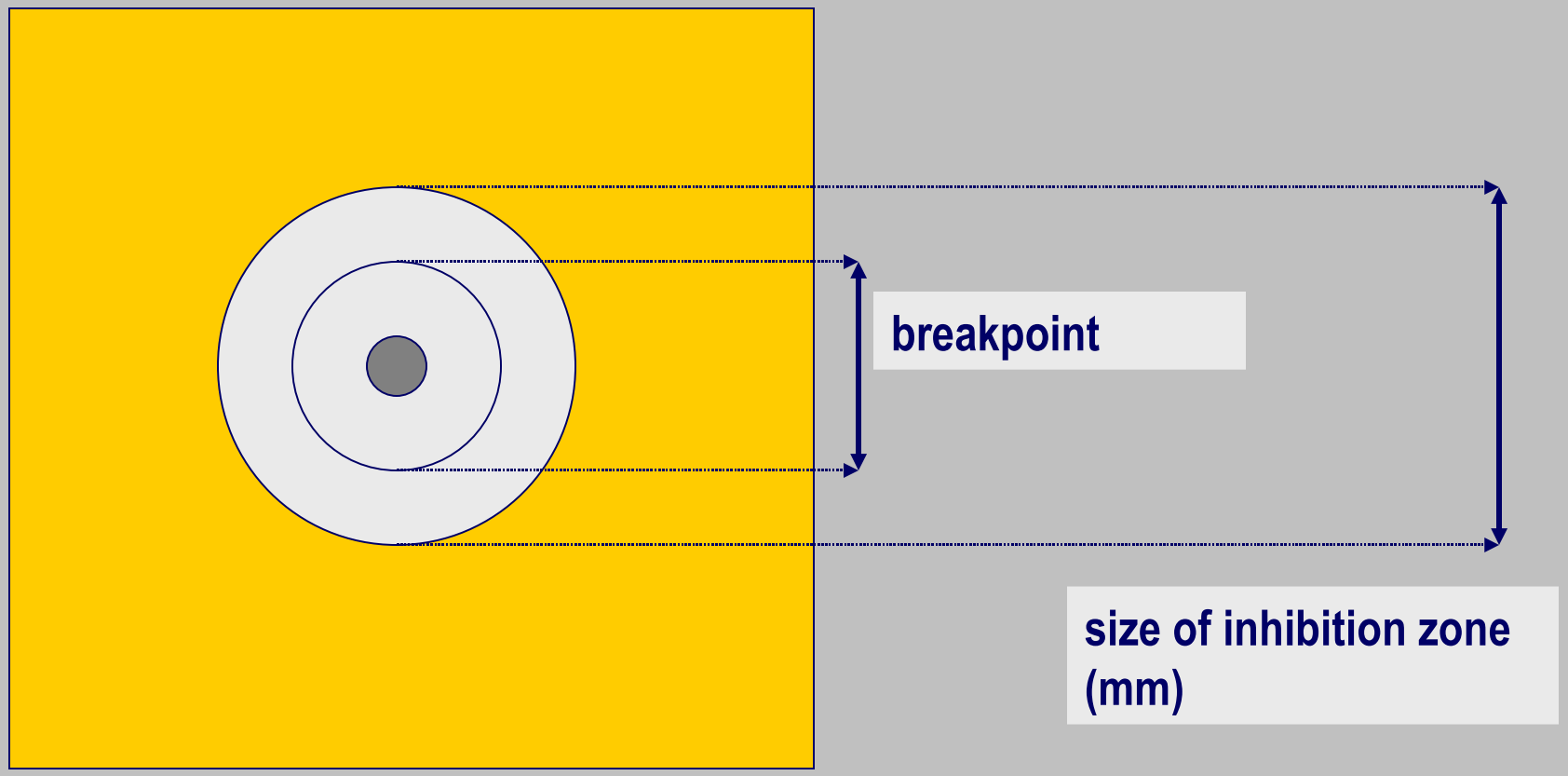
- clinical failure of treatment with therapeutically reachable dosage of particular antibiotic

