

## REVIEW OF ANTIBIOTICS

### THE SHORT HISTORY OF ANTIBIOTICS AND OF DEVELOPING RESISTANCE

S.A. Waksman introduced the term „antibiotic“ in 1942. In forties to sixties, the term “antibiotic” was clearly differed from the term “chemotherapeutic drug”: Antibiotics were natural drugs produced by several fungi or bacteria. Chemotherapeutic drugs were man-made substances. Nevertheless the differences were abolished after chemical synthesis of some antibiotics has been realized and new drugs have been developed from the natural products with binding various side chains to the basic structure.

From this point of view, the history of antibiotics begun in 1932 when the first sulfonamide was prepared. The boom of sulfonamides appeared thereafter with about 5.000 substances developed during years 1932-1945. Sulfonamides were effective in urinary tract infections, shigellosis, pneumococcal pneumonia and even in purulent meningitis. But the effect of sulfonamides was totally exceeded with penicillin and streptomycin. It was a happy chance that these two antibiotics covered the whole spectrum of bacteria. Penicillin was very effective against the most danger microbes of that time – pneumococci and streptococci – and also against other important pathogens like staphylococci, meningococci, gonococci, *Corynebacterium diphtheriae*, or *Treponema pallidum*. Streptomycin killed the gram-negative aerobic bacteria and *Mycobacterium tuberculosis*.

The nice ideas of solving the problems of infectious diseases were lost some years later because of two new phenomena: 1) The new bacterial agents were discovered that were not affected with penicillin or streptomycin. Typical representatives of such agents were mycoplasmata, chlamydiae or rickettsiae. 2) The much more important phenomenon was the advent of resistance. Staphylococci were the first important pathogens that developed resistant strains (first described in 1946, 5 years after introduction of penicillin) and these resistant variants spread throughout the whole world within fifties. The other microbes followed up in this way.

Both the above mentioned problems seemed to be solved with extensive discovering of new antibiotics. But many of them were too toxic (neomycin, colimycin) and/or poorly purified (original form of vancomycin) and their use had to be diminished. A new step in progress was done in 1960 when first semisynthetic antibiotics were prepared from the penicillin molecule – methicillin and ampicillin. These drugs were active against staphylococci and common gram-negative bacteria like *E.coli*, *H.influenzae* or *S.enterica* (including *S.typhi abdominalis*). Later on, many other semisynthetic antibiotics were made.

Coherently to the U.S. war in Vietnam in late sixties, the requirements of better health care raised for injured, burn or shocked soldiers. It was the time of advancement and expansion of intensive care. The patients became able to survive the acute phase of trauma or shock but died for infectious complications. These infections in critically ill patients were caused by microbes of little virulence that have not been known as pathogens so far. These new pathogens recruited from the hospital environment (*Pseudomonas sp.*, *Serratia sp.*, *Acinetobacter sp.*): their common feature was inherent resistance to antibiotics and disinfecting substances. The treatment of these infections – that are typically of nosocomial origin - was very difficult and led to extensive research. Many new antibiotics are products of this effort: modern aminoglycosides, anti-pseudomonadal penicillins and other beta-lactams.

Later on, another group of pathogens became important: In critically ill patients whose immunity was diminished and whose natural barriers were broken with multiple invasive devices or procedures, the native skin or mucosal colonizing flora asserted: coagulase-negative staphylococci, enterococci, *Candidae*. Despite some new discoveries (teicoplanin, triazol antimycotics), the account of anti-infective drugs in this field is unsatisfactory.

Many new antibiotics with high level of compatibility for patients were introduced for treatment of community infections as well. Oral cephalosporins, new macrolides, doxycyclin and fluoroquinolones are examples of these modern – and sometimes fashionable – drugs. Nevertheless, production of the easy-to-take and relatively safe antibiotics often led to the overuse and rapid rise in resistance in bacterial populations.

Some types of resistance can be reversed with introducing new sorts of drugs. Unfortunately, microorganism can race with introduction new drugs successfully. In addition, some mechanisms of resistance are not revertible. It is clear that the threat of resistant bacteria has been growing in community as well as in hospital environment.

The problem of resistance can be solved only with accepting following demands (the specification is not complete):

- Diminishing the overuse of antibiotics. The commonest mistake in the community is prescribing antibiotics to patients with an infection of (probable) viral origin and/or with a mild and easily self-limited disease. The commonest mistake in hospitals is an unnecessary and/or too long antibiotic prophylaxis in surgery.
- Consistent preference of narrow spectrum antibiotics whenever possible.
- Preference of a short course of higher dosed antibiotic to a long course of lower dosed drug.
- Isolation of inpatients or hospital staff in whom infection or colonization with multiresistant strain is recognized.
- Skilled experts must control prescription of antibiotics in both hospitals and community.

## **BETA-LACTAM ANTIBIOTICS**

**Basic characteristics:** They are bactericidal drugs. They inhibit building of bacterial cell wall by interference with the synthesis of peptidoglycan. The bacterial enzymes that are affected by beta-lactams are called penicillin-binding proteins (PBPs). There are various PBPs differing in their detail function, quantity, and affinity for beta-lactams.

Principally, the effect of beta-lactams is mostly expressed against multiplying bacteria that are building their cell wall intensively. On the other hand, beta-lactams could not be effective against microbes without the peptidoglycan-containing cell wall (chlamydiae, mycoplasmata, rickettsiae, mycobacteria).

**Pharmacokinetics:** The great number of individual drugs can not be described with a uniform pattern. Many beta-lactams are acid-labile and decompose with gastric juice. In addition, absorption of beta-lactams from the gastrointestinal tract is limited. The majority of beta-lactams has been prepared only in parenteral form. Esterification of the original drug is sometimes performed in order to facilitate the absorption; these esterified beta-lactams should be administered with food.

Beta-lactams are spread mostly in the extracellular space. The penetration across biological barriers is limited, sometimes it can be reversed with higher dosing. Intracellular penetration of beta-lactams is poor.

The vast majority of beta-lactams are excreted through the kidneys but exceptions do exist (oxacillin, cefoperazone, ceftriaxone).

The half-life of beta-lactams is rather short and varies from a half an hour (penicillin, oxacillin, cephalotin) to 2-2,5 hours. An exceptional long half time has ceftriaxone (8 hrs) allowing once daily administration.

**Pharmacodynamics:** The effect of beta-lactams depends on the „time above MIC“. The target of dosing is to keep the level of antibiotic above MIC at the site of infection as long as possible. The peak concentration is not very important. In mild infections, the level of drug is sufficient that exceed MIC for 40-50% of the dosage interval.

Beta-lactams – with exception of carbapenems - perform only short or none postantibiotic effect.

**Undesirable effects:** Beta-lactams are not toxic and have minimum concentration-dependent adverse effects. The extent of dosing is extremely high, especially in penicillins.

