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Review

Polyene Antibiotics and the Effect of them on Kidney

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Abstract

In recent decades, the applied status of antibiotics has been ambiguous. On the one hand, living organisms are increasingly losing sensitivity to a certain group of antibiotics, the use of which is becoming increasingly limited, and on the other hand, new opportunities for the use of these drugs are emerging. Among a huge group of antibiotic drugs, polyene antibiotics (PA) take a special place. In this review, we studied the antibiotics, especially amphotericin B and the effect of them on the kidney.

Keywords: Acute kidney injury, Amphotericin B, Mycosis, Polyene antibiotics

INTRODUCTION

Antibiotics are a substance of microbial, animal or plant origin capable of suppressing the growth of certain microorganisms or cause their death. Most often produced by actinomycetes. They have a strong inhibitory effect on the growth and reproduction of microorganisms and relatively little damage to macroorganism cells. They have some side effects: allergic reactions, toxic reactions (kidney damage, liver, vestibular disorders, etc.), dysbacteriosis (microflora composition disorder of Intestine), superinfection (secondary infections), etc. The discovery of penicillin, and then other antibiotics play an important role in the treatment of infectious diseases. The discovery of penicillin helped the treatment of some diseases: plagues, (the antibiotics Streptomycin, sulfanilamide used in anti-plague serum and prophylaxis), cholera (Tetracycline, Streptomycin, Sigmamycin, Oletetrin, Levomicetin) meningitis (bacterial), pneumonia (Streptococcus pneumonia), typhus, sepsis, dysentery, wound infections.

Classification of the antibiotics

It could be classified as: I. Depending on the mechanism of action: 1. Antibiotics - inhibitors of synthesis of a cellular wall of a microorganism (Penicillins, cephalosporins, Vancomycin, Teikoplanine, etc.); 2. Antibiotics that disrupt the molecular organization, functions of the cell membranes (Polymixin, Nystatin, Levorin, Amphotericin, etc.); 3. Antibiotics suppressing the synthesis of protein and nucleic acids, in specifically inhibitors protein synthesis in the level of the ribosome, (Chloramphenicol, Tetracyclines, macrolides, Linkomycin, aminoglycosides) and RNpolymerase inhibitors, etc. (Rifampicin) II. Depending on the type of action on the microbial cell: 1. Bactericidal (penicillins, cephalosporins, aminoglycosides, rifampicin, polymixins, etc.); 2. Bacteriostatic (macrolides, tetracyclines, lincomycin, chloramphenicol, etc.), III. Depending on the spectrum of activity: 1. affect the procariota, 2. Act on tumor cells, 3. Affect on the viruses IV. Depending on the chemical structure: 1. Beta-lactam, 1.1. Group of Penicillin,1.2. Karbapenema (Biapenem, Imipenem), 1.3. Tsefalosporina (Tsefaloridin, Tsefalexin), 2. Tetracycline, 3. levomycetins, aromatic series (Chloramphenicol), 4. Aminoglycosides (Streptomycin, Kanamycin, Neomycin), 5. Glycopeptide (vancomycin, bleomycin), 6. Polymixin, 7. Macrolides (Erythromycin, Oleandomycin, Clarithromycin, Azithromycin),8. Polyene antibiotics (antifungal), 8. Lincosamides (Linkomycin) et al.