Susceptibility testing

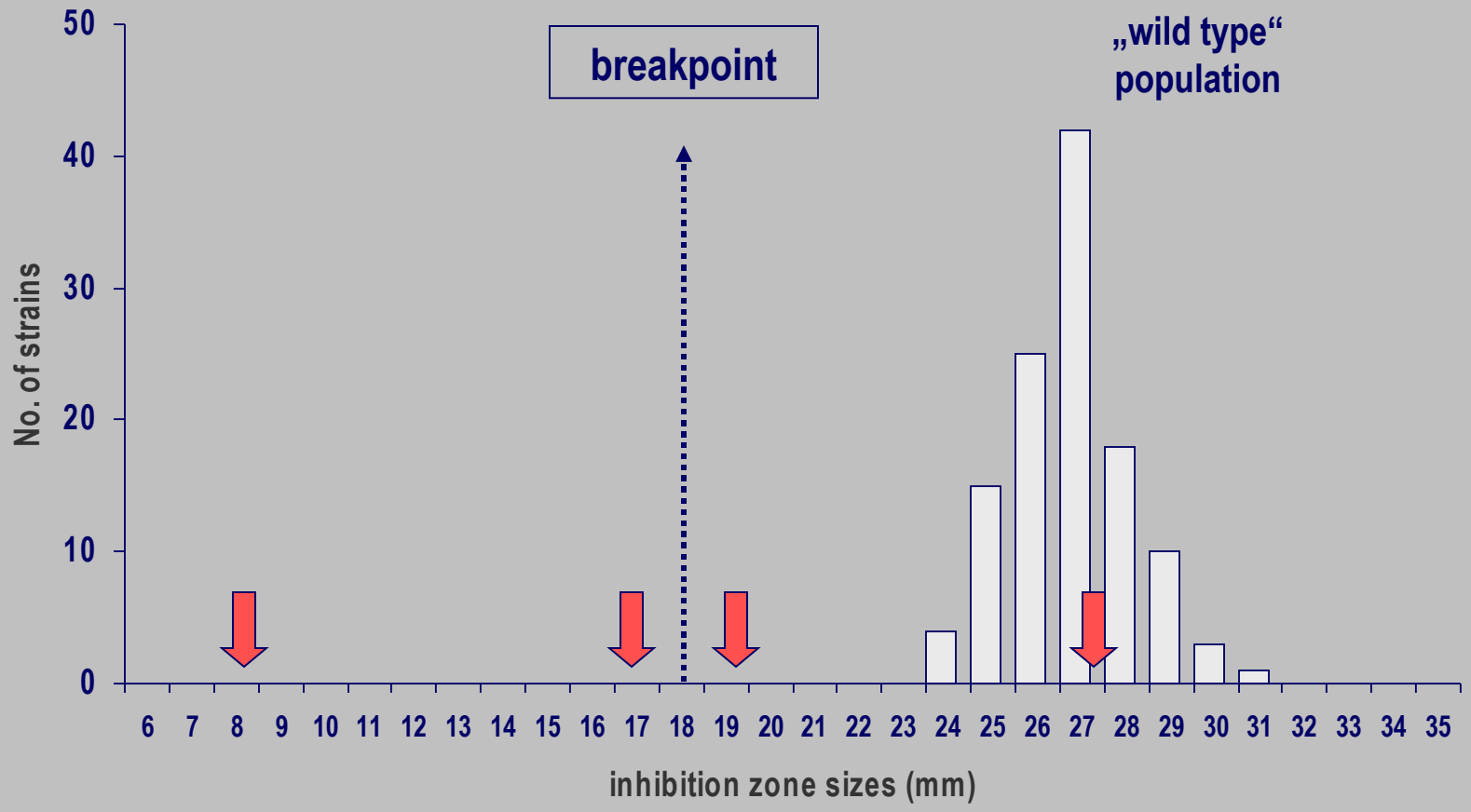


Susceptibility testing

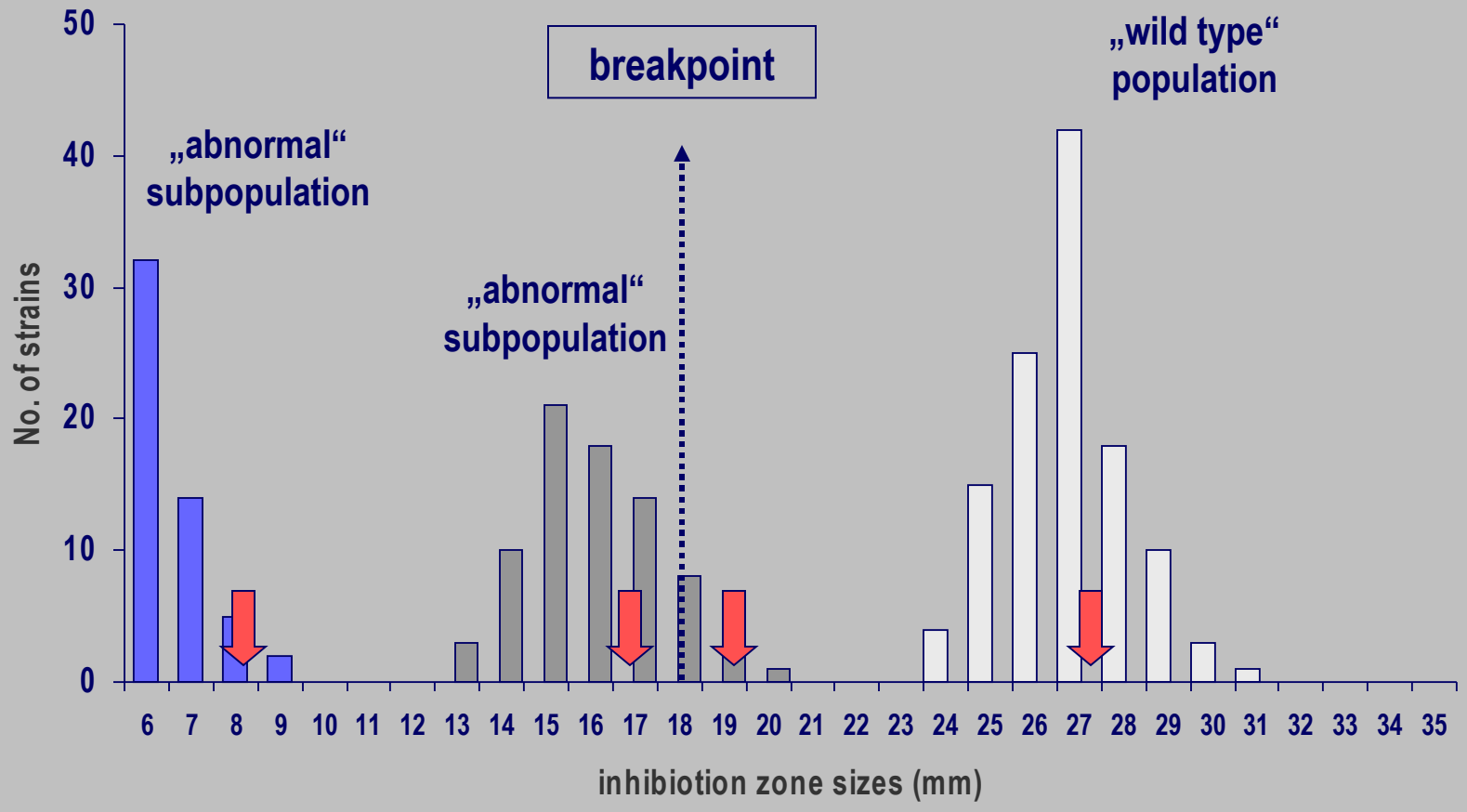
evaluation criteria - breakpoints



Evaluation of susceptibility testing - breakpoints



Evaluation of susceptibility testing - breakpoints



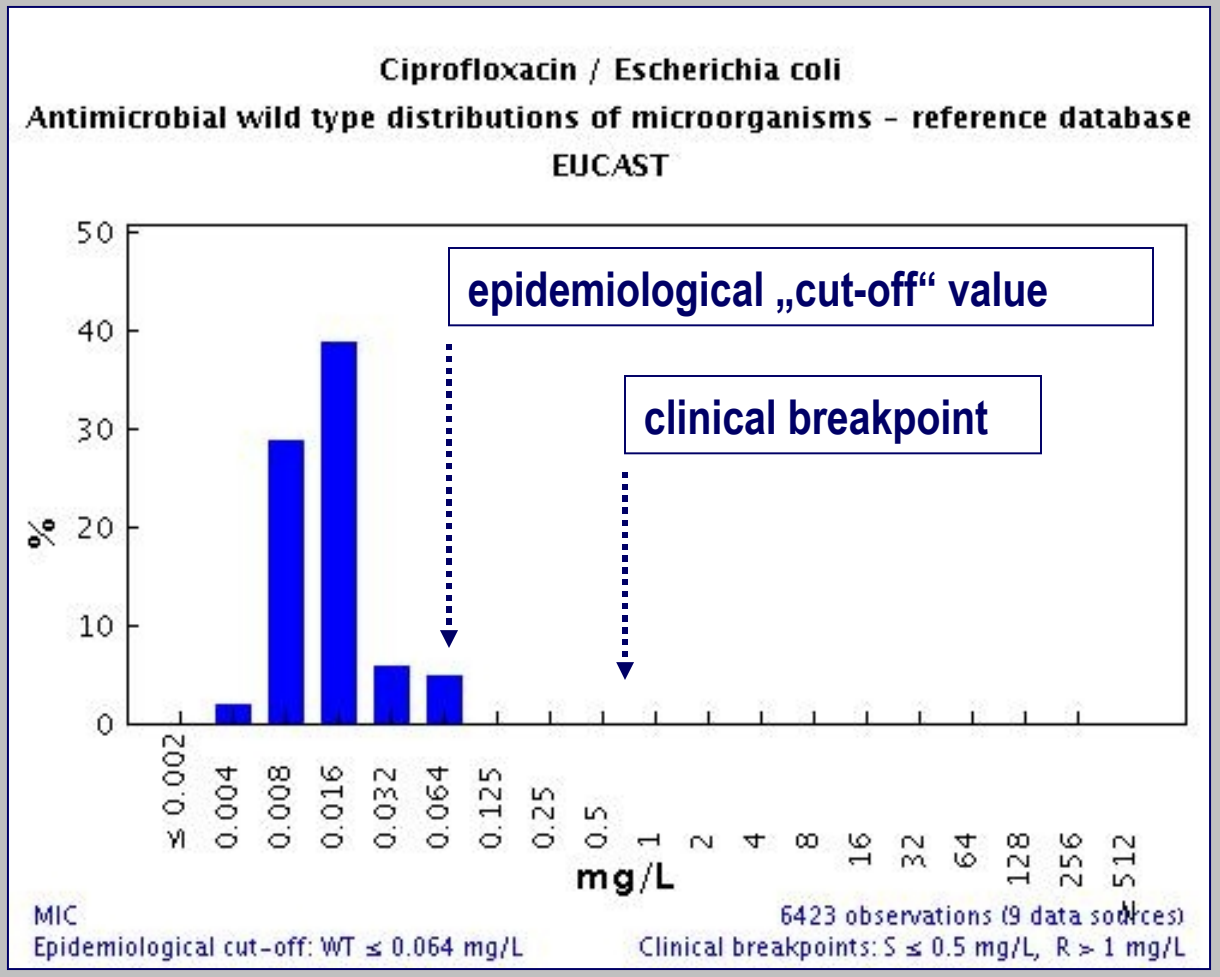
Evaluation of susceptibility testing
microbiological and clinical breakpoints