Most important undesirable effects are allergic reactions of various intensity (mainly caused with penicillins), phlebitis while intravenous administration (hyperosmolar solutions), local pain and infiltrates while intramuscular administration, and thrombocytopenia or other changes of blood picture (mainly during cephalosporin treatment). The broad-spectrum antibiotics dispose to dysmicrobia including postantibiotic colitis. Any allergy to penicillins or cephalosporins should be proven with examination of antibody level in blood. The true allergy to any penicillin drug must be interpreted as allergy to all penicillins. The allergy to a cephalosporin need not necessarily imply the allergy to all other cephalosporins (the reaction can be targeted against the complicated side chain of drug). The cross-allergy between penicillins and cephalosporins is possible but not frequent. The probability of allergy to cephalosporins in patients allergic to penicillins was estimated 5-10%. Therefore, cephalosporins can be given with caution in patients with history of a mild penicillin allergy (exanthema). On the other hand, allergy to cephalosporins implies high probability of cross-allergy to penicillins. Beta-lactams can be used in gravid or breast-feeding women, and in newborns.

**Disposal:** Beta-lactams are best employed for treatment of acute infections in a well perfused tissue, or for treatment of sepsis. Some drugs are also suitable for surgical prophylaxis.

More frequent dosing is advisable to reach the strong effect. The enhancing the individual doses is necessary when penetration to the site of infection is problematic.

### **A) Penicillins**

The group can be divided in four subgroups:

#### **1) Natural penicillins**

They have narrow spectrum containing gram-positive and –negative cocci (streptococci, pneumococci, enterococci, meningococci), gram-positive bands (corynebacteria, L.monocytogenes), spirochetes (Leptospira sp., Treponema sp., Borrelia sp.), and most of anaerobes (peptostreptococci, clostridial species, Actinomyces).

**penicillin G or benzylpenicillin** (unstable in gastric acid juice, suitable only for intravenous administration)

**penicillin V or phenoxymethylpenicillin** (acid-stable form, for oral administration)

**procain-penicillin** (depot form, for intramuscular administration, usually once daily)

**benzathinpenicillin** (depot form, creating stable low level of antibiotic for 2-4 weeks, useful for prophylaxis of streptococcal reinfections)

The dosage spectrum of penicillin is extremely broad (1 mill.U. till 40 mill.U. daily for adult person according to the type and severity of infection). For comparison 1,000,000 units equals 625 mg of penicillin.

The typical situations for the low-dose penicillin treatment are pseudomembranous tonsillitis, streptococcal skin infections (impetigo), or animal bite and scratches. High-dose treatment is given to patients with infective endocarditis (caused by viridans streptococci or enterococci), streptococcal, pneumococcal or meningococcal sepsis, clostridial wound infection.

#### **2) Anti-staphylococcal penicillins**

They are resistant to staphylococcal beta-lactamase but not to other beta-lactamases produced by gram-negative microbes. The drugs have a very narrow spectrum because the effect against gram-positive bacteria other than staphylococci is weaker comparing to penicillin G.

**methicillin** (only parenteral forms), **nafcillin**, **oxacillin**, **cloxacillin**, **dicloxacillin**

Oxacillin is the only drug registered in the Czech Republic. The daily dosage of oxacillin is 2g - 12g.

*Remember: Methicillin-resistant strains of Staphylococcus aureus (MRSA) or Staphylococcus epidermidis (MRSE) have changed their PBP receptor and therefore are resistant to all beta-lactam antibiotics. These microbes used to be simultaneously resistant to macrolides and lincosamides. Drug of choice in this situation is vancomycin.*

3) Aminopenicillins

The drugs owe spectrum similar to natural penicillin with extension against common gram-negative bacteria like Escherichia coli, Salmonella enterica, Shigella sp., Proteus mirabilis, Helicobacter pylori, or Haemophilus influenzae. They are more effective than natural penicillin against enterococci and listeriae.

**ampicillin** (the basic representative of the subgroup, suitable for parenteral administration)

**amoxicillin** (better adsorption after oral administration than ampicillin: 70-80% vs. 40-50%)

The daily dosage of ampicillin is 2g - 12g.

*Remember: Aminopenicillins should not be prescribed for patients suffering from tonsillitis until infectious mononucleosis has been excluded. Patients with mononucleosis readily develop severe maculopapular exanthema even after a few tablets of aminopenicillin. This effect is caused by production of heterophile antibodies and should not be interpreted as true and lasting allergy.*

Because many strains of the above-mentioned gram-negative bacteria have become resistant due to plasmide-related production of beta-lactamase, new formulae were made containing the antibiotic together with a beta-lactamase inhibitor. Two combinations are available, both for oral and parenteral administration:

**ampicillin + sulbactam**

**amoxicillin + clavulanic acid**

The combinations are effective against above-mentioned gram-negative microbes owing beta-lactamase, and against Staphylococcus aureus. On the other hand, these antibiotics are needless and should not be prescribed against streptococci, enterococci or other bacteria that do not produce beta-lactamase.

Aminopenicillins with or without beta-lactamase inhibitor are widely used in clinical practice. They are given in bacterial sinusitis, mesotitis and lower respiratory tract infections, urinary and hepatobiliary tract infections, purulent gynecological infections, and other community-acquired infections.

*Remember: 1) Bacteria have developed many beta-lactamases, and only some of them can be destroyed with inhibitors. Many bacteria causing community acquired infection use to dispose plasmide-transmitted lactamases that can be inhibited with sulbactam, clavulanic acid or tazobactam. However these inhibitors do not work against lactamases produced by majority of nosocomial pathogens.*

*2) Beta-lactamase inhibitors possess weak, in any, natural antibacterial activity. From general point of view, minimal clinically important difference exists between the three drugs.*

4) Penicillins effective against pseudomonads (and other problematic gram-negative pathogens owing natural resistance)

**karbenicillin**, **ticarcillin**, **azlocillin**, **mezlocillin**, **piperacillin** (only for parenteral usage)

These drugs are given in intensive care infections, according to the cultivation results. The only route of administration is intravenous. Usually, the third generation cephalosporins are preferred to these drugs because of lower costs.

Combination of these antibiotics and beta-lactamase inhibitors were made as well:

**ticarcillin + clavulanic acid**, **piperacillin + tazobactam**

Their use is similar to the basic drugs.

**B) Cefalosporins**

Cephalosporin antibiotics are divided in four subgroups called generations. The individual drugs are arranged into generations according their spectrum of antibacterial activity (including the susceptibility/resistance to beta-lactamases) – not according to their date of synthesis or introducing to the market.

More than one hundred cephalosporins have been developed in numerous pharmaceutical companies all over the world. Only the drugs registered in the Czech Republic are listed below.

*Remember: Although cephalosporins are relatively broad-spectrum antibiotics, none of them is effective against enterococci and listeriae.*

1<sup>st</sup> generation

The drugs are used predominantly against gram-positive cocci (streptococci and staphylococci). Their spectrum further includes corynebacteria, meningococci, and some community-acquired stems of gram-negative rods like Escherichia coli or Proteus mirabilis. The drugs are active against anaerobes in the extent similar to penicillin.

**cefalotin** - CLT, **cefazolin** – CZL (for parenteral administration)

**cefalexin** - CLX, **cefadroxil** - CDR, **cefactor** – CCL (for oral administration)

(cefactor has moderate effect against Haemophilus, so it belongs to „one-and-half generation“)

The drugs are predominantly used for treatment skin and soft tissue infections, and for prophylaxis in surgical procedures (except colorectal surgery and situations when methicillin-resistant staphylococci are spread in the surgery department).

### 2<sup>nd</sup> generation

The drugs contain antibacterial activities of the 1<sup>st</sup> generation and extend to further community-acquired gram-negative bacteria like *Haemophilus influenzae*, *Moraxella catarrhalis*, or less susceptible strains of *E. coli* or similar pathogens.

**cefuroxim** - CRX, **cefamandol** – CMN (for parenteral administration)

**cefuroxim-axetil** (for oral administration)

The drugs are prescribed for treatment respiratory tract infections (bacterial sinusitis or mesotitis, pneumonia), and urinary and hepatobiliary tract infections. They can be used for prophylaxis in surgery as well.

**cefoxitin** – CXT (only parenteral administration)

It is a representative of cefamycines. These antibiotics are closely related to true cephalosporins differing in one substituent on cephem nucleus. Their common feature is a very good activity against relatively resistant anaerobe *Bacteroides fragilis*. With its antibacterial activity against other microbes, cefoxitin has been joined to the 2<sup>nd</sup> generation cephalosporins. Its typical disposal is intra-abdominal, pelvic, and gynecological infections, foot infections in diabetics, infected decubitus ulcers and other mixed aerobic-anaerobic infections.

Unfortunately, resistance to cefoxitin raises quickly in departments where this drug used to be given frequently.

### 3<sup>rd</sup> generation

The drugs can be divided in two subgroups according to their activity against *Ps. aeruginosa*:

The subgroup A consists of antibiotics of similar spectrum as 2<sup>nd</sup> generation but with enhanced activity against gram-negative bacteria and weaker effect against staphylococci.

**cefotaxim** – CTX, **ceftriaxon** – CTR (for parenteral administration)

These drugs are used for treatment of severe and life-threatening infections caused by community gram-negative pathogens like *E. coli*, *H. influenzae*, meningococci, salmonellae etc. The relevant clinical diagnoses are purulent meningitis, epiglottitis, sepsis of urinary or hepatobiliary tract origin etc.

Ceftriaxon is an antibiotic of extreme long half-time (8 hrs) in addition that allows once-daily administration.

This feature makes the treatment easier but is of especial importance in treatment of outpatients or in home treatment.

**cefetamet-pivoxil**, **cefpodoxim-proxetil**, **cefixim**, **ceftibuten** (for oral administration)

The position of these antibiotics is rather problematic. They can be used for treatment of mild or moderate community acquired infections but cephalosporines of 2<sup>nd</sup> generation suffice in these situations usually. The only rational indication remains infection caused by pathogens of microbiologically verified intermediate sensitivity where 2<sup>nd</sup> generation cephalosporins perform only a weak effect.

The subgroup B included antibiotics effective against *Ps. aeruginosa* and other “problematic gram-negative pathogens”. However, the stronger is the anti-pseudomonadal effect, the weaker is the activity against staphylococci and other gram-positive microbes.

**ceftazidim** – CTZ, **cefoperazon** – CPR (for parenteral administration)

These antibiotics are used in nosocomial infections/sepsis caused by gram-negative bacteria. Ceftazidim is strongest anti-pseudomonadal cephalosporin. Cefoperazon’s unique feature is predominant excretion via the bile: this advocates for its usage in hepatobiliary tract infections and in renal insufficiency. Cefoperazon is available in a mixture with beta-lactamase inhibitor as well: **cefoperazon/sulbactam** that can be worthy against *Acinetobacter* sp. and some “problematic pathogens” owing beta-lactamase activity.

### 4<sup>th</sup> generation

Antibiotics of this group have a broad spectrum summarizing the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> generation. They can resist some potent beta-lactamases. Nevertheless, their activity against staphylococci is not better than with cephalotin and activity against *Ps. aeruginosa* is not better than with ceftazidim.

**cefpirom**, **cefepim** (only parenteral administration)

These antibiotics are used in nosocomial infections of special resistance pattern (stable derepression of ampC gene) or in nosocomial sepsis of unknown origin where covering the broad spectrum of pathogens is necessary (i.e. febrile neutropenia).

### C) Carbapenems

They are very potent antibiotics of extremely broad spectrum including majority of gram-positive and gram-negative pathogens. These antibiotics resist effect of many beta-lactamases, too. The group of not affected microbes embraces methicillin-resistant staphylococci, *Clostridium difficile*, *Stenotrophomonas maltophilia*, *Pseudomonas cepacia* and some exceptionally resistant strains of enterococci, *Acinetobacter*, or *Pseudomonas*.

**imipenem**, **meropenem** (only parenteral administration)

These antibiotics are reserved for extreme resistant nosocomial infections/sepsis.

### D) Monobactams

Monocyclic beta-lactams are active against Enterobacteriaceae, *Pseudomonas*, and other gram-negative aerobic microorganisms. They resist many bacterial beta-lactamases.

**aztreonam** (only parenteral administration)

This antibiotic is reserved for nosocomial infections/sepsis caused by resistant gram-negative bacteria. Because of its lack of cross-reactivity, it can be given to patients with allergy to penicillin or cephalosporins.

### **GLYCOPEPTIDES**

**Basic characteristics:** They are bactericidal drugs inhibiting bacterial cell wall synthesis in a step prior to beta-lactam action. They may also injure bacterial protoplasts or interfere with RNA synthesis.

Because of their large molecule that does not penetrate into the periplasmic space of gram-negative bacteria, their antibacterial spectrum is narrow and involves only gram-positive microbes.

**Pharmacokinetics:** The drugs are not absorbed from the gastrointestinal tract. Penetration across biological barriers is poor. The drugs are excreted almost exclusively by glomerular filtration.

**Pharmacodynamics:** The effect of glycopeptides depends on the „time above MIC“. They perform a postantibiotic effect of about 2 hours.

**Disposal:** Reserve antibiotics for the treatment of serious gram-positive infections. They are used when beta-lactams can not be given because of allergy of the patient or because of resistance of the microbe. The typical indications are staphylococcal, enterococcal, or streptococcal infections: sepsis, endocarditis, joint infection, (nosocomial) pneumonia.

#### **vancomycin**

Its usage requires special caution: The drug must be administered in a slow infusion ( $\geq 1$  hour) and serum concentration should be measured. The dosage must be balanced very carefully because of significant nephrotoxicity and ototoxicity of the drug. In the treatment period, renal function should be monitored thrice or twice a week.

Adverse effects of vancomycin involve fever, chills, exanthema, and phlebitis at the site of infusion. Reversible leukopenia, thrombocytopenia, or eosinophilia may develop as well. Flushing due to histamine release (“red man syndrome”) and/or hypotension frequently occur after rapid intravenous administration. Renal failure and hearing loss are the most feared sequelae of treatment with vancomycin: nevertheless, they are not frequent when the above mentioned recommendations are kept.

