

**Ministry of health of the Republic of Belarus
Educational institution
«Gomel State Medical University»**

Department of general and clinical pharmacology

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METHODOLOGICAL RECOMMENDATIONS

for a practical lesson on the discipline "Pharmacology"
for the third-year students of the Faculty of Foreign Students,
studying at the specialty 1-79 01 01 "General medicine"

**TOPIC 28: "CHEMOTHERAPEUTIC AGENTS.
THE CONCEPT OF CHEMOTHERAPY. ANTIBIOTICS (β-LACTAM ANTIBI-
OTICS, MACROLIDES, TETRACYCLINES)"**

Time: 3 hours

Approved at the meeting of the department of general and clinical pharmacology
the protocol № 18 of 30.06.2022

LEARNING AND EDUCATIONAL GOALS, OBJECTIVES, MOTIVATION FOR LEARNING THE TOPIC

Antibiotics are substances of natural, microbial, plant, animal and synthetic origin that have a pronounced biological activity and inhibit the vital activity of infectious agents. By vital importance antibiotics take a leading place among other drugs. At one time they dramatically limited the spread of infectious diseases. Nowadays they have found wide application in genetic engineering, growth stimulation of farm animals, decontamination of egg shells, treatment of animals and protection of plants against diseases caused by bacteria and fungi. This widespread introduction of antibiotics into human life creates a potential danger to human health, for example, when you eat agricultural products treated with antibiotics, there is a risk of allergic reactions, the emergence of resistant strains of bacteria, etc. For the effective and safe use of antibiotics the future physician needs to study the mechanisms and spectrum of their antimicrobial action, the characteristics of individual drugs and the mechanisms of antibiotic resistance formation.

Learning objective:

- formation of specialized competence of the application of knowledge of the main pharmacological effects, providing therapeutic and preventive effect of drugs on the topic of the class, indications and contraindications for their use, the interaction of drugs, their combined use.

Educational purpose:

- to develop their value-personal, spiritual potential, to form the qualities of a patriot and citizen, ready for active participation in the economic, industrial, socio-cultural and public life of the country; to realize the social significance of their future professional activities, to learn to follow academic and work discipline, standards of medical ethics and deontology.

Tasks:

As a result of the study lesson, the student should

know:

- classification and basic characteristics of the studied drugs, pharmacodynamics and pharmacokinetics, indications and contraindications for their use, side effects;
- features of pharmacokinetics and pharmacodynamics, advantages and disadvantages of different dosage forms of these drugs;
- principles of research and testing of new drugs; information and reference and search systems.

be able to:

- analyze the effect of the studied drugs on the set of their pharmacological properties and the possibility of their use in medical practice; to write them in prescriptions;
- use different dosage forms of these drugs, based on the peculiarities of their pharmacodynamics and pharmacokinetics;
- work with scientific literature, search for information about the use and action of the studied drugs.

possess:

- skills in choice of drugs on the topic of the lesson;

- the rules of prescribing the studied drugs in the treatment of various diseases and pathological conditions, taking into account the indications;
- skills of dosage regime correction in case of pathological changes in functions of organs or systems responsible for biotransformation and elimination of drugs or in case of joint use of different drugs;
- skills to search, analyze and summarize information about the use and effects of the studied drugs.

Motivation for learning the topic:

- the specifics of training doctors in this specialty determines the need for students to purposefully study the main pharmacological effects, providing therapeutic and preventive effects of drugs on the topic of the class, indications and contraindications for their use, the interaction of drugs, their combined use, which will successfully complete the specialized disciplines of the specialty.

MATERIAL EQUIPMENT

Reference and informational literature, charts, tables, presentations, drug collections.

CONTROL QUESTIONS FROM RELATED DISCIPLINES

1. The concept of antibiosis and antibiotics.
2. Types of pathogens of various infectious diseases.
3. Methods for determining the sensitivity of microorganisms to antibiotics.
4. The concept of chemotherapy, its types and principles.

CONTROL QUESTIONS ON THE TOPIC OF THE CLASS

1. Modern sources of antimicrobial agents and promising areas of creation. Criteria and principles of rational chemotherapy of infections. Principles of combination antibiotic therapy. Possible causes of ineffectiveness of antimicrobial therapy.

2. Principles of classification of antibiotics. Basic mechanisms of action of antibiotics. Side effects and complications of antibiotic therapy, their prevention and treatment. Microbial resistance to antibiotics; mechanisms and ways to overcome it.

3. β -Lactam antibiotics that inhibit cell wall synthesis. Classification. Penicillins: benzylpenicillin (sodium and potassium salts), benzathine benzylpenicillin (bicillin-1); phenoxymethylpenicillin, oxacillin, amoxicillin, carbenicillin, piperacillin, pivmecillin; combined penicillin preparations with β -lactamase inhibitors: clavulanic acid, sulbactam, tazobactam. Spectrum of action. Routes of administration, distribution, duration of action and dosing. Peculiarities of action and use. Side effects.

4. Cephalosporins and cefamycins: cefazolin, cefuroxime, cefoxitin, cefotaxime, ceftazidime, ceftriaxone, cefepime. Classification of cephalosporins by generations (I-IV), spectrum of antimicrobial activity, resistance to β -lactamases, routes of administration. Indications and contraindications for use. Side effects.

5. Carbapenems (imipenem, meropenem, ertapenem). Spectrum and mechanism of action, use and side effects. Monobactams (aztreonam). Spectrum and mechanism of action, use and side effects.

6. Antibiotics that inhibit protein synthesis. Macrolides and azalides (erythromycin, clarithromycin, azithromycin, spiramycin). Tetracyclines (tetracycline, doxycycline).

Pharmacodynamics, spectrum of antibacterial action of antibiotics of various groups, routes of administration, dosing principles, side and toxic effects, contraindications for prescription. Principles of combination antibiotic therapy.

PROCESS OF THE STUDY

Theoretical part

Theoretical questions are described in the appendix to the methodological recommendations.

Practical part

1. Take notes on theoretical material demonstrated by the teacher.
2. Master the methods of solving the tasks and writing out prescriptions on the topic of the class.

Theme learning control

Conducted in the form of independent written work (solution of practical problems and prescriptions for individual task).

METHODOLOGICAL RECOMMENDATIONS FOR ORGANIZATION AND EXECUTION OF STUDENTS' INDEPENDENT WORK (SIW)

The time given for independent work can be used by students for:

- preparing for the practical classes;
- completing the tasks on the topic of the class in the workbook;
- preparing thematic reports, essays and presentations;
- taking notes from academic literature.

The main methods of organizing independent work:

- completing tests and practical tasks of the electronic educational-methodical complex (EEMC) for self-monitoring and self-assessment.

The list of tasks of the SIW:

- solving practical problems in the EEMC;
- completing the test tasks of the EEMC.

Control of the SIW is carried out in the form of:

- assessment of an oral answer to a question, report, report, or solution of a task in a practical class;
- individual conversation.

METHODOLOGICAL RECOMMENDATIONS FOR ORGANIZATION AND EXECUTION OF CONTROLLED INDEPENDENT WORK OF STUDENTS (CIWS)

Recommended forms of CIWS organization:

- doing exercises on the topic of the class in the workbook;
- writing an essay on a given topic;
- preparing a report and a multimedia presentation on a given topic.

The list of tasks of the CIWS:

Topics of essays / multimedia presentations:

1. History of the discovery and use of chemotherapeutic agents in clinical practice (completion of workbooks).
2. Medicinal plants with antimicrobial activity in the practice of modern doctor.

Forms of control of CIWS realization:

- checking and grading an essay on a given topic;
- checking and grading a multimedia presentation on a given topic.

LIST OF REFERENCES

1. Kharkevitch, D.A. Pharmacology: textbook for med. students: transl. of 12th ed. of Russ. textbook "Pharmacology" (2017) / D.A. Kharkevitch. - 2nd ed. - Москва: ГЭОТАР-Медиа, 2019. - 676 с.: ил., табл. - Рек. ФГАУ "ФИРО". – Режим доступа: <http://www.studmedlib.ru/book/ISBN5970402648.html> – Дата доступа: 23.05.2022.
2. Кратко о лекарственных средствах: учебно – методическое пособие для студентов 3 и 6 курсов факультета иностранных студентов, учреждений высшего мед. образования: в 2 ч.=Drugs in short: partial workbook for 3 and 6 year students Faculty for International Students of medical higher educational institutions: in 2 parts / Е.И. Михайлова [и др.]. – Ч. 1. – Гомель: ГомГМУ, 2020. – 56с. – Режим доступа: <http://elib.gsmu.by/xmlui/handle/GomSMU/7128> – Дата доступа: 23.05.2022.
3. Кратко о лекарственных средствах: учебно – методическое пособие для студентов 3 и 6 курсов факультета иностранных студентов, учреждений высшего мед. образования: в 2 ч.=Drugs in short: partial workbook for 3 and 6 year students Faculty for International Students of medical higher educational institutions: in 2 parts / Е.И. Михайлова [и др.]. – Ч. 2. – Гомель: ГомГМУ, 2020. – 76с. – Режим доступа: <http://elib.gsmu.by/xmlui/handle/GomSMU/7129> – Дата доступа: 23.05.2022.
4. Rang and Dale's Pharmacology / J.M. Ritter [et al.]. - 9th ed. - Edinburg [et al.]: Elsevier, 2020. - xvi, 789 p.: ill., tab. + Student consult online.

Educational material

Chemotherapeutic agents are medicinal substances suppressing the vital functions of pathogens of infectious diseases or tumor cells.

Antibiotics are medicinal substances of predominantly microbial origin, as well as their semisynthetic and synthetic analogues, which have the ability to suppress the viability of susceptible microorganisms [1,2].

Currently, 3 types of antibiotic treatment are used:

1. *Preventive treatment* - prescribing antibiotics for the prevention of infectious diseases (for example, for seasonal prevention of acute rheumatic fever or postoperative complications).

2. *Empirical or initial treatment* – administration of broad-spectrum antibiotics suppressing microorganisms associated with the given pathology without the results of bacterial culture and antibiotic susceptibility testing (eg, community-acquired pneumonia is most often caused by pneumococcus susceptible to aminopenicillins).

3. *Final treatment* – administration of narrow-spectrum antibiotics in accordance with the results of bacterial culture test (type of detected pathogens and its susceptibility to antibiotics).

Principles of rational chemotherapy [1,2].

The choice of the drug should be carried out taking into account:

- 1) Diagnosis (therapy can be empirical and etiotropic);
- 2) The spectrum of drugs activity (it is preferable to administer narrow-spectrum antibiotics);
- 3) The state of the patient's organism taking into account his age, pregnancy and concomitant diseases;
- 4) Toxicity of drugs, their side effects;
- 5) Localization of the infection (the substance should reach the focus of infection);
- 6) Route of administration (In severe cases, drugs are administered parenterally);
- 7) The possibility of combining drugs in order to enhance the pharmacological effect and prevention of the development of resistance of microorganisms to antibiotics;
- 8) Drugs cost [1-4].

When prescribing treatment adequate dose of the drug, frequency of its administration and duration of the course of antibiotic therapy should be chosen.