- microbiological breakpoints (epidemiological cut-off values) are established according distribution of quantitative results of phenotype susceptibility tests in „wild type“ strains of particular microbial species. Values of microbiological breakpoints are objective and stable
- clinical breakpoints are arbitrary established and can be changed in case of existence appropriate reasons

EUCAST website: www.escmid.org

EUCAST – distribution of wild type MIC's

Escherichia coli - ciprofloxacin



Clinical (pharmacodynamic) breakpoints

Streptococcus pneumoniae – susceptibility to penicillin

- **BP - wild type:** **0,06 mg/l**
- **BP - intermediate susceptibility:** **0,12 - 1,0 mg/l**

  0,12 mg/l predictive value for meningitis

- **BP - high level resistance:** **2,0 mg/l**

  2,0 mg/l predictive value for respiratory infections and bacteremia (high dose penicillin)

Antibiotics

- Antimicrobial activity
- **Pharmacokinetics**
- Pharmacodynamics and dosing
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Pharmacokinetics of antibiotics

- pharmacokinetic parameters determine availability of active antimicrobial agent in place of infection
- **pharmacokinetic characteristics of antimicrobial agent determine optimal route of its administration and dosing in particular indication:**
  - route of administration
  - quantity of single dose
  - dosing interval
  - duration of administration

Basic pharmacokinetic parameters of antibiotics

• biological availability	**F** (%)
• maximum plasmatic concentration	$\mathbf{C_{max}}$ (mg/l)
• plasmatic protein binding	**fb** (%)
• volume of distribution	**Vd** (l/kg)
• clearance	**CL** (ml/min/kg)
• clearance non-renal	$\mathbf{CL_{nr}}$ **(%)**
• biological half life	$\mathbf{t_{1/2}}$ (h)
• penetration to the body fluids and tissues	
• intracellular penetration	

Pharmacokinetics of antibiotics
biological availability

- **determines fraction of extravasculary administered drug (%), which is absorbed and reach systemic circulation**

- i.v. administration absolute biological availability (100%)
- other routes <100%

Pharmacokinetics of antibiotics

plasmatic proteins binding

- only free fraction of antibiotic (not bind on plasmatic proteins) is pharmacologically active

Pharmacokinetics of antibiotics

volume of distribution

- **parameter determined as relationship between administered dose of drug and its concentration in blood**

- **its value determined need of augmented dose of antibiotic at the moment of treatment initiation**

Pharmacokinetics of antibiotics

clearance

- **parameter determined as relationship between speed of drug elimination and concentration in blood**

- **quantitative parameter determines ability of organism to eliminate drug**
- **clearance determines size of maintenance dose in case of intermittent dosing**

Pharmacokinetics of antibiotics

biological half-life

- **time needed for decrease of drug concentration in organism (blood) to 50%**
- **after single dose determines duration of action**
- **during intermittent dosing is useful for estimation of time needed for establishing steady-state and determining dosing interval**

Farmacokinetics of antibiotics

penetration to body fluids and tissues

- **fraction of drug penetrating to the body fluids and tissues (percentage from concentration reached in blood)**

- urine, bile, CSF, bronchial secretion, breast milk, synovial fluid, intra-ocular fluid, exudates, pathological fluids, …
- bone, lung tissue, tonsil, abscesses, transplacentar penetration, ...

Pharmacokinetics of antibiotics
intracellular penetration

- **intracellular penetration of antibiotic determines clinical efficacy in the situation of treatment infections due to intracellular pathogens**