Vancomycin can also be given orally when pathogenic bacteria are localized in intestinal lumen. The typical example is colitis caused by *Clostridium difficile*.

Vancomycin is sometimes used in mixture with other non-absorbable antibiotics for “disinfecting” of the gastrointestinal tract – in neutropenic patients, in ICU patients requiring mechanical ventilation, or in patients preparing for great colic surgery. Nevertheless, the arguments for using vancomycin in these indications are rather doubtful because of limited benefit and impressive threat of selection resistant enterococci and other microbes when this prophylaxis is given frequently in a hospital.

#### **teicoplanin**

This antibiotic penetrates better in tissues except brain. It has a very long half-time (33-70 hours) and can accumulate in organism. The first three doses should be given in 12-hour period for saturation, then the drug can be given once daily or in every-other-day regime.

Teicoplanin is well tolerated and can be administered in a rapid infusion, slow intravenous injection, or intramuscular injection. The adverse effects are much less frequent. The allergy and also resistance is only partially crossed between vancomycin and teicoplanin. The main limiting factor of teicoplanin prescription is its relatively high cost.

In practice, teicoplanin used to be given when vancomycin treatment can not be continued because of allergy, renal failure, impossibility of further intravenous administration etc. Because of its long half-time, teicoplanin is very useful for the outpatient therapy.

### **AMINOGLYCOSIDES**

**Basic characteristics:** They have very strong and rapid bactericidal effect on bacteria. They act in several sites of bacterial cell (outer membrane, ribosomes). A very important feature of aminoglycosides is synergism with the wall-affecting antibiotics (beta-lactams, glycopeptides). This synergism is expressed against some gram-positive (streptococci, enterococci) as well as gram-negative (*E.coli*, *Pseudomonas*) bacteria.

Aminoglycosides are not effective against anaerobes, spirochetes (genus *Leptospira*, *Borrelia*, *Treponema*), obligatory intracellular pathogens (*Chlamydiae*, *Rickettsiae*, *Legionellae*), and capsulated pathogens (*Pneumococci*, *Salmonella typhi*, *Haemophilus influenzae*).

**Pharmacokinetics** of aminoglycosides is similar to that of vancomycin. They are not absorbed from the gastrointestinal tract. Penetration across biological barriers is poor. Volume of distribution correlates closely with the volume of extra-cellular fluid. The drugs are excreted unchanged by glomerular filtration.

**Pharmacodynamics:** The bactericidal effect is concentration-dependent. It relates to the peak concentration of the antibiotic at the site of infection. Postantibiotic effect (PAE) lasts several hours depending on the reached peak concentration.

The effectiveness of aminoglycosides is influenced with pH: It is optimal in mild alkaline pH and loses activity rapidly with lowering pH under 6.5.

**Disposal:** Aminoglycosides are preferably used in combination with other antibiotics. Typical indications for usage aminoglycosides include

- a) severe infections or sepsis caused by gram-negative microbes, staphylococci, or *M.tuberculosis*: Aminoglycosides are given especially at the onset of therapy, for rapid lowering of the massive bacterial load.
- b) severe infections caused by semi-resistant microbes when monotherapy is not bactericidal: In these situations, synergistic effect of aminoglycosides and wall-affecting antibiotics is often utilized. Examples: nosocomial infections caused by resistant gram-negative bacteria, infective endocarditis caused by streptococci or enterococci, infections in immunocompromised patients in whom bactericidal activity of antibiotics is necessary.

*Remember: Aminoglycosides work excellent in blood, in extracellular fluid, and in urine. Their effect in the inner area of inflammation may be poor due to limited penetrance and acidic condition.*

**Undesirable effects:** Allergic reactions are rare. Gastrointestinal disorders are uncommon because of pharmacokinetics passing the gastrointestinal tract. Local events (irritation, thrombophlebitis) are rare as well. Nevertheless, the drugs are nephrotoxic and ototoxic: They can cause necrosis of the proximal tubular cells leading to reversible renal failure within several weeks or even days. They can cause irreversible hearing loss (cochlear damage) as well. The less feared side effect is vestibular toxicity. Another important side effect is neuromuscular blockade that can occur in predisposed patients (hypocalcemia, hypomagnesemia, myasthenia gravis) or in patients being treated with succinylcholin or other drug interfering with neuromuscular transmission.

In order to minimize the toxic effects, it is recommended

- to be careful of good water supply (daily diuresis  $\geq 2$  liters)
- to prefer higher doses for few days at the onset of therapy
- to respect a maximal treating period of 2-3 weeks, than a pause should follow of minimum 4-6 weeks
- to prefer once-daily administration (except infective endocarditis where multiple daily doses are preferred)
- while intravenous infusion, the time of administration should be 30-45 minutes (the period more than 1 hour enhances nephrotoxicity, the period less than 20 minutes enhances the risk of neuromuscular blockade)
- to monitor renal and auditive functions three times weekly
- to measure serum levels of aminoglycosides (especially the minimum serum level)

#### **Account of drugs:**

##### **streptomycin**

It is an old drug used in the treatment of tuberculosis. There are some more indications for the very special situations (severe infections caused by enterococci highly resistant to gentamicin).

##### **gentamicin, tobramycin, netilmicin**

Gentamicin is a standard and most widely used aminoglycoside in the Czech Republic. Tobramycin is somewhat more effective against *Pseudomonas*. Netilmicin is slightly less nephrotoxic. In practice, the difference between these antibiotics is not very significant.

##### **amikacin, isepamicin**

These antibiotics resist various bacterial destructive enzymes, so can be used against some more resistant stems of nosocomial gram-negative pathogens. They do not work stronger than gentamicin but are somewhat less nephrotoxic.

*Remember: The nomenclature of aminoglycosides may be confusing. The suffix "-mycin" is used for drugs produced by or derived from *Streptomyces* whereas "-micin" is reserved for drugs produced by or derived from other genus - *Micromonospora*.*

## **(FLUORO)QUINOLONES**

**Basic characteristics:** They are bactericidal antibiotics but are not as potent as beta-lactams or aminoglycosides. They interfere with DNA metabolism in the bacterial cell. They are active mainly against gram-negative bacteria but the modern drugs are effective against gram-positive bacteria, intracellular pathogens, and even some anaerobes.

The classification of quinolones is not stable. Some authors divide quinolones in three or four generations like cephalosporins but no system has been accepted generally. For not using the problematic terms of generations, I prefer speaking in descriptive way:

The group of older drugs consists of **nalidix acid, pipemidic acid, and oxolinic acid**. They are quinolones without fluorine substituent on their ring. They are only oral preparations. They absorb well from the gastrointestinal tract but achieve therapeutic concentration only in urine and partly in adjacent tissues like prostate. They also have a relatively high incidence of side effects and can induce resistance easily. They can be used in lower urinary tract infections caused by *E.coli* and other enterobacteria, and in prostatitis. At the border between the first and the second group is **norfloxacin**. This drug is fluorinated and more effective than the above mentioned antibiotics but still has the same unfavourable pharmacokinetic profile.

The second group of drugs consists of fluoroquinolones owing systemic effect. They spread well in the most tissues and penetrate into cells. Their spectrum is wider than in the former group: gram-negative bacteria including *Pseudomonas aeruginosa* and other less susceptible microbes, staphylococci, chlamydiae, legionellae, and some mycobacteria. However, they are not effective against pneumococci, streptococci, spirochetes, and

anaerobes. The most important representatives of this group are **ciprofloxacin, ofloxacin, and pefloxacin**. They differ especially in their route of elimination: Ofloxacin is excreted almost entirely by the kidney. Ciprofloxacin and pefloxacin are partly metabolized in the liver; and excreted via urine and feces.

These antibiotics are easy-to-take, cheap and popular in the treatment of urinary tract infections, intestinal infections, biliary tract infections, bone and joint infections, many sexually transmitted infections etc. They are also very effective against antropozoonoses caused by G-bacteria (Salmonella, Yersinia, Francisella, Campylobacter, Brucella,...), and against legionellosis. Unfortunately, resistance in some microbes is increasing.

The third group is composed of fluoroquinolones with a very broad spectrum of affected microbes: gram-negative and gram-positive bacteria, intracellular pathogens (chlamydiae, mycoplasmata), legionellae, majority of mycobacteria, and anaerobes including Bacteroides fragilis. They should remain reserve antibiotics for special situations but are offered for treatment respiratory infections when resistance to macrolides has been developed. Some of promising antibiotics of this group were withdrawn because of serious adverse reactions (sparfloxacin, trovafloxacin, grepafloxacin, clinafloxacin, sitafloxacin). New drugs are gatifloxacin, gemifloxacin and some others. They have not been approved for therapy in the Czech republic yet.

**Adverse events** in quinolone antibiotics are heterogenous and differ in various drugs in both frequency and severity. They are gastrointestinal disorders, fotosensibilisation, allergy, leucopenia, thrombocytopenia, spasms, tendinitis, and even tendon ruptures. They affect pharmacokinetics of drugs metabolized in liver cytochrome P450 system.

Quinolones are not approved for gravid or breast feeding woman and children until 18 years. This was decided by authorities of all developed countries because of studies that demonstrated damage of growing chondrae in tested animals. It is true, however, that this adverse reaction has not been reported in man. Therefore, some experts recommend giving these drugs to children who can not be treated with safer antibiotics. A typical example of this situation is pseudomonadal respiratory infection in a patient with mucoviscidosis.

## **NITROIMIDAZOLES**

**Basic characteristics:** They are bactericidal narrow-spectrum antibiotics, effective against most anaerobes (except aktinomycetes, Propionibacterium acnes and anaerobic-growing streptococci) and some protozoa (Trichomonas vaginalis, Entamoeba histiolytica, and Giardia lamblia). The antibiotics interfere with electron transport in anaerobic metabolic pathways of bacterial or protozoal cells.

**Pharmacokinetics:** The drugs are very well absorbed from the gastrointestinal tract. After absorption, they posse excellent penetration across biological barriers including blood-brain and placental barrier. The drugs are metabolized in the liver by 40% and excreted mainly by the kidney.

**Adverse events** are usually mild and include gastrointestinal disorders (glossitis, metallic taste, dry mouth, nausea), allergy, headache, dizziness etc. Neurotoxicity was reported as a seldom reaction (seizures, encephalopathy, peripheral neuropathy, ataxia). The drugs have some mutagenic and cancerogenic activity in laboratory studies but it has not been proven in man. In patients ingesting alcohol, nitroimidazoles cause disulfiram-like effect with severe vomiting. The drugs also inhibit the metabolism of oral anticoagulants. Nitroimidazoles are not approved for gravid women. They and not advised for long treatment (polyneuropathy).

**Disposal:** Nitroimidazoles are used in

- moderate to severe anaerobic infections including life-threatening clostridial infections (gas gangrene) and pseudomembranous colitis caused by Cl.difficile,
- mixed bacterial infections (in combination with other antibiotics),
- above mentioned protozoal infections.

### **metronidazol**

It is the most widely used nitroimidazole because of persisting in prescription habits and low cost.

### **ornidazole, tinidazole**

They have more advantageous phamacokinetic parameters (a half-time of 13 hours allowing once-daily administration) and less frequency of adverse events.

## **CHLORAMPHENICOL**

**Basic characteristics:** The antibiotic posse bacteriostatic or -cidal activity against a variety of microbes including gram-positive and gram-negative bacteria, anaerobes, spirochetes, and obligatory intracellular pathogens (chlamydiae, rickettsiae, mycoplasmata). Mechanism of action is inhibiting protein synthesis on the ribosomal level.

**Pharmacokinetics:** The drug is well absorbed from the gastrointestinal tract: its serum levels after oral and intravenous administration are equivalent. Chloramphenicol penetrates excellently across biological barriers including the blood/brain and blood/liquor barrier. It enters the cell compartment as well.

Chloramphenicol is metabolized in the liver and then excreted by the kidney.

**Adverse events:** The most important undesirable effect of chloramphenicol is its toxicity for bone marrow. It is manifested by anemia, leucocytopenia, thrombocytopenia, or any combination thereof. Two forms of toxicity are distinguished:

- a) early toxicity occurring usually after 2 weeks of treatment. It is dose-dependent and reversible.

- b) delayed toxicity (aplastic anemia) that can develop several weeks or months after the cure. It is dose-independent and irreversible. The frequency of this event was estimated as 1:40.000 (range 1:20.000 to 1:200.000).

The other adverse events are rare. Nevertheless, numerous drug interactions were described with chloramphenicol.

Chloramphenicol must not be prescribed for gravid women and it is not advisable for newborns and sucklings: the liver in very young organism can not metabolize chloramphenicol sufficiently and the drug cumulates in tissues constituting so-called gray baby syndrome.

**Disposal:** Because of the risk of aplastic anemia, chloramphenicol is used only as a reserve drug – despite its broad spectrum and advantageous pharmacokinetic parameters.

The acceptable indications are:

- brain abscess and purulent meningitis (because of excellent penetration)
- severe infections/sepsis caused by mixed aerobic and anaerobic flora (peritonitis, septic thrombophlebitis in abdominal area, severe forms of pelvic inflammatory disease, chest empyema caused by mixed flora)
- severe rickettsial infections (Q fever, Rocky Mountains spotted fever, typhus)

Former indications (typhoid fever, invasive Salmonella infections, pertussis, epiglottitis etc) are left because cephalosporines of 2<sup>nd</sup> or 3<sup>rd</sup> generation or fluoroquinolones can be given instead.

## LINCOSAMIDES

**Basic characteristics:** They are two static antibiotics reversibly inhibiting protein synthesis on ribosomal level in the same way as macrolides. However, they have narrow spectrum and are active only against gram-positive bacteria (mainly staphylococci and streptococci) and anaerobes. Clindamycine is also active against some protozoa. Resistance to lincosamides is completely crossed mutually, and partially crossed with macrolides.

**Pharmacokinetics:** Both antibiotics are absorbed from the gastrointestinal tract or can be given parenterally. They penetrate well in most tissues including bone but do not pass the blood-brain barrier. Like macrolides, they concentrate in phagocytic cells and achieve high levels in pus. They are partly metabolized in the liver and excreted in the bile and urine.

**Undesirable effects:** The antibiotics are not toxic. Allergic reactions or gastrointestinal intolerance can occur. The most important adverse reaction in antibiotic-associated pseudomembranous colitis caused by *Clostridium difficile*. These reaction can occur in association with administration of other antibiotics (aminopenicillins, some cephalosporines) as well.

**Disposal:** The antibiotics suit better to subacute infections than to acute infections or sepsis (static effect, good penetration). Their usage is more appropriate in community-acquired than in nosocomial infections. Methicillin-resistant staphylococci (MRSA, MRSE) are readily resistant to lincosamides.

Lincosamides are used especially in mixed staphylococcal/streptococcal infections or in infections caused by mixed aerobic/anaerobic flora. Main indications are skin and soft tissue infections, diabetic foot, odontogenic infections, tonsillitis and peritonsillar abscess, and aspiratory pneumonia. Clindamycin in combination with anti-parasitic drugs is prescribed for treatment malaria, toxoplasmosis, or amebiasis.

### **lincomycin**

It is somewhat weaker than clindamycin and was replaced with clindamycin in majority of indications. Its only advantage is a possibility of enhancing the dosage up to 10-15 g daily. It may be important in some situations where penetration into the site of infection is problematic. However, these high doses must be given in slow infusions because of risk of hypotension.

### **clindamycin**

The antibiotic works stronger and is better absorbed when administered orally. The drug is prepared in a form of phosphate and must be decomposed in organism with enzymes (phosphatases) to make an active antibiotic. Because of saturability of these enzymes, the total daily doses of clindamycin should not exceed 4,8 g.

## TETRACYCLINES

**Basic characteristics:** They are static antibiotics reversibly inhibiting protein synthesis. They block bacterial ribosomes in other site than do macrolides and lincosamides. Originally, their antimicrobial spectrum was broad including many gram-positive and –negative bacteria, and anaerobes. Unfortunately, many pathogens have developed resistance. At present time, tetracyclines are preferentially used in treatment of various infections caused by non-pyogenic bacteria. Resistance within tetracycline family is completely crossed.

**Pharmacokinetics:** Tetracyclines are well absorbed from the gastrointestinal tract. They penetrate excellently into various tissues and into cells. They are excreted into mucosal fluid, breast milk, bile and urine in clinically significant concentrations (see below). Nevertheless the drugs excreted into bile is reabsorbed in the gut (enterohepatic circulation).

**Adverse events:** Gastrointestinal and neurovegetative disorders of variable intensity are relatively frequent. Oral, intestinal, vaginal and skin dysmicrobia is common as well: candidial superinfection is a frequent consequence. Mild to moderate liver or renal damage can occur. Photosensitivity reactions can be seen in patients who stay in the sun shine. In children, permanent teeth discoloration develops related to the total amount of absorbed tetracycline.

Tetracyclines must not be prescribed for gravid and breast feeding women and for children until 8 years.



Many interactions were reported at concomitant treatment with tetracyclines and various other drugs.

**Disposal:** There are several indications which tetracyclines are used in:

- 1) Respiratory, genitourinary or ocular infections caused by chlamydiae, mycoplasmata, and ureaplasmata. These infections include “atypical pneumonia”, acute and chronic urethritis and/or urethral syndrome, epididymitis, cervicitis, some of pelvic inflammatory diseases, inclusion conjunctivitis and trachoma. (Alternative drugs are macrolides.)
- 2) Rickettsial infections: Q fever, ehrlichiosis, typhus fever etc. (Alternative drug is chloramphenicol.)
- 3) Spirochetal infections: Lyme borreliosis, relapsing fever (*Borrelia recurrentis*), leptospirosis, syphilis and other treponemal infections. (Alternative drugs are penicillins, cephalosporines, macrolodes.)
- 4) Some other anthroozoonoses caused by non-pyogenic bacteria: brucellosis, campylobacteriosis, malleus, pasteurellosis, plague, rat-bite fever, or tularemia. (Alternative drugs are fluoroquinolones.)
- 5) Mild to moderate infections caused by anaerobes: acne, actinomycosis, some pelvic inflammatory diseases. (Alternative drugs are lincosamides and other antibiotics effective against anaerobes.)

*Remember: In majority of above-mentioned pathogens, no systematic monitoring of resistance exists due to problems with cultivation. The percentage of resistance (and probability of successful treatment with various antibiotics) is not known.*

#### **tetracycline, oxytetracycline**

These drugs are rather of historical importance. They are replaced with new tetracyclines:

#### **doxycycline, minocycline**

These tetracyclines are better absorbed from gastrointestinal tract and have longer half-time (about 17 hours) allowing once-daily administration. They have substantially lower frequency of adverse events. Doxycycline is excreted via intestinal secretion, too, allowing treatment even in renal insufficiency.

### **MACROLIDES and relative drugs**

**Basic characteristics:** They are static antibiotics reversibly inhibiting protein synthesis on ribosomal level. In some microorganisms, the effect of macrolides can be cidal in appropriate circumstances. The structure is derived from a 14- to 16-member macrocyclic lactone ring, therefore the class name “macrolide”.

Macrolides undergone an impressive evolution: Originally, they exhibited a broad-spectrum antibacterial activity involving gram-positive and gram-negative bacteria, anaerobes, spirochetes, and obligatory intracellular pathogens (chlamydiae, mycoplasmata). The most important drug of that time was erythromycin. Its usage was limited because of frequent disagreeable side effects like nausea and vomiting. In 80ties, modern macrolides were introduced widely. They became very popular because of low frequency of side effects and comfortable usage. Nevertheless, frequent resistance has been developed mainly in gram-positive cocci (staphylococci, streptococci, and pneumococci) and in gram-negative bands (enterobacteria, *H.influenzae*) as a consequence of their massive prescription. The number of resistant pathogens exceeds 50% in many countries and their further destiny become problematic.

*Note: Some antibiotics of the macrolide family interfere with gastric motility and with cell differentiation and growth. Special drugs used in gastroenterology and oncology were derived from these originally antibacterial medicaments.*

*Macrolides have not only anti-bacterial but also anti-inflammatory effect. That is why they can seem effective even in viral infections or in some chronic respiratory diseases where allergy to bacterial or environmental antigens are the main cause of illness.*

**Pharmacokinetics:** The drugs are fairly absorbed from the gastrointestinal tract. They penetrate into most tissues and host cells excellently. The concentrations in phagocytic cells exceed peak maximum serum levels by severalfold. On the other hand, macrolides penetrates poorly into brain, synovial fluid and fetal tissues. The drugs are excreted into mucosal fluid, breast milk, bile and urine. The ratio of urinary/fecal excretion is variable. The portion of drug excreted into bile is partially reabsorbed in the gut (enterohepatic circulation). Some drug is metabolized in the liver as well.

**Adverse reactions:** Macrolides are very safe and non-toxic antibiotics. Nevertheless, gastrointestinal disorders may occur, especially with 14-chain macrolides like erythromycin (see below). Allergic reactions (rash, fever or eosinophilia) are infrequent. Liver damage can occur after esterified erythromycin, especially in pregnancy. Various interactions have been reported between macrolide and other drugs. They are based on inactivating the cytochrome P-450 hepatic enzyme system or on changes in bioavailability due to affecting gut flora. Generally, macrolides can be prescribed for gravid woman. Claritromycin was reported to interfere with angiogenesis and produce teratogenic effect in animals when high dosed but it is approved with caution for gravid woman.

**Disposal:** Macrolides are used in respiratory infections, mainly in “atypical pneumonia” and in legionellosis. The other indication is urogenital infections caused by chlamydiae, mycoplasmata, and ureaplasmata. Macrolides may be used for treatment tonsillitis or lyme borreliosis (erythema migrans) in patients with allergy to beta-lactam antibiotics.

Special indications include campylobacteriosis, tularemia in children, mycobacteriosis (in association with other antibiotics) etc.

*Remember: Except legionellosis, macrolides should not be used for treatment severe infections. Their prescription must be correlated to the frequency of resistance in pathogenic microbes in every country or district. Generally, macrolides are not appropriate for treatment staphylococcal infections as well.*

**Account of drugs:** The family of macrolides is divided according to the number of members in their lactone ring. The 14-chain macrolides have stronger antibacterial effect but higher frequency of adverse reactions

#### **erythromycin**

The oldest macrolide. Its usage is associated with relatively frequent vomiting or reversible hepatic damage mainly in older preparations.

#### **roxithromycin, claritromycin**

Modern macrolides. Roxithromycin works somewhat weaker than erythromycin, claritromycin is relatively strong. Clarithromycin's influence on angiogenesis was mentioned above.

Members of the 16-chain lactone subgroup work relatively weaker than the 14-chain macrolides but have minimum adverse events.

#### **spiramycin, josamycin**

They are especially suitable for infants and children or for long-time administration (therapy of toxoplasmosis in gravid women, long time prophylaxis of streptococcal infections in patients with allergy to beta-lactams).

Similar to macrolides are azalides. The representative of those drugs is **azithromycin**. This drug is somewhat more active against sensitive gram-negative microbes and has very special pharmacokinetic parameters:

- very long half-time (2-4 days): a 3-day administration can make therapeutic levels in tissues for 7-14 days
- the drug is transported to a locus of inflammation in leukocytes. Consequently, drug concentration in the site of inflammation is high, whereas serum concentration is extremely low.

### **CO-TRIMOXAZOL**

**Basic characteristics:** The drug consists of synergistic combination of two inhibitors of folic acid metabolism: **sulfamethoxazole + trimethoprim**. Both the sulfonamides and trimethoprim are static but the combination can have cidal effect against some bacteria. Sulfonamides were introduced before true antibiotics (table 1). Their usage as isolated drug is limited nowadays because of frequent side effects and increased resistance.

Co-trimoxazol is active against common community pathogens like pneumococci, staphylococci, Neisseriae, E.coli other enterobacteria, and Haemophilus. Nevertheless, significant differences in local resistance do occur. Co-trimoxazol is not effective against most anaerobes, enterococci, streptococci, Pseudomonas sp.

*Remember that in vitro effectiveness of co-trimoxazol against enterococci is completely false: in vivo, enterococci can use folic acid from the host tissues, so the metabolic block of folic acid synthesis is not important.*

**Pharmacokinetics:** Both sulfamethoxazole and trimethoprim are well absorbed from the gastrointestinal tract and penetrate excellently into tissues and cells. They penetrate across blood-brain barrier and placental barrier, too. The drugs are partly metabolized in the liver and excreted almost entirely through the kidney.

**Adverse events** are relatively frequent and include allergy (rash or fever but also erythema multiforme including Stevens-Johnson syndrome, vasculitis and anaphylaxis), gastrointestinal disorders (nausea, vomiting, diarrhea), headache, hematotoxicity (neutropenia, thrombocytopenia, anemia), nephrotoxicity and fototoxicity. Sulfonamides compete for bilirubin-binding sites on plasma albumin and may increase blood levels of unconjugated bilirubin. Therefore, co-trimoxazol can not be given to pregnant women or to newborns and sucklings up to the age of 2 months. Frequent drug interactions also were reported between co-trimoxazol and other drugs.

**Disposal:** severe diarrheal diseases with fever (especially if salmonella is expected to be the cause), urinary tract infections, respiratory infections where pneumococcal or H.influenzae etiology can be expected (lobar pneumonia, sinusitis, otitis media). However, co-trimoxazol is rather a drug of second choice for most of these infections because safer and/or more effective alternatives do exist.

Special indications include therapy or prophylaxis in HIV/AIDS patients (pneumocystosis, toxoplasmosis, isosporosis), nocardiosis, brucellosis, long-term treatment of staphylococcal osteomyelitis etc.

Monotherapy of **trimethoprim** is used for treatment urinary tract infections in regions with isolated resistance to sulfonamides.

### **NITROFURANTOIN**

Bacteriocidal drug, nevertheless effective concentrations are reached only in urine.

**Spectrum:** good effect against enterobacteria (E.coli, Klebsiella, Enterobacter, ..), excellent effect against enterococci

**Adverse events:** frequent: allergy, gastrointestinal disorders, neuropathy, autoimmune pneumonitis  
The drug must not be used in gravid women

**Disposal:** therapy and prophylaxis of urinary tract infections

Local administration: vaginal globulae, pastae for dermatological praxis)

Table 1: Evolution of antibiotics/chemotherapeutics: Discovery of the first important preparations till 1950.

antibiotic	natural source	first description as anti-infective drug	discoverer
sulfanilamide (prontosil)	-	1932	G.Domagk
penicillin	Penicillium notatum	1941 <sup>1</sup>	A.Fleming, Florey, Chain
streptomycin	Streptomyces griseus	1944	S.A.Waksman
cephalosporin	Cephalosporium acremonium	1945	G.Brotzu
bacitracin	Bacillus subtilis	1945	B.A.Johnson
chloramphenicol	Streptomyces venezuellae	1947	I.Ehrlich
polymyxin	Bacillus polymyxa	1947	C.G.Ainsworth
chlortetracyclin	Streptomyces aureofaciens	1948	B.M.Duggar
neomycin	Streptomyces fradiae	1949	S.A.Waksman
oxytetracyclin	Streptomyces rimosus	1950	A.C.Finlay
colimycine	Bacillus colistinus	1950	Y.Koyama

<sup>1</sup> Penicillin was discovered by A.Fleming in 1928 but the first therapeutic usage was realized by Florey only in 1941.

Table 2: The much-feared resistant bacteria

nosocomial environment	<ul style="list-style-type: none"> <li>• MRSA = methicillin resistant Staphylococcus aureus<sup>1</sup></li> <li>• MRSE = methicillin resistant Staphylococcus epidermidis</li> <li>• VISA/GISA = vancomycin or glycopeptide intermediate (resistant) Staphylococcus aureus</li> <li>• VISE/GISE = vancomycin or glycopeptide intermediate (resistant) Staphylococcus epidermidis</li> <li>• VRE = vancomycin resistant enterococci</li> <li>• high-level gentamicine-resistant enterococci</li> <li>• gram-negative bacteria producing ESBL (= extended spectrum beta-lactamase)<sup>2</sup></li> <li>• multiresistant gramnegative bacteria<sup>3</sup></li> </ul>
community environment	<ul style="list-style-type: none"> <li>• Streptococcus pneumoniae resistant to penicillin</li> <li>• Streptococcus pneumoniae resistant to macrolides</li> <li>• Streptococcus pyogenes resistant to macrolides and to lincosamides (partially crossed resistance)</li> <li>• MRT = multiresistant Mycobacterium tuberculosis</li> </ul>

<sup>1</sup> MRSA strains are resistant to virtually all beta-lactams and usually resistant to macrolides and lincosamides: the only reliable antibiotics for empiric therapy are glycopeptides.

<sup>2</sup> The highest frequency of ESBL producing strains are in Klebsiella species, nevertheless this pattern of resistance was reported in E.coli and other gram-negative microbes as well.

<sup>3</sup> The most important multiresistant strains occur in following species: Pseudomonas, Acinetobacter, Serratia, Burkholderia, and Stenotrophomonas.

*However, remember that resistance in gram-positive bacteria became a hot problem nowadays.*

## MECHANISMS OF RESISTANCE

- 1) enzymatic destruction of ATB  
easy to transfer and to spread  
several genes bond in one plasmide
- 2) block of ATB penetration into cell (gram-negative bacteria)
- 3) efflux of ATB
- 4) change of the target molecule (MRSA, MRSE)  
difficult to develop

## WHAT DO WE NEED ATB FOR ?

What is the target: To kill the bacteria ??  
To stop bacteria to grow ??

CIDAL: cell wall ATB: beta-lactams  
glycopeptides  
peptides (colimycine)  
+ aminoglycosides

DNA/RNA metabolism: fluoroquinolones, rifampicin

STATIC/CIDAL co-trimoxazol  
chloramphenicol

STATIC: sulfonamides alone  
trimethoprim  
macrolides  
tetracyclines  
lincosamides

Remember: The bactericidal antibiotics can be given in a static regime (intermittent dosing) !!!

## FARMACOKINETIC/FARMACODYNAMIC INDEXES:

- A) time-dependent killing (short or none PAE)  
“time above MIC” =  $\text{time}/\text{MIC}$   
→ beta-lactams
- B) concentration-dependent killing  
+ long PAE (PAE = post-antibiotic effect)  
“peak concentration” ...  $c_{\text{max}}/\text{MIC}$   
→ aminoglycosides
- C) mixed type of killing  
“area under inhibitory curve” ...  $\text{AUC} = \text{AUC}/\text{MIC}$   
→ fluoroquinolones

## MAIN MISTAKES IN ATB TREATMENT:

- 1) usage in diseases of non-bacterial origin  
(x non-antiinfective effect of ATB - macrolides!)
- 2) not taking material for cultivation before starting ATB treatment
- 3) not respecting individual pharmacokinetic parameters  
especially in critical care patients where extreme changes of volume of distribution  
(edemas x dehydration) and of half-time (polyuria x oliguria) do occur
- 4) not requesting quantitative data of sensitivity (MIC, MBC) in difficult-to-treat infections  
(infective endocarditis, osteomyelitis, sepsis in immunocompromised person)
- 5) uncorrect interpreting ATB failure in outpatient's treatment  
patients compliance ?
- 6) uncorrect answer to ATB failure  
to early change of ATB, prescribing a drug of the same spectrum  
cultivation attempts after the ATB treatment used to be distorted
- 7) blind confidence in various studies results  
pharmaceutical companies influence ?

# **MECHANISMS OF RESISTANCE**

- 5) enzymatic destruction of ATB**  
easy to transfer and to spread  
several genes bond in one plasmide
- 6) block of ATB penetration into cell**
- 7) efflux of ATB**
- 8) change of the target molecule**  
MRSA, MRSE  
difficult to develop

## **MAIN MISTAKES IN ATB TREATMENT**

- 8) usage in diseases of non-bacterial origin  
(x non-antiinfective effect of ATB !)**
- 9) not taking material for cultivation before  
starting ATB treatment**
- 10) uncorrect interpreting ATB failure  
patients compliance ?**
- 11) uncorrect answer to ATB failure  
change ATB ?  
cultivation attempt ?**
- 12) blind confidence in various studies results**

## **THE EARLY HISTORY OF ANTIBIOTICS**

<b>1940</b>	<b>penicillin</b>	<b>A.Fleming</b>
<b>1943</b>	<b>streptomycin</b>	<b>S.A.Waksman</b>
<b>1945</b>	<b>cefalosporin C</b>	<b>G.Brotzu</b>
<b>1947</b>	<b>chloramphenicol</b>	<b>I.Ehrlich</b>
<b>1948</b>	<b>chlortetracyclin</b>	<b>B.M.Buggar</b>
<b>1949</b>	<b>neomycin</b>	<b>S.A.Waksman</b>
<b>1952</b>	<b>erythromycin</b>	<b>Mc.Guire</b>
<b>1955</b>	<b>vancomycin</b>	<b>M.H.Cormick</b>
<b>1957</b>	<b>kanamycin</b>	<b>H.Umezawa</b>
<b>1959</b>	<b>rifampicin</b>	<b>P.Sensi</b>

**... and so on**

# WHAT DO WE NEED ATB FOR ???

Dilemma: Kill the bacteria ??  
Stop bacteria to grow ??

**CIDAL:** cell wall ATB: PNCs, CEFs, ....  
VAN  
AMG, COL

**DNA/RNA metabolism:** FQ, RIF

**STATIC:** metabolic blocks: SULF/TMP  
ribosomal dysfunction  
(translation blocks): ERY, LIN, TET, CMP



## **FARMACOKINETIC/FARMACODYNAMIC INDEX**

**D) time-dependent killing (short or none PAE)**

**“time above MIC” = time/MIC**

**beta-lactams**

**E) concentration-dependent killing**

**+ long PAE**

**“peak concentration” ...  $c_{\max}/\text{MIC}$**

**aminoglycosides**

**F) mixed type of killing**

**“area under inhibitory curve” ...  $\text{AUIC} = \text{AUC}/\text{MIC}$**

**fluoroquinolones**

# What to prefer: killing effect or penetration?