PENICILLINS [1-4]

Classification	Natural	Semisynthetic			
		β -lactamase-resistant	Aminopenicillins	Antipseudomonal	Penicillinase-resistant
Drugs	<i>Short acting:</i> 1. Benzylpenicillin sodium and potassium salts 2. Phenoxymethylpenicillin <i>Long-acting:</i> 3. Benzylpenicillin novocaine salt 4. Bicillin-1. bicillin-5	5. Oxacillin 6. Cloxacillin	7. Ampicillin 8. Amoxicillin	<i>Carboxypenicillins:</i> 9. Carbenicillin 10. Ticarcillin <i>Ureidopenicillins:</i> 11. Piperacillin 12. Azlocillin	13. Amoxicillin / clavulanic acid (Augmentin) 14. Ampicillin / sulbactam (Unazine) 15. Ticarcillin / clavulanic acid (Timentin) 16. Piperacillin / tazobactam
Mechanism of action	Suppress the synthesis of the bacterial cell wall (bactericidal action)				+ Inhibition of β -lactamases due to sulbactam, clavulanate → Are active against PRSA
Spectrum of activity	1. Gr (+) cocci: non-penicillinase producing staphylococci: streptococci, pneumococci 2. Gr (-) cocci: meningococci 3. Gr(+) палочки: Listeria, causative agents of diphtheria, anthrax 4. Spirochetes, anaerobes	See natural penicillins + 5. Penicillinase-producing staphylococci (PRSA)	1. Gr (-) bacteria: E. coli, hemophilic rod, salmonella, shigella 2. Gr (+) cocci: non-penicillinase producing staphylococci, Streptococci (enterococcus), pneumococci 3. Gr (-) cocci: meningococci 4. Gr (+) sticks: listeria, excitors of diphtheria, anthrax 5. Spirochetes, anaerobes	Similar to Ampicillin, but + 1. <i>Pseudomonas aeruginosa</i> 2. Ampicillin-resistant Gr (-) m/o: Enterobacter, Proteus, Morganella 3. Gr (-) non-sporeforming anaerobes	The broadest spectrum of activity among all penicillins
Indications for use	1. Erysipelas, scarlet fever 2. Syphilis 3. Bacterial endocarditis 4. Anaerobic infections 5. Borreliosis, anthrax	1. Staphylococcal infections (infections of the skin and soft tissues, bones and joints, hospital pneumonia, etc.)	1. Urinary tract infection 2. Upper respiratory infection (Acute otitis media, acute sinusitis) 3. Lower respiratory infection (bronchitis, community-acquired pneumonia)	1. Diseases caused by Pseudomonas aeruginosa (skin, abdominal organs, urinary and biliary tracts infections, etc.)	1. Severe infections of the respiratory and musculoskeletal system, urinary and biliary tracts and soft tissues. 2. Hospital infections
Side effects	Allergy , headache, nausea, vomiting, pseudomembranous colitis, pain in i/m administration, phlebitis in i/v administration				
Contraindications	Allergy , I semester of pregnancy (amoxicillin / clavulanic acid)				

m/o – microorganisms, i/v – intravenous

CEPHALOSPORINS [1-4]

Classification	I generation	II generation	III generation	IV generation	V generation
Drugs	<i>i/v i/m</i> 1. Cefazolin (Kefzol) <i>per os</i> 2. Cephalexin (Keflex) 3. Cefadroxil (Duricef)	<i>i/v i/m</i> 4. Cefuroxime (Ceftin) 5. Cefamandole (Mandol) <i>per os</i> 6. Cefaclor (Ceclor) 7. Cefuroxime (Zinacef)	<i>i/v i/m</i> 8. Cefotaxime (Claforan) 9. Ceftriaxone (Rocephin) 10. Cefoperazone (Cefobid) 11. Ceftazidime (Fortu) <i>per os</i> 12. Cefixime (Fixx) 13. Ceftibuten (Cedax)	<i>i/v i/m</i> 14. Cefepime (Maxipime) 15. Cefpirome (Cefrom)	<i>i/v i/m</i> 16. Ceftobiprole 17. Ceftaroline
Mechanism of action	Suppress the synthesis of the bacterial cell wall (bactericidal action)				
Spectrum of activity	1. Gr (+) cocci: streptococci, staphylococci 2. Gr (-) cocci and bacilli <i>insignificantly</i>	1. Gr (-) bacteria: hemophilic rod, Klebsiella, proteus 2. Gr (+) cocci: streptococci, staphylococci	1. Gy (-) bacteria (including polyresistant strains of enterobacteria) 2. Anaerobes (8,9) 3. Gr (+) cocci: strepto-, pneumococci (8,9) 4. <i>Pseudomonas aeruginosa</i> (10, 11)	<i>See III generation</i>	1. MRSA (methicillin-resistant <i>Staphylococcus aureus</i>) 2. Penicillin-resistant streptococci and enterococci
Indications	1. Perioperative chemoprevention 2. Strepto- and staphylococcal infections of the musculoskeletal system, skin, soft tissues	+ 3. Urinary tract infection 4. Respiratory infections (community-acquired pneumonia, acute sinusitis and otitis media)	1. Infections of the respiratory system (including, hospital pneumonia) 2. Urinary tract infection 3. Abdominal, pelvic infections	+ 4. Infections caused by hospital strains of Enterobacteria, staphylococci, <i>Pneumococcus</i> and <i>Pseudomonas aeruginosa</i>	1. Infections of the skin and soft tissues
Side effects	Allergic reactions; hematological reactions: in rare cases - leukopenia, eosinophilia; disulfiram-like reaction with alcohol intake (5,10); headache; nausea, vomiting; Superinfections caused by enterococci, MRSA; pain and thrombophlebitis in the site of injection				
Contraindications	Allergy				
NB!	1. Cephalosporins are resistant to bacterial beta-lactamases, BUT combination of cefoperazone + sulbactam (Beta-lactamase inhibitor) expands the spectrum of action up to resistant enterobacteria and akinetobacter; suppresses nesporenous anaerobes → therapy of abdominal and pelvic infections. 2. Each subsequent generation is superior to the previous when comparing the spectrum of activity among the Gp (-) bacteria, but loses activity against Gr (+). AN EXCEPTION! IV generation (high activity against Gr +)				

Per os –orally

CARBAPENEMS AND MONOBACTAMS [1-4]

Classification	Carbapenems	Monobactams
Drugs	1. Imipenem-cilastatin (Tienam) 3. Doripenem (Doriprex) 2. Meropenem (Meronom) 4. Ertapenem (Invanz)	3. Aztreonam
Mechanism of action	Suppress the synthesis of the bacterial cell wall (bactericidal action)	
Spectrum of activity	Record wide: 1. Gr (+) cocci: streptococci, staphylococci, pneumococci 2. Gr (-) cocci: neisseria, gonococcus and meningococcus 3. Gr (-) bacteria: Listeria, Hemophilus rod, Proteus, Shigella, Salmonella, Escherichia coli, Klebsiella, Citrobacterium, Campylobacter, Pseudomonas aeruginosa, Serratia 4. Anaerobes: clostridia, fusobacteria, bacteroides	1. Gr (-) flora: gonococcus, meningococcus, Escherichia coli, Salmonella, Shigella, Klebsiella, Proteus, Citrobacterium, Pseudomonas aeruginosa .
Indications	<i>Last resort antibiotic</i> 1. Infections of the lower respiratory and urinary tracts, abdominal organs, skin, soft tissues 2. Meningitis 3. Sepsis * <i>Including caused multidrug-resistant bacteria</i>	<i>Last resort antibiotic (infections caused by strains of Gr(-) bacteria resistant to other β-lactam antibiotics and aminoglycosides or in cases of aminoglycoside intolerance)</i> 1. Sepsis 2. Urinary tract infection (cystitis, pyelonephritis) 3. Hospital pneumonia, cystic fibrosis 4. Infections of the skin, musculoskeletal system
Side effects	1. Nausea, vomiting, diarrhea, abdominal pain 2. Thrombophlebitis at the injection site 3. Allergy 4. Pseudomembranous colitis (rarely)	1. Pain and swelling at the injection site (i/m), thrombophlebitis (i/v) 2. Nausea, vomiting, diarrhea, abdominal pain, pseudomembranous colitis 3. Hepatitis, jaundice
Contraindications	1. Hypersensitivity to carbapenems	1. Hypersensitivity in anamnesis
NB!	1. Carbapenems are resistant to most β -lactamases of m/o (but MRSA is resistant to carbapenems). 2. Cilastatin inhibits the enzyme dehydropeptidase I which destroys the imipenem in the renal tubules.	It is destroyed by β -lactamases of many microbes.

m/o – microorganism

TETRACYCLINS AND MACROLIDES [1-4]

Classification	Tetracyclines		Macrolides	
	Natural	Semisynthetic	Natural	Semisynthetic
Drugs	1. Tetracycline	2. Metacyclin (rondomycin) 3. Doxycycline (vibramycin)	<i>14- membered:</i> 4. Erythromycin 5. Oleandomycin <i>16- membered:</i> 6. Josamycin 7. Midekamycin (macropen)	<i>14-membered:</i> 8. Roxithromycin (rulid) 9. Clarithromycin (clamed) <i>15- membered:</i> 10. Azithromycin (Sumamed) <i>16- membered:</i> 11. Midequamyacin acetate
Mechanism of action	Suppress the synthesis of the protein of the microbial cells at the level of the ribosomes (bacteriostatic). In high doses bactericidal action (macrolides).			
Spectrum of activity	1. Gr (-) bacteria: plague, cholera, brucellosis, tularemia, hemophilic rod, E. coli, salmonella, shigella, Klebsiella 2. Gr (-) cocci: moraxella 3. Gr (+) bacteria: anthrax, listeria 4. Others: spirochaetes, rickettsia, chlamydia, mycoplasmas, protozoa (tropical malaria and amoebiasis)		1. Gr (+) cocci: strepto-, pneumo-, staphylococcus, enterococcus (including β -lactamase-producing) 2. Intracellular pathogens (mycoplasmas, chlamydia, legionella) 3. Gr (+) sticks: listeria, pathogens of diphtheria 4. Gr (-) bacteria: causative agent of whooping cough, hemophilic rod, 5. Gr (-) cocci: gonococcus (10); Others: spirochetes	
Indications	1. Especially dangerous infections (plague, tularemia, anthrax) 2. Borreliosis (Lyme disease), rickettsiosis 3. Community-acquired pneumonia 4. STIs (non-gonococcal urethritis, chlamydial infection, syphilis)5. Acne		1. Infections of the upper and lower respiratory tract (streptococcal tonsillopharyngitis, acute sinusitis, acute otitis media, community-acquired pneumonia, exacerbation of chronic bronchitis, whooping cough, diphtheria) 2. Chlamydiosis, ureaplasmosis, syphilis 3. Eradication of H. pylori (9)	
Side effects	1. Gastrointestinal disorders 2. Dysbacteriosis, superinfection 3. Violation of bone and dental tissue formation 4. Photosensibilization 5. Hepatotoxicity 6. Allergy		1. Gastrointestinal disorders Rarely: 2. Reversible hear impairment 3. Thrombophlebitis at the injection site 4. Superinfections 5. Allergy	
Contraindications	1. Age before 8 2. Pregnancy, lactation 3. Severe liver pathology		1. Hypersensitivity in anamnesis 2. Pregnancy (1-9) 3. Lactation (6-9)	
NB!	The majority of Gr (+) cocci: strepto-, pneumo-, staphylococcus and anaerobes (clostridia, actinomycetes) are resistant to tetracyclines		Azithromycin: prolonged $T_1/2 \rightarrow$ is given once a day (0,5 g daily during 3 days or 0,5 g in the first day, 2 nd -5 th day –0,25 g daily). The bactericidal concentration in the focus of infectious inflammation is being maintained for 5-7 days after the last dose	