Antibiotics

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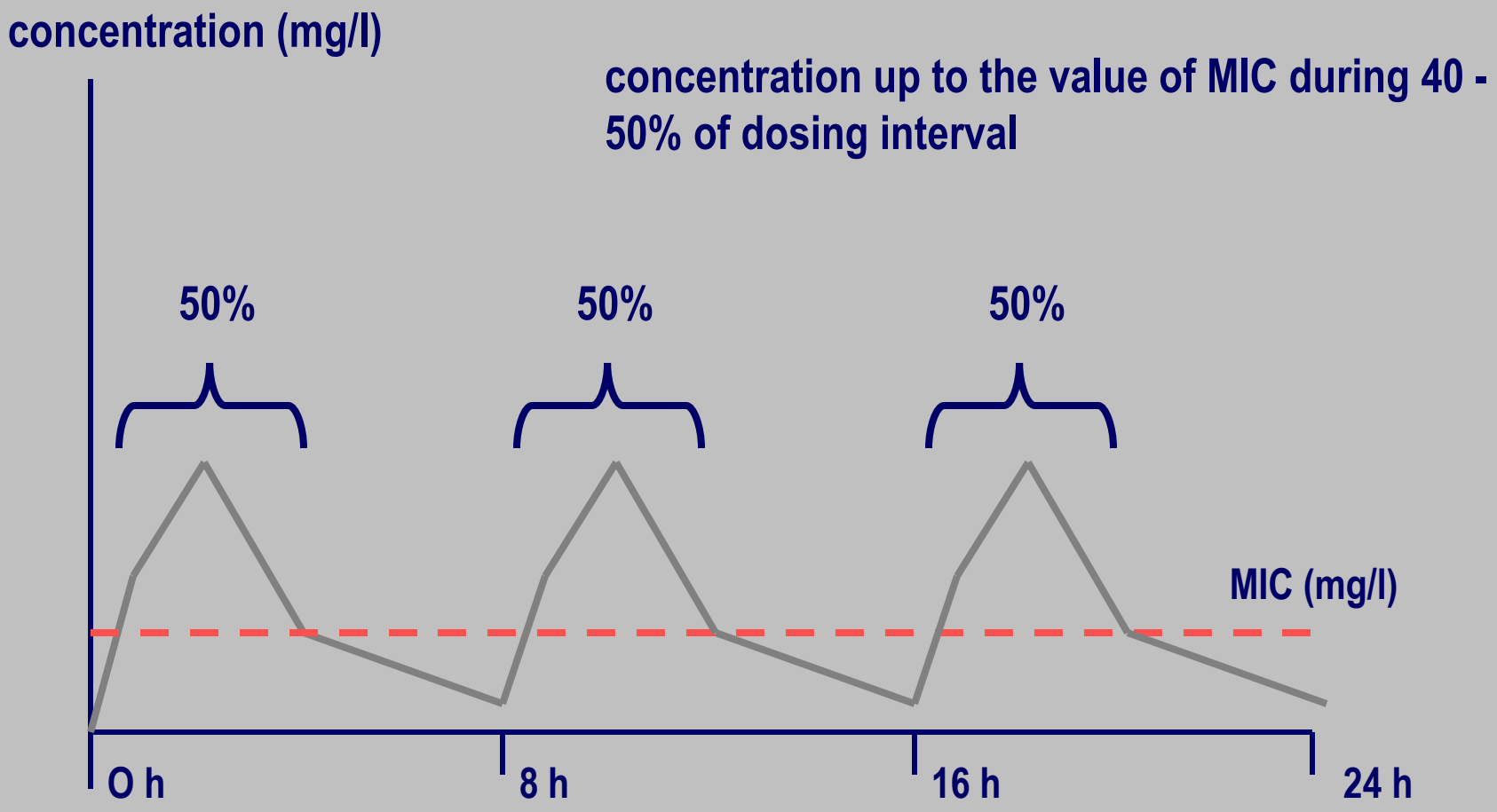
Pharmacodynamics of antibiotics

- **Pharmacodynamics describes initiation and quantity of antibiotic action in relationship to the concentrations reached in body fluids and tissues**

- **time-dependent action**
- **concentration-dependent action**

Time-dependent action

betalactams



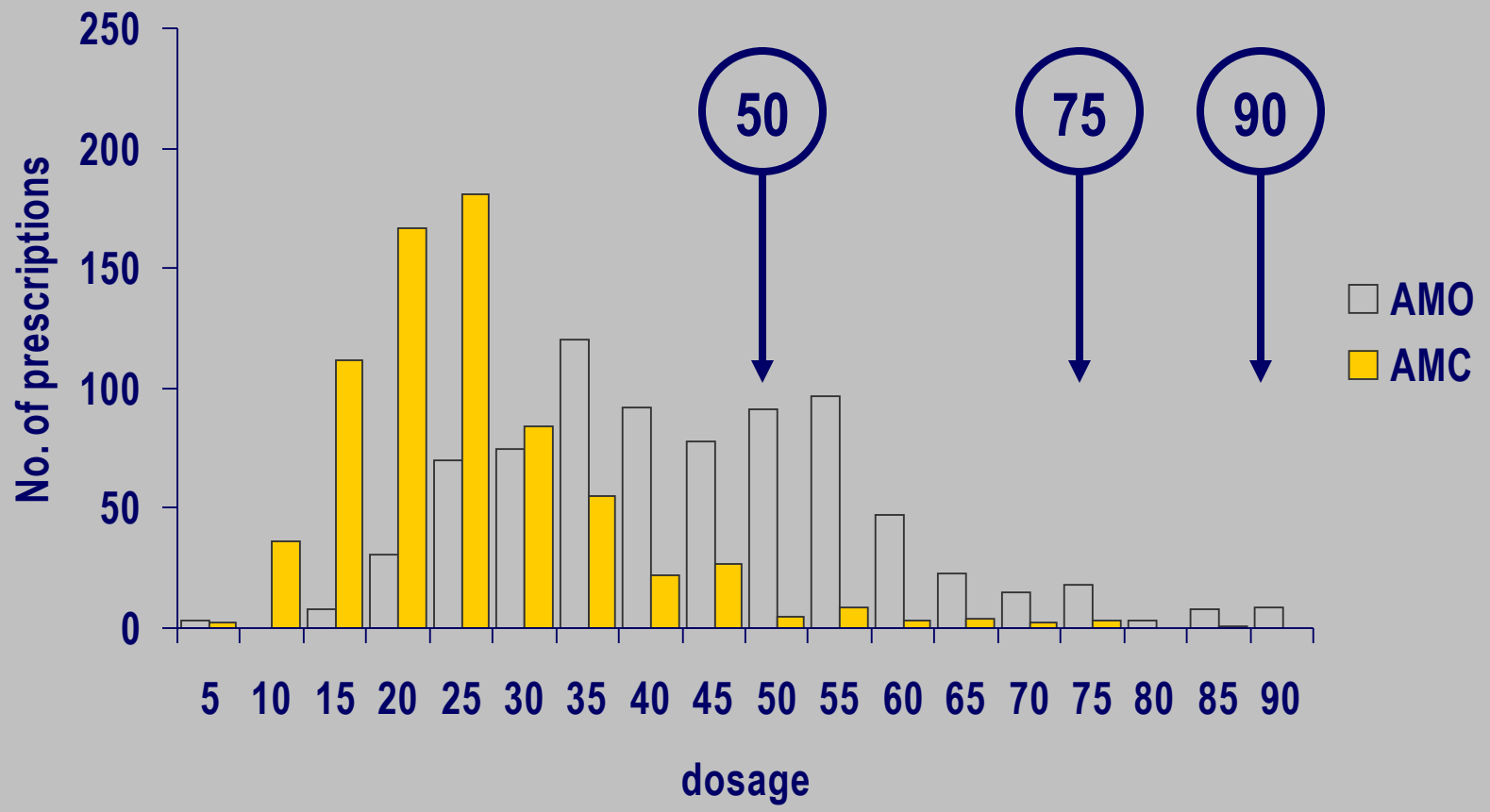
Clinical example:
streptococcal tonsillopharyngitis

- **administration of oral penicillin 10 days in the 8 hours dosing interval is clinically effective and safety approach, including prevention of post-infection complications**