Mode of action and mechanisms of resistance

The mechanism of action of antibiotics and antimicrobials

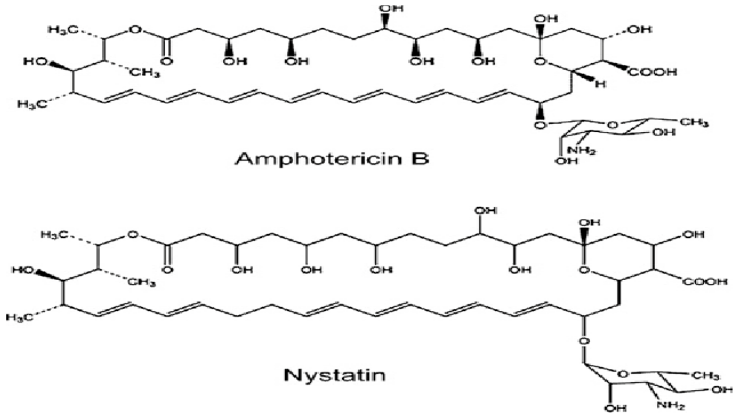

Figure 1. The structure of amphotericin B and Nystatin

can be classified also according to the function of the agents. These include inhibition of cell wall or nucleic acid synthesis, inhibition of ribosomal function, or inhibition of cell membrane function, and inhibition of folate metabolism. Antimicrobial drugs are one of the most successfully used therapies in medicine, but the effectiveness of antimicrobial drugs is compromised by numerous antibiotic-resistant pathogens. Resistance can be described in two ways: A) Internal resistance - in which case the microorganisms are not naturally the target sites for antimicrobials and the antimicrobials do not affect them. B) Acquired resistance mechanisms include the presence of enzymes that inactivate antimicrobial agents, post-transcription or post-translational modification of the target of the antimicrobial agent, active excretion of the antimicrobial agent (Dowling et al., 2017).

In this review, we want to discuss some polyene antibiotics and the effect of them on the kidney. Macrolide PAs belong to a group of antifungal drugs with more than 200 members. These antibiotics are isolated from strains of *Streptomyces* culture and have to a certain extent pronounced antifungal properties. Moreover, their use is increasingly associated with the treatment of certain bacterial and viral diseases. According to the version and modern data of some scientists (Tulio Simonchini), a fungus such as *Candida albicans* leads to metastases in cancer patients, in these cases people taking antibiotics of another species not in complex with PA are at risk. There is a possibility that the action of PA to suppress the growth of carcinogenic cells is very high. Among PA, amphotericin B, levorin, nystatin and mycoheptin were the most used. The biological aspect of the study of PA is related to their membrane-active function, that is, to the change in the conductivity of cell membranes in the presence of them and various derivatives differing in chemical structure. Polyene molecules contain a macrocyclic lactone ring with a certain number of double bonds. They define the chromophoric properties of a given substance, from which their common name is polyenes, classifying them all as a group of compounds with a certain n-th number of double bonds. Figure 1 shows the structure of some PA. Thus, a complex of hydroxyl groups with carboxyl constitutes is the hydroxyl moiety of the molecule. The amino group (mycosamine) is bound to the hydrophobic part of the antibiotic by an oxygen bridge. Mycosamine together with a carboxyl group and hydroxyl groups impart amphoteric properties to the antibiotic molecule.

Action Mechanism of Polyene Antibiotic. The study of the action mechanism of PA was carried out on the analysis of data on the conductivity of amphotericin B, nystatin, levorin and filipin and their derivatives to the cell and bilayer lipid membranes (Samedova, 1984). Binding of these antibiotics to *Candida, Neurospora* and *Saccharomyces* cells has been found to serve as the primary criterion for their biological action. It has been found that PA interacts with one of the sterol components in the cell membranes, which in turn provides penetration into the cell of ions and low molecular weight substances. Based on these studies, a "sterine" hypothesis of the mechanism of action of PA and a hypothetical model of an ion channel formed by an equal number of antibiotics and sterol molecules in the cell membrane were put forward. This opens up the possibility of ions and low molecular weight compounds entering the cell and is the basis for the fungicidal action of antibiotics and causes their specific toxicity to fungi (Bittman et al., 1983). Thus, only membranes and eukaryotic organisms containing sterols are sensitive to PA. Cell membranes of bacteria are substantially free of sterol components (Asselieau and Lederer, 1960). The specific toxicity of PA to fungi, but not to bacteria, is due to the presence of sterols in the cell membrane of fungi, yeast-like organisms, molds, and algae, but their complete absence in bacterial cells (Ermolenko and Nikolaev, 2010). As for the polyenes themselves, they all exhibit these properties to varying degrees. Nevertheless, the biological function of sterol

components is not quite unambiguous and according to some researchers sterols in cytoplasmic membranes also serve as support elements (Lampen, 1966). It should be noted that in many studies cell membranes have been replaced with model membranes, which are an alternative to natural membranes and have identical physical and chemical characteristics. BLMs (bilipid membranes) are used in complex with cholesterol or ergosterol in different ratios with phospholipids and are considered to be more advanced than their cellular counterparts (Baginski et al., 2002). Concerning PA, it should be noted that although they all respond to the presence of a sterol component, depending on the structure of the molecule (by the number of double bonds, the presence of an aromatic group, the localization of carboxyl and amine groups), as well as depending on the conditions of the experiment, they behave differently. For example, nystatin was found in a membrane fraction containing high amounts of sterol in single-cell *Leishmania donowani* (Ghosh and Chattergee, 1963). Here, nystatin exhibits biological activity in membranes and is complexed with a sterol component. *Acholeplasma laidlawii* cells cannot synthesize sterols themselves, but when these cells are grown in a medium with sterols, the latter is easily inserted into the cytoplasmic membranes of the cells. Undergrowth conditions on medium with cholesterol, ergosterol or cholestanol, the microorganisms *Acholeplasma laidlawii* are sensitive to philippine, amphotericin B, nystatin and etruscomycin (Kasumov and Liberman, 1974). It has also been found that PAs interact only with sterols of a certain configuration. Thus, only 3-beta-OH isomers of sterins included in the cell membranes of *Acholeplasma laidlawii* interact with PA. It is necessary to have an intact ring B and hydrophobic chain in sterol molecule at C17. The 3-alpha-OH isomers of sterol do not substantially interact with PA (Neumann et al., 2009). The process of complex formation of PA with sterols was studied by methods of electron microscopy, circular dichroism, UV spectroscopy, fluorescence. By a fluorescent method, the specificity of the interaction of antibiotics with cholesterol, the kinetics of the formation of the PA-cholesterol complex and the stoichiometry of their interaction can be determined (Bolard et al., 1980; Bolard et al., 2009). The molecules of these antibiotics have their spectrum of fluorescence intensity with maximum absorption in the near UV region. From the studied antibiotics (amphotericine, nystatin, Philippines) the greatest maximum of a range gives the Philippines (Kasumov, 1971). The maximum fluorescence spectrum of philippine is 480 nm. As the polarity of the medium decreases, the maximum of the spectrum does not change. On the other hand, the removal of cholesterol from the aqueous solution leads to a decrease, while in other PA, on the contrary, the addition of sterols to the aqueous solution leads to a decrease in the maximum UV spectrum. Regarding the biological activity of PA in membranes, it should be noted that the main criterion, in this case, is the change in cell permeability. As noted above, the interaction of PA with the sterol component results in the formation of ion channels and, accordingly, changes in the conductivity of cell membranes. Ion channels carry out the transport of ions and low-molecular organic compounds. Experiments on model lipid membranes allow studying the molecular mechanism of PA action. The data obtained on cells and, accordingly, on BLM are well correlated and provide an opportunity to study in detail the mechanism of PA action in membranes and ion transport (Kasumov, 1971). The first studies to determine the integral conductivity and membrane potential were conducted by comparing the voltage drop across the equivalent resistance and the membrane (Andreoli, 1973; Finkelstein and Holz, 1973). Through an electrometric amplifier (У5-9) membrane resistance was recorded, and using an electronic self-recorded the kinetics of membrane potential and resistance was recorded. A similar technique has been used by us further to study various PA in phospholipid bimolecular membranes. Thus, the integral characteristics of BLM in the presence of PA were investigated, as well as single ion channels were obtained and their physicochemical characteristics were studied (Samedova, 1984). However, it must be borne in mind that membrane permeability is selective. The selectivity of the membranes depends to some extent on the sterol composition of the membrane and the chemical structure of the antibiotic. In the presence of amphotericin B, mycoheptin and nystatin, membranes are selectively permeable for monovalent anions, and in the presence of aromatic PA (levorin A2, trichomycin) for alkali metal cations. In the 1970s, based on experimental data, several scientists independently presented a hypothetical molecular model of an ion channel or pore in the BLM, which results from the formation of a complex of PA with a sterol component (Finkelstein and Holz, 1973). Amphotericin B was presented as a model from antibiotics and sterol cholesterol was presented as a model. Amphotericin B and phospholipid molecules are almost the same size and are about 24 angstroms long. Hydