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CURRENT ASPECTS OF RATIONAL ANTIBIOTIC USE IN PAEDIATRICS

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Antibiotics are frequently used in the therapy of numerous infectious diseases in children and neonates. The organism of a child cannot be considered a small-size adult organism. Children differ from adults in a physiological, psychological and developmental sense, so the use of drugs in this population, including antibiotics, requires special knowledge and skill. Therefore, from the aspect of safety, neonates and children comprise a particular, so-called risk or vulnerable, patient group. The basic characteristics of antibiotic use in children is the fact that the majority of antibiotics are not properly assessed for use in children, and even those that are properly assessed, are seldom prescribed in the adequate dose, interval and for adequate duration of therapy. Besides that, the selection of commercial preparations that can be used by children is very limited, which additionally complicates the therapy of paediatric patients. This text contains general and specific principles of adequate antibiotic use in paediatrics, with particular stress on pharmacokinetic and pharmacodinamic particularities, as well as on interactions, adverse effects and other characteristics of the most used antibiotics in paediatrics. Irrational antibiotic use and self-medication can lead to inefficiency of therapy, appearance of adverse effects and development of resistance to drugs, which has become an alarming issue in the recent years.

Key words: Paediatric ▪ Antibiotic ▪ Rational use

Introduction

Antibiotics represent one of the greatest discoveries of the 20th century (1). The introduction of penicillin in 1941 extended human life expectancy for 10 years (1, 2). Howe-

ver, as early as during his speech at the Nobel award ceremony, Alexander Fleming expressed concern that bacteria could develop resistance to antibiotics, which soon proved correct. The development of resistance to a large number of antibiotics is one of the hot issues in contemporary pharmacotherapy and requires urgent responses, among which the most important are restrictions on self purchasing of antibiotics and rational use, with strict respect for a reserve list of antibiotics (3).

General principles of antibiotic use in paediatrics

Antibiotics should be prescribed to children only when the benefits are scientifically proven. In practice, antibiotics are unnecessarily prescribed to children for high temperature, throat inflammation and diarrhea caused by viral infections (4).

The choice of antibiotics should be based on the sensitivity of an isolated culture or known pathogens, characteristic for that state (empirical use), as well as on information on resistance forms (resistance maps). The empirical use is justifiable only when the patient's life is endangered (immunocompromised patients with severe systemic diseases, septicemia, neutrophilic leukocytosis, etc) and there is not enough time available to isolate and identify the cause. When choosing an antibiotic it is essential to consider the type of infection, the location where the infection appeared, as well as the source and the intensity of the infection (5).

Antibiotics should be used only if the antimicrobial spectre of a chosen drug is the narrowest, i.e. if it specifically eliminates a known or probably known pathogen or more causes. Combined therapy should be evoided and the priority should be given to monotherapy that is often as efficient as a combined therapy. In cases where combined therapy is necessary, apart from interactions, it is essential to pay attention the type of effect of the antibiotic (2, 5). Antibiotics can act: bacteriostatically (prevention of growth and reproduction of microorganisms) and bacteriocidally (killing of microorganisms). The difference is quantitative, i.e. it depends on the concentration of antibiotics achieved at the location of infection. Generally, small concentrations act bacteriostatically, whilst large concentrations act bacteriocidally. Whether an antibiotic achieves bacteriostatic or bactericidal effect depends only on its selectivity for bacteria and host tissues.

It is interesting that some antibiotics have different activities with regard to different bacteria. For instance, linezolid acts bactericidally in the treatment of *S. Pneumoniae*, and bacteriostatically in the treatment of meticillin (sensitive or resistant) and vancomycin resistant *S. aureus-a,* as well as of vancomycin resistant *E. faecium-a (6).* In clinical conditions bactericidal concentrations cannot be achieved with many antibiotics. Due to the fact that bactericidal antibiotics can act only if bacteria are in the process of reproduction, it is not permitted to combine bactericidal and bacteriostatic antibiotics. This combination significantly decreases the effect of a bactericidal antibiotic and facilitates the rapid development of resistance. In clinical practice, the combination of a bactericide and bacteriostatic is permitted only in some cases, for instance, in the treatment of severe forms of pneumonia with multiple causes (including *Mycoplasma pneumoniae*) treatment with macrolides (bacteriostatic) and penicillins and/or cephalosporins (bactericidal) is recommended (7). Bacteriostatic antibiotics are not efficient in patients with decreased immunity, osteomyelitis, bacterial endocarditis, bone marrow depression and in carriers. Besides that, the choice of drug depends on the pharmacokinetic characteristics of the antibiotics, toxicity and the general condition

of the organism: age, gender, allergies, condition and development of particular organs (kidneys, liver etc). For example, in children with impaired renal function, it is not necessary to reduce the dose of erythromycine, which is not the case with azithromycine and clarithromycine (8).

When choosing antibiotics, it is necessary to observe the lists of the first (standard) or the second (reserve) choice drugs. With the aim of prevention of resistance development to new, efficient antibiotics, the World Health Organization (WHO) suggested the list of reserve antibiotics (9). That group comprises piperacillin, cephalosporins (III and IV generation), monobactams, carbapenems, fluoroquinolones, vancomycin, teicoplanin, amikacin, streptogramins, linezolid, ketolides and tigecycline. In the majority of developed countries these antibiotics can only be purchased in a pharmacy with the special approval of the director of a clinic, which should be based on the reasoned request of a medical specialist, and/or on antibiogram and/or MIC. This measure has significantly reduced resistance in some Western European countries in recent years (Belgium, Scandinavian countries etc.) (10).

The antibiotic dose should be high enough to provide efficacy and reduce the resistance risk to a minimum, and still small enough to reduce to a minimum the toxicity linked with therapeutic dose. However, it must be stressed that every subdosing of antibiotics, i.e. a reduction of the dose below therapeutic values, will not diminish the manifestation of toxicity, but rather significantly reduce the therapeutic efficacy and facilitate rapid resistance development. The duration of antibiotic treatment should be as short as possible, from 3 to 5 days, and should not exceed 7 days, unless there is proof that this is necessary (i.e. pulmonary abscess – from 2 to 8 weeks, tuberculosis – from 6 to 24 months) (11). When choosing the route of administration of a drug, priority should certainly be given to oral administration. In comparison with oral use of antibiotics, parenteral administration has several shortcomings, including a higher risk of serious adverse effects. The majority of pharmacoeconomic studies have shown that the efficacy of orally administered antibiotics is the same as parenteral, whilst the costs are several times lower (12). Parenteral use of antibiotics in children is justifiable only if there is no drug available in a form that children can use orally or there are difficulties in swallowing, when there is need for urgent treatment due to serious infections that progress quickly or when a high drug concentration in tissue is required which is impossible to achieve with oral formulations (septic arthritis, meningitis, osteomyelitis etc), as well as with problems with absorption from the gastrointestinal tract: gastrointestinal pathology, diarrhea, vomiting etc. In any case, the change from the parenteral to oral therapy should be made as soon as possible. The local use of antibiotics should be limited to several proven indications (for instance, eye infection). The adverse effects of locally administered antibiotics are often manifested due to the increased systemic absorption (13). Besides that, increased sensitivity as well as high risk for development of resistant forms of microorganisms have also been observed.

Specific principles of antibiotic use in paediatrics

Apart from basic principles, rational use of antibiotics in paediatrics also requires specific knowledge (13, 14). The infantile organism cannot be observed as a diminished adult organism, because the physiological characteristics of a child's organism differ from the organism of a healthy adult (13). From the safety aspect, neonates and children form a particular group of patients, a so called risk

or vulnerable group. They differ from adults in a physiological, psychological and developmental sense. Growth and development are dynamic processes. Growth is the continuous change of mass, shape, proportions and physiological functions during ontogenesis, whilst development consists of qualitative changes during biological maturation – changes in the function of cells, tissues and organs, enzyme induction, reorganization of regulatory mechanisms.

With the aim of improvement of antibiotic use in children, it is important to possess knowledge of complex processes of growth and development due to their influence on pharmacokinetics and pharmacodynamics of a drug (14, 15). In addition, it is necessary to pay attention to the specifics of diseases in children, the influence of the environment and hereditary factors. The lack of pharmacokinetic and pharmacodynamic data for drugs used in children increases the risk of overdose and subdose, adverse affects and inefficacy of a generally efficient drug (16). Besides that, due to the lack of original oral preparations on the market for children younger than 5 years, the improvised preparation of liquid drug forms in local hospital pharmacies by crunching tablets or opening capsules for adult use, also contributes to the risk of inefficacy and unpredictable safety of the treatment, especially with antibiotics.

Our study has shown that small, unprofitable markets, such as Serbia, have significantly smaller availability of oral formulations of antibiotics that can be used by children, compared with the major markets such as the USA and Germany (17). In any case, for a large number of drugs, in none of the surveyed three markets is there any single preparation in a formulation for oral use that may be used by children less than 12 years old. Besides that, the majority of antibiotics for parenteral administration are designed for adult use, and are produced in much higher concentrations than those used in paediatric patients (18).

PK/PD access to determining optimal antibiotic therapy in children

From birth to adolescence, children pass through at least four specific periods of development, where each of them requires characteristic pharmacotherapy (Table 1).

Antibiotic dosing regimens in children have traditionally been determined only by pharmacokinetic (PK) parameters extrapolated from clinical studies in adults and, since recently, from PK studies performed in children. PK is the study of the time course of absorption, distribution, metabolism and elimination of antimicrobial drugs. Clinical PK monitoring has been used in children in order to overcome the PK variability of antimicrobials and enable individualised dosing regimens that attain desirable antimicrobial serum concentrations. Pharmacodynamics (PD) is the study of the relationship between the serum concentration of a drug and the antimicrobial effects observed in a patient. However, PD plays an equal, if not more im-

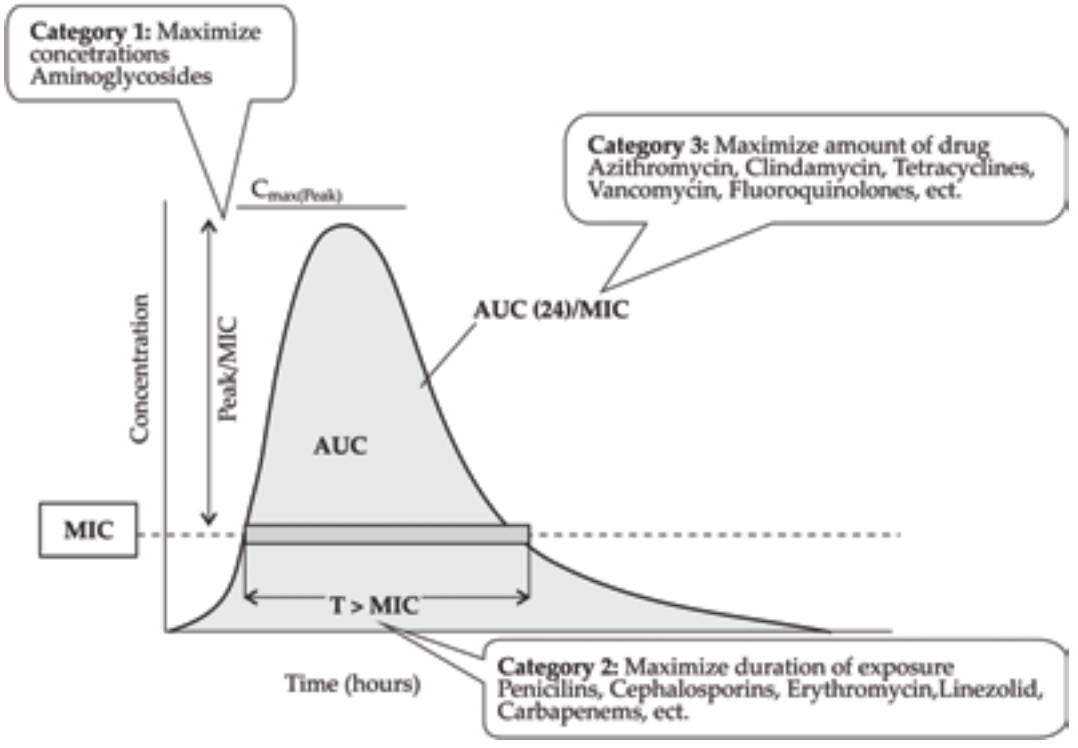
Table 1 Age classification of paediatric patients (19)

Paediatric patients	Age
Preterm newborn infants	<36 week of gestation, 0 to 27 days
Newborn infants	0 to 27 days
Infants and toddlers	28 days to 23 months
Children	2 to 11 years
Adolescents	12 to 18 years

portant, role. The primary measures of antibiotic activity are the minimum inhibitory concentrations [MIC] or minimum bactericidal concentrations [MBC], bactericidal or bacteriostatic killing, post-antibiotic effects. While these parameters are good indicators of the potency of an antibiotic, they indicate nothing about the time course of antimicrobial activity. The PK parameters that are most important for evaluating antibiotic efficacy are the peak serum level [C(max)] or trough [C(min)] serum concentrations, half-life, and area under the curve [AUC]. However, these parameters do not describe the killing activity of an antibiotic. By combining pharmacokinetic and pharmacodynamic properties, unique PK/PD parameters T>MIC, Peak/MIC, and AUC(24)/MIC can be defined (20). The Peak /MIC ratio is simply the C(max) divided by the MIC. The T> MIC (time above MIC) is percentage of dosing interval in which the serum level exceeds the MIC. The AUC(24)/MIC ratio is determined by dividing the 24 hours AUC by the MIC (Fig. 1).

Using PK/PD parameters, antibiotic activity can be divided into 3 categories: 1. concentration dependent killing and prolonged persistent effects, 2. time dependent killing and minimal persistent effects and 3. time dependent killing and moderate to prolonged persistent effects. Depending on the killing characteristics of a given class of antimicrobials (concentration-dependent or time-dependent), specific PK/PD parameters may predict *in vitro* bacterial eradication rates and correlate with *in vivo* microbiologic and clinical cures.

PK/PD parameters, t>MIC and AUC (24)/MIC ratio are important predictors of antibiotic efficacy for category 1. The ideal dosing regimen for antibiotics such as ami-



MIC- minimum inhibitory concentrations, Cmax(peak)-peak serum level, AUC-area under the curve, T-time (hours).

Fig. 1 *PK/PD parameters of antibiotics efficacy.*

noglycosides, ketolides, fluoroquinolones etc. from category 1, would maximize concentration, because the higher the concentration, the more extensive and faster the degree of killing. Antibiotics (beta lactams, linezolid, erythromycin etc.) belonging to category 2, demonstrate the completely opposite properties. The ideal dosing regimen for these antibiotics maximizes the duration of exposure. The t >MIC is the parameter that best correlates with efficacy. The PK/PD parameter AUC(24)/MIC ratio is the parameter that correlates with antibiotic efficacy from category 3. The ideal dosing regimen for vancomycin, tetracycline, azithromycin, etc. maximizes the amount of drug received.

A recently published paper summarized evidence about increasing use of population analyses to understand pharmacokinetic/pharmacodynamic (PK/PD) parameters in children (21). Nonlinear mixed effect modelling is widely accepted as the method of choice for analyses of PK/PD data. Another, equally important, factor is communicating the quality of PK/PD studies, which allows clinicians to gauge the robustness of the evidence. The possibility of grading PK/PD studies is discussed, along with using systematic reviews and PK/PD meta-analysis for generating high-quality evidence. Given that many doses in existing formularies are based on outdated evidence, there is an obvious need to update formularies to account for new evidence, including population changes (e.g. obesity). Also, changing patterns of resistance requires a more systematic evaluation of antimicrobial PK/PD relationships in children. Regulators should act as a support in the re-evaluation of off-patient dosing guidelines, whilst possibilities of e-formularies linked directly to the evidence should be taken into account. The constant advance of our knowledge of the evidence behind paediatric antimicrobial therapeutic regimens is a key to improvement of both clinical outcomes and patient safety (21). Using a combination of international collaboration, electronic communication, and PK/PD modelling techniques, we can now define the gaps in our knowledge base and develop the techniques to answer them (21).

Adverse effects and toxicity of antibiotics

The profile of adverse effects in children is the same as in adults. However, some drugs manifest adverse effects characteristic exclusively for childhood, so separate paediatric research and monitoring of the adverse effects are of utmost importance. Some antibiotics can manifest serious adverse effects characteristic for childhood, and as a result, limit their use in children and in pregnant women (22):

- fluoroquinolones – arthropathy and tendon damage (23),
- tetracyclines (including tigecycline) – discoloration of teeth, dental hypoplasia and bone deformities (8),
- chloramphenicol - „grey baby syndrome“ (circulatory collapse, grey skin colour, decreased body temperature, diarrhea, vomiting), myelotoxicity (8).

In practice, use of these antibiotics is avoided, tetracyclines are contraindicated in children younger than 8 or 12 years (depending on the regulations of the country in which the drug is registered), as well as fluoroquinolones that can be used only in the case of treatment of respiratory infections in children with cystic fibrosis and complicated urinary infections (with antibiogram and/or MIC) in children older than 1 year of age (8, 23).

Gentamicin and other aminoglycosides can permanently damage hearing and the kidneys, therefore, they are not recommended to be prescribed to neonates and infants. However, common practice requires the use of these drugs so that their safe application is possible only under strict monitoring, i.e. following the drug concentration in the blood (24).

These examples indicate the necessity of timely assessment of the toxicity of drugs used in children, with the aim of preventing the tragedies from history. Recently published studies have shown a statistically significant connection between the appearance of adverse events and death and off-label and unlicensed drug use in paediatrics (16, 25). Therefore, when choosing the treatment it is very important to give priority to the pediatrically evaluated drugs. If they have not been evaluated, and there is additional risk of adverse effects (for instance, small therapeutic width, elimination through kidneys in neonates etc.), it is necessary to follow the therapeutic concentration of that drug in the blood.

Generally, children show excellent tolerance to antibiotics. Drugs that are mostly prescribed to children are penicillin and cephalosporine antibiotics, known for their high therapeutic width and ideal selective toxicity. The most common adverse effects of the antibiotics most often prescribed to children (penicillins, cephalosporins and macrolides) are:

- allergic reactions (itch, rash, urticaria, anaphylactic reactions etc.)
- mild irritation of the gastrointestinal tract: nausea, vomiting, diarrhea,
- superinfections (mouth moniliasis and pseudomembranous colitis) (26).

Superinfection caused by *Clostridium difficile* (pseudomembranous colitis) may lead to difficult consequences for the child, including death. Therefore, lincosamides (lincomycin, clindamycin) should always be avoided when possible (27). These antibiotics have been withdrawn from use in most developed countries.

Besides that, one should also be careful with safe preparations, such as penicillins (penicillins, carbapenems), which apart from anaphylactic reaction may cause convulsions in neonates and infants. If anaphylactic or allergic reaction is the consequence of the use of penicillin antibiotics, therapy should be performed with some of the macrolide preparations, because proof exists of cross hypersensitivity with cephalosporin preparations, which makes them unsuitable (28).

Interactions

Antibiotics are the most frequently prescribed drugs in paediatrics and are usually prescribed in combination with other medication (e.g. antipyretics, analgesic, etc.). Therefore, it is of utmost importance to take into account possible interaction with other medication, but also with the food children consume. Interactions can be *pharmacodynamic* and *pharmacokinetic*.

Pharmacodynamic interactions (synergism, antagonism) are clinically important in the sense that one needs to be careful when combining two antibiotics with different types of effects (bactericide vs. bacteriostatic) in order not to diminish the effect of the (bactericide) antibiotic. Besides ineffectiveness, this kind of interaction also enables fast developing resistance towards both types of antibiotics. On the other hand, the combination of antibiotics enables the expansion of the antibacterial spectre (e.g. penicillin+gentamicin in therapy of bacterial endocarditis) and/or reinforcement of the antibacterial effect (e.g. sulphonamides – bacteriostatic + trimethoprim-bacteriostatic = co-trimoxazole-bactericide) (5).

Pharmacokinetic interactions may be interactions with other drugs, but also with food. They may occur in all phases of the drug's pharmacokinetics.

In the *absorption phase*, interactions with food are significant, therefore it is highly important to know the characteristics of the antibiotics in the sense that one must have a notion of which ones may be taken with food, and which must be consumed on an

empty stomach. An inadequately used drug may cause further inefficiency of the therapy and it may lead to the development of drug-resistance. For example, the most widely prescribed cephalosporin antibiotic of the third generation for oral consumption – ceftibuten – must be taken two hours prior to any food intake, or one hour afterwards. The food significantly diminishes the rate and extent of the absorption of ceftibuten (29). Also, certain food ingredients can also cause interactions. For example, tyramine, that may be found in fermented products (e.g. cheese, cured meat etc.), chocolate, olives etc. if used along with linezolid, the monoamine-oxidase inhibitor, could cause a hypertensive crisis (30). Interactions of the most frequent orally consumed antibiotics and food are shown in Table 2.

In the *distribution phase*, the most important interactions are related to the drugs that connect to plasma proteins in high percentages. If antibiotics that are competitors for the same carriers (e.g. ceftriaxone, co-trimoxazole) are simultaneously used, they can suppress other drugs that share an affinity for the same carrier (e.g. warfarin) and therefore cause serious adverse effects (e.g. bleeding) (Table 3).

In the *biotransformation phase* it is of utmost importance to know the characteristics of the antibiotics in order to be able to determine whether they are inhibitors or inductors of liver enzymes. The most hazardous interaction is that of macrolides – erythromycin, clarithromycin and telithromycin, inhibitors of enzyme CYP3A4, with antiarrhythmics, diuretics and antihistamines (terfenadine), and as a result it can lead to an elongation of the QT interval and the start of an arrhythmia of the *torsades de pointes* type (8). Besides that, chloramphenicol and antifungal antibiotics are also strong inhibitors of CYP3A4, and ciprofloxacin of CYP1A2 (8, 31). In the *elimination phase*, sulfonamides and penicillins can reduce the elimination of methotrexates.

Strictly controlled clinical trials, primarily pharmacokinetic studies, that include children, have been stimulated and encouraged in the recent years. The majority have been performed in the USA, where, thanks to a series of legalislation in 1998, clinical examinations conducted on children have been approved. In the EU, a law concerning mandatory evaluation of drugs used in paediatrics was enacted in January 2007. Since then, many of the drugs, old and new, have been evaluated with the goal of obtaining a license for paediatric usage. Still, many of the drugs, including antibiotics, are applied in a dosage that is extrapolated according to clinical trials conducted on adults. The right selection and dosage of antibiotics in paediatrics implies daily information amendments obtained from the clinical trials conducted on children, regardless whether it is an old or a new drug. Specialized paediatric drug registries, as well as summaries of drug characteristics (SmPC), are available on the web sites of the Medicines Agencies of EU countries and the Food and Drug Administration – the FDA in the USA, and are an excellent source of new information on possible dosage changes, indications, contraindications and adverse effects of antibiotics.

Conclusion

The optimal availability of paediatric-evaluated antibiotics in a formulation suitable for children less than 12 years of age is the basic precondition for effective, safe and qualitative antimicrobial drug therapy to be conducted. A strict control of selection, dosage and duration of the therapy is essential in order for the therapy to be effective and to prevent the development of bacterial resistance to antibiotics. It is necessary for every paediatric institution on all levels of health care to have a joint stance on the rational usage of antibiotics, based on the data concerning bacterial sensitivity and resistance to antibiotics.

Table 2 Interactions of most commonly used pediatric antibiotics and food

Antibiotic	Food interaction	Usage
Ampicillin	Yes[1]	1-2 hours prior to any food intake or on an empty stomach
Ampicillin/Sulbactam	Yes[2]	1-2 hours prior to any food intake or on an empty stomach.
Amoxicillin	No	Immediate release: on an empty or a full stomach; can be mixed with an infant formula, milk, cold drinks or juice. Sustained release: within an hour after finishing a meal.
Amoxicillin/ clavulanic acid	No	At the beginning of a meal in order to reduce the frequency and seriousness of the GIT adverse effects; not to be used with high fat meals (clavulanic absorption is reduced); can be mixed with (infant) formula, milk or juice.
Phenoxymethylpenicillin	Yes[3]	On an empty stomach, one hour before or two hours after a meal.
Cefalexin	Yes[4]	On an empty stomach, one hour before or two hours after a meal.
Cefadroxil	No[5]	Can be used regardless of the food intake; food can help reduce the feeling of sickness or vomiting.
Cefuroxime	Yes[6]	Cefuroxime acetil suspension must be taken with food; tablets can be used with or without food.
Cefaclor	Yes[7]	One hour before or two hours after a meal; chew on tablets before swallowing.
Cefprozil	No	With or without food; take with food in case of stomach pain; cooling (not freezing) betters the taste of the suspension.
Ceftibuten	Yes[8]	Capsules: take regardless of food intake; suspension: two hours before or one hour after a meal.
Sulfamethoxazole trimethoprim	No	On an empty stomach.
Erythromycin		Avoid milk and sour drinks one hour before or after taking the drug; taking it after a meal reduces the GIT distress; ethylsuccinate tablets should not be swallowed in whole; do not grind or split tablets with sustained release, film tablets and capsules.
Clarithromycin	Yes[9]	Tablets or oral suspension can be taken regardless of the food intake; tablets with sustained release must be taken with food; do not split or chew on tablets with sustained release; can be taken with milk.
Azithromycin	Yes[10]	Oral suspension, tablets or 1 g suspension can be taken regardless of the food intake; do not use along with products that contain aluminum or magnesium; oral suspension with sustained release: on an empty stomach one hour before or two hours after a meal, can be used regardless of the products containing aluminum or magnesium.
Ciprofloxacin	Yes[11]	Tablets: two hours after a meal; medicine taken with food minimizes the GIT distress; tablets and oral suspension with sustained release can be taken regardless of the food intake.
Linezolid	Yes[12]	Can be taken with or without food and drinks under the condition that there is no more than 100 mg/per meal of tyramine.

[1,2,8] The food reduces the rate and extent of the absorption. [3]Food and milk can reduce absorption. [4]Food can reduce absorption. [5] Simultaneous usage with food, infant formulas or cow milk does not have any significant affect on absorption. [6]Food and milk increase the bioavailability and maximal level of the drug. [7]Capsules and suspension: food or milk decelerate or reduce maximal concentration. [9]Immediate release type of drug: food can delay the speed, but not the extent of oral absorption. The drug with sustained release: food increases AUC by 30%. [10]Presence of food affects the bioavailability when using tablets with immediate release, oral suspension, or 1g suspension. Azithromycin suspension with sustained release has an increased absorption (23%) when taken with a high-fat meal. [11]Milk products (milk, yogurt) and mineral additives (iron, zinc, calcium), reduce the concentration of ciprofloxacin; avoid simultaneous usage with dairy products, with juices rich with calcium; ciprofloxacin increases the caffeine concentration; caution with food and drinks that contain xanthine; film tablets must not be grinded. [12]Food and drinks that contain tyramine can cause hypertensive crisis.

Table 3 Pharmocokinetic characteristics of selected penicillins, cephalosporins and macrolides

Name	Elimination half-time (h)	Protein binding (%)	Elimination
Penicillin G	0.5 – 1.2	55 - 65	Kidneys
Penicillin V	1	80	Kidneys
Oxacillin	0.5 – 1.2	90 - 95	Kidneys, liver
Cloxacillin	0.5	90 - 95	Kidneys, liver
Dicloxacillin	0.8 – 1.0	96 - 98	Kidneys, liver
Nafcillin	0.5	87 - 90	Liver, kidneys
Ampicillin	1	15 - 25	Kidneys
Amoxicillin	1	17 - 20	Kidneys
Ticarcillin	1.0 – 1.2	45 - 65	Kidneys
Piperacillin	0.5 – 1.3	22	Kidneys
The first generation of cephalosporins			
Cefazolin	1.4	86	Kidneys
Cephalexin	1.2	14	Kidneys
Cefadroxil	1.3	15	Kidneys
The second generation of cephalosporins			
Cefuroxime acetil	1.4	33	Kidneys
Cefoxitin	0.8	73	Kidneys
Cefotetan	3.5	88	Kidneys
The third generation of cephalosporins			
Cefotaxime	1	38	Kidneys
Ceftriaxone	6 – 8	90	Kidneys 65%, bile 35%
Ceftazidime	1.9	20	Kidneys
Cefixime	3.8	69	Kidneys 50%
Cefpodoxime	2.2	40	Kidneys
Ceftibuten	1.9 – 2.5	65	70% intact in urine
Cefoperazone	1.5 – 2.5	90 - 93	Bile 70%, Kidneys 20%-30%
The fourth generation of cephalosporins			
Cefepime	1.5 – 1.7	19	Kidneys
Macrolides			
Erythromycin	1 – 1.5	75-90	Bile, 5% urine
Clarithromycin	3-9*	65-70	40% urine,10-15% metabolite 4% feces
Roxithromycin	4**	86-96	53% feces,10% urine
Azithromycin	54.5****	7-51***	50% bile, urine

*Depending on the dosage: 250 mg 3-4h; 500 mg 5-7h; 14- hydroxy metabolite: 250 mg 5-6h; 500 mg 7-9h; **Increased in patients with liver and kidney insufficiency; ***Depending on the concentration of alpha1-acid glycoprotein; ****Children between 4 months and 15 years of age.

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