• single dose for adults	750mg
• dosing interval	8 hours
• duration	10 days

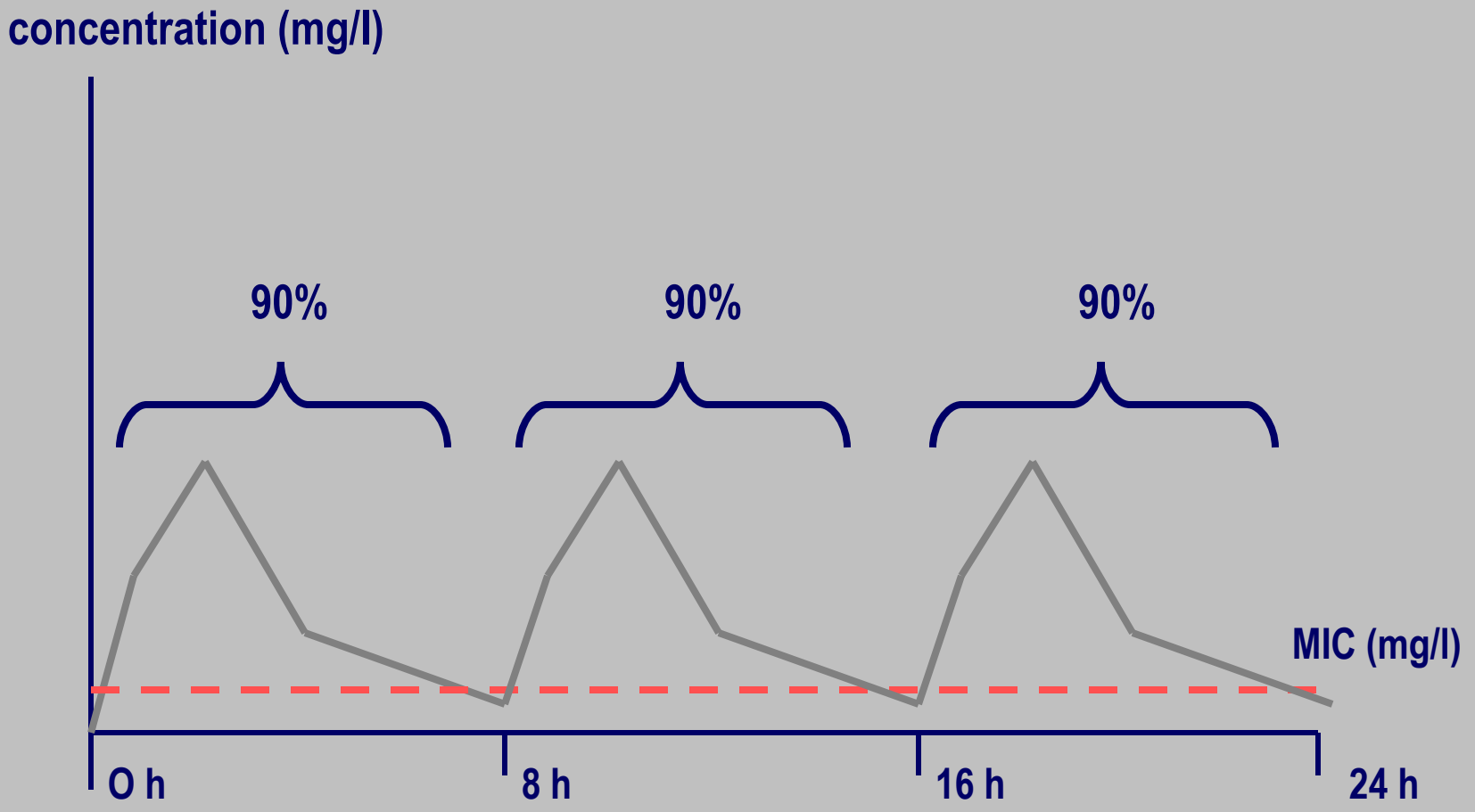
Dosage of amoxicillin (respiratory infections in children)

amoxicillin (AMO), amoxicillin klavulanate (AMC) - mg/kg/den



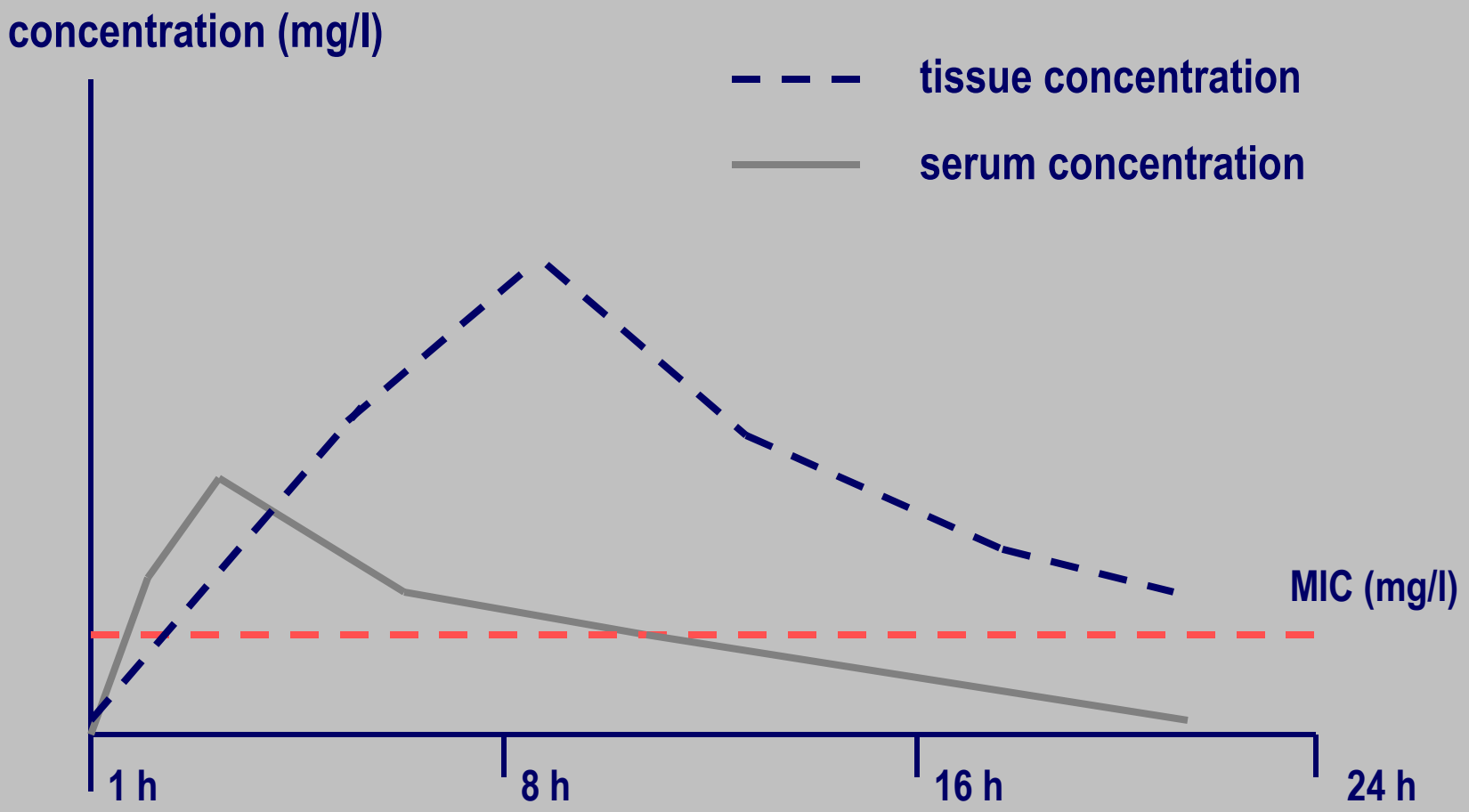
Time-dependent action - febrile neutropenia

betalactams



Time-dependent action with tissue cumulation

macrolides



Clinical example:
streptococcal tonsillopharyngitis

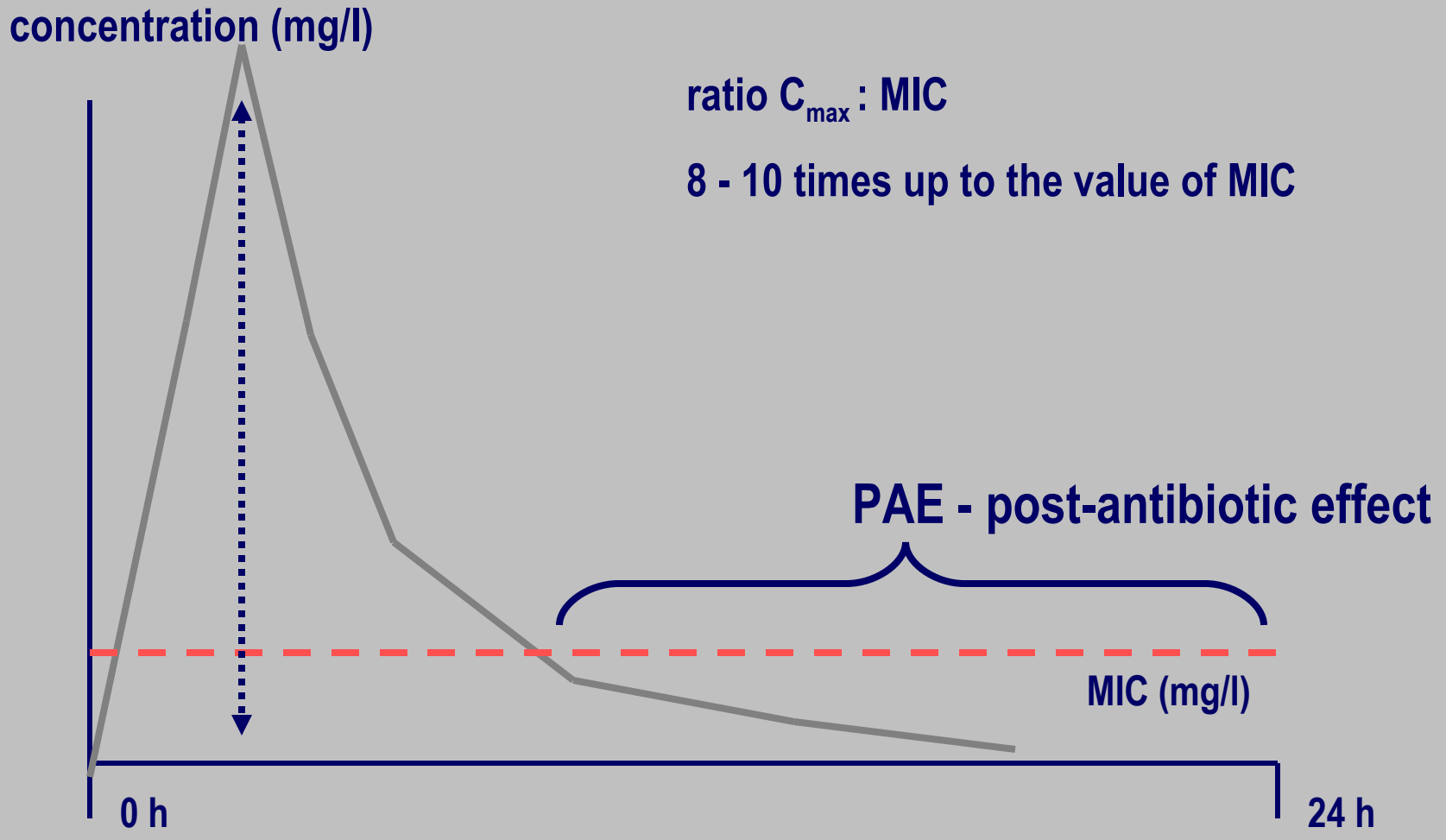
- administration of oral azithromycine (once daily for 3days) is clinically effective, comparable to 10 days administration of penicillin

- single dose for adults 500mg
- dosing interval 24 hours
- duration 3 days

- eradication is lower (in comparison with penicillin)
- long-term persistence of sub-inhibitory concentration represents risk for selection of resistance to macrolides

Concentration-dependent action

aminoglycosides



Clinical example:

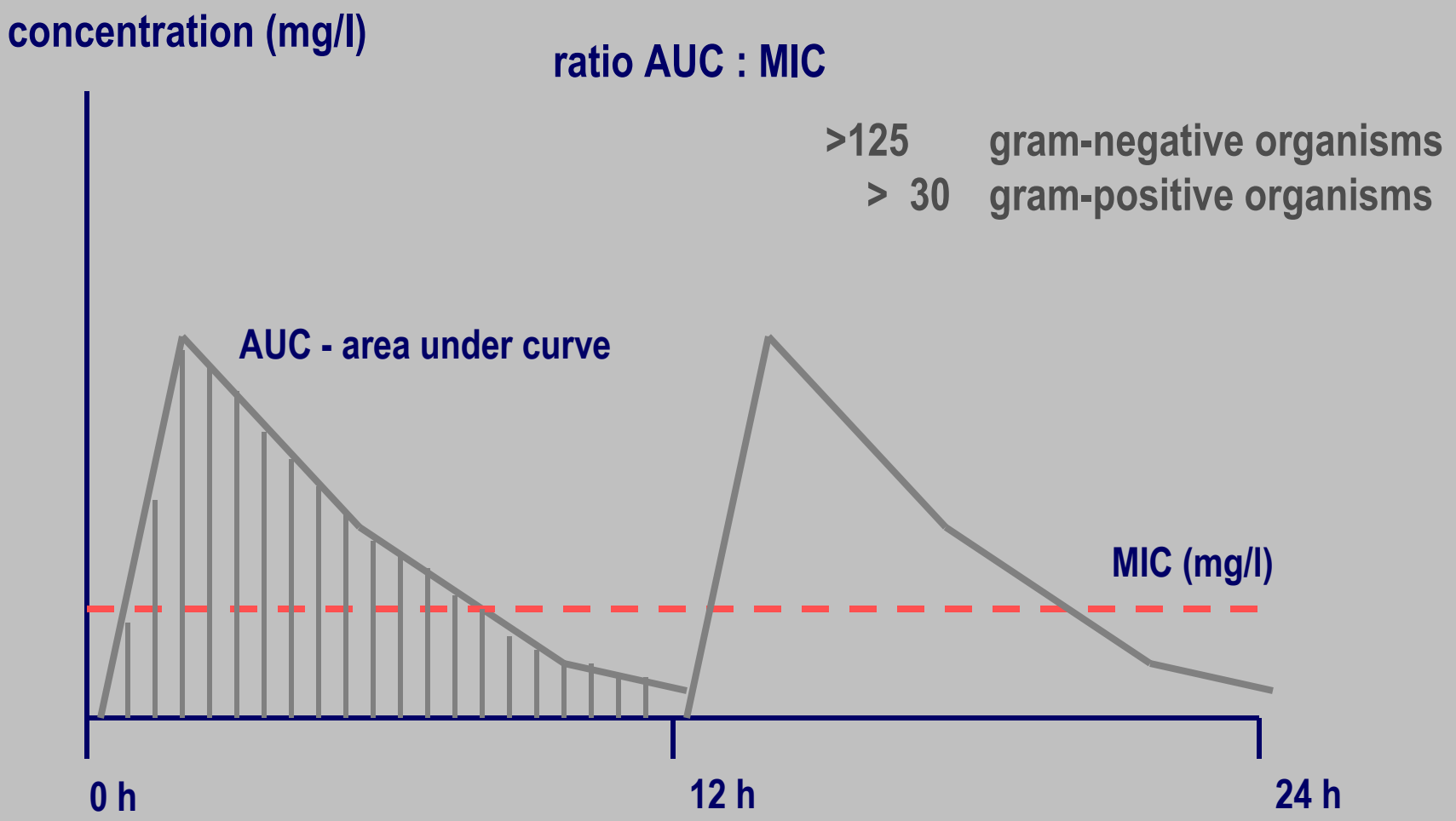
acute pyelonephritis and urosepsis due to *E.coli*

- cefotaxime 1g, interval 8 hours, duration 10 days
- gentamicin administered once daily, duration 2 - 3 days (elimination pathogen from blood)

	single dose	interval	duration
• CTX	1g	8 h	10 days
• GEN	320mg	24 h	3 days

Concentration-dependent action

quinolones



Clinical importance of PK/PD parameters
strategy of initial treatment of severe CAP

- rapid bactericidal action against invasive pathogen, localised in the extra-cellular space and blood (pneumococci)

  betalactam antibiotics (penicillins, cephalosporins)

- action against intracellular pathogens (legionellae, chlamydiae)
- action against pathogens without cell wall (mycoplasmas)

  macrolides

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Clinical use of antibiotics

- therapeutic indications
- prophylactic indications

Clinical use of antibiotics
therapeutic indications

- common (self-limited) infections
- serious (life threatening) infections
- antibiotic use in specific groups of patients
  - critically ill in ICU
  - neutropenic patients
  - transplant patients
  - neonates
  - pregnant women

Clinical use of antibiotics

approaches to indication of antimicrobial treatment

- **empirical therapy**
- **initial therapy**
- **pathogen-specific therapy**

- **step-down therapy, de-escalating therapy**
- **community versus nosocomial infections**
- **guidelines for antibiotic therapy**

Clinical use of antibiotics
prophylactic indications

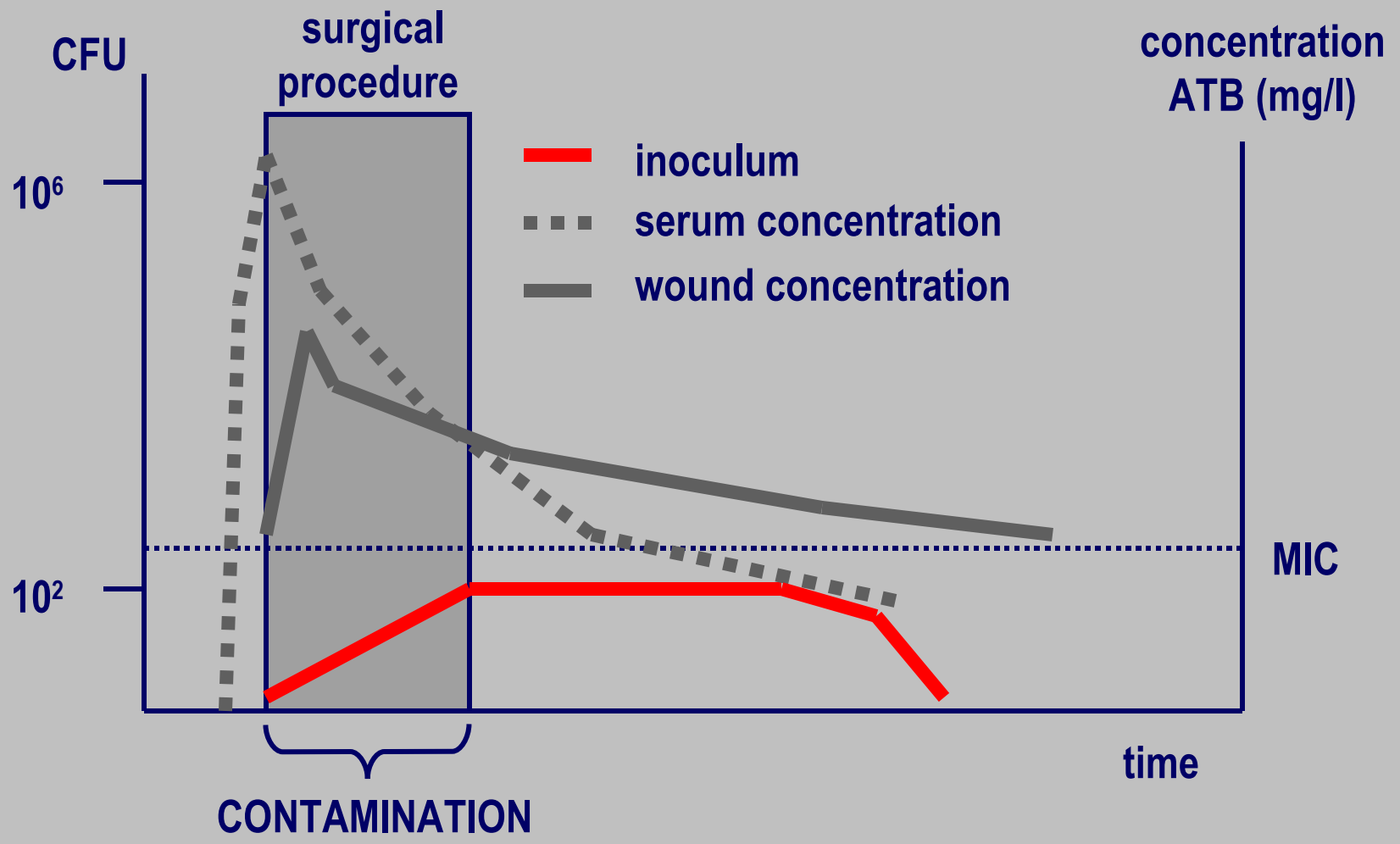
- **prophylaxis in surgery**
- **prophylaxis of infective endocarditis**
- **prophylaxis of invasive meningococcal disease**
- **prevention of traveller diarrhoea**
- **prophylaxis in immunocompromised patients**
  - **transplantation** (Pneumocystis, HSV, CMV, candidae)
  - **neutropenia** (bacterial and mycotic infections)
  - **asplenia** (pneumococcal disease)
  - **HIV infection** (Pneumocystis, Toxoplasma, atyp. mycobacteria, neonatal HIV transmission)

Antimicrobial prophylaxis in surgery
aim, principal and conditions of efficacy

- Aim:
  - to decrease risk of surgical site infection becoming due to contamination of wound and space of surgical procedure
- Principal:
  - to get effective (bactericidal) concentration of antibiotic in the space of surgical procedure in time of incision and during total duration of operation
- Conditions of efficacy:
  - intravenous administration of optimal dose of appropriate bactericidal antibiotic, shortly before incision (20-30 minutes)

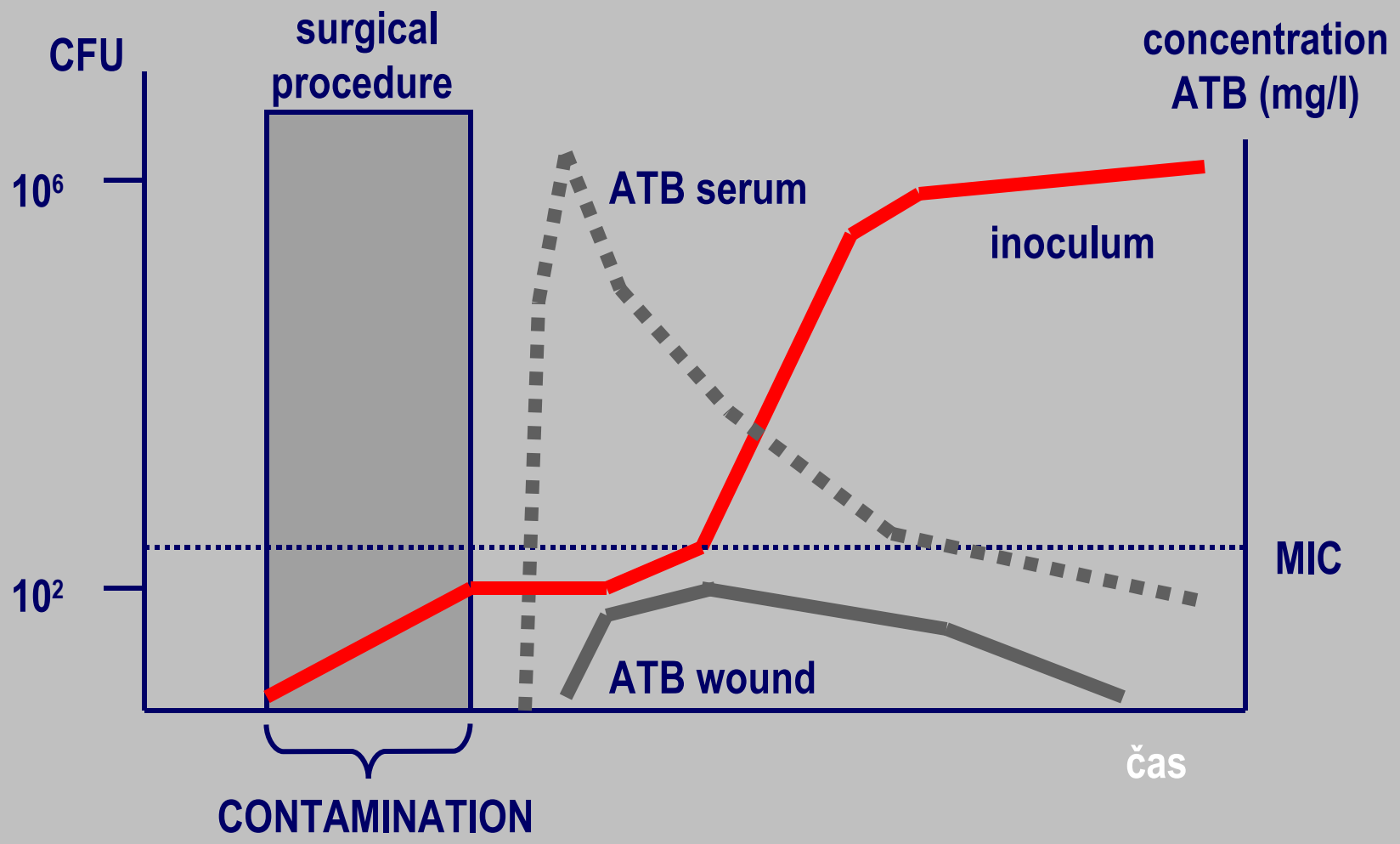
Antimicrobial prophylaxis in surgery

preoperative administration of antibiotic



Antimicrobial prophylaxis in surgery

postoperative administration of antibiotic



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Clinical safety of antibiotics
toxic and ecological adverse effects

- **toxic adverse effects**
  - nephrotoxicity, ototoxicity, hepatotoxicity, hematotoxicity, …

- **ecological adverse effects**
  - postantibiotic colitis (CDAD)
  - superinfection (systemic candidasis)
  - selection of resistance *intra therapiam*
  - risk of previous antibiotic exposure in critically ill patients

Epidemiological safety of antibiotics

epidemiological changes and antimicrobial resistance

- **changes in etiological spectrum of infectious diseases**
  - changes in aetiology of blood stream infections (enterococci, candidae)
  - new pathogens (*Burkholderia cepacia* - patients with cystic fibrosis)

- **origin and spread of antimicrobial resistance**
  - lose of clinical efficacy of antibiotics
  - pandemia of resistance in community and hospital setting

Antibiotics

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Antibiotic policy - definition

Antibiotic policy is collection of interventions, focussed on high quality of antibiotic usage (clinically effective, safety and cost effective therapy and prophylaxis), aimed to the limiting risk of increase antimicrobial resistance.

- clinical efficacy (clinical cure)
- microbiological efficacy (microbiological cure)
- clinical safety (elimination of adverse effects)
- epidemiological safety (elimination of epidemiological risks)
- cost-effectiveness (cost-benefit parameters)

Priorities of antibiotic policies

- use antibiotics only for treatment of infections
- target, narrow spectrum, pathogen-specific therapy

- elimination of inappropriate indications
- elimination of inappropriate choice of antibiotic
- elimination of inappropriate dosing and duration

The role of antibiotic centres

- Surveillance of resistance in hospitals and commmunity
- Surveillance of antibiotic usage and consumption
- Consulting of antibiotic use
- Interventions for high quality antibiotic usage
- Categorisation of antibiotics (drugs under supervision)
- Guidelines for antimicrobial therapy and prophylaxis
- Education in the field of good antimicrobial practice

Network of antibiotic centres in the Czech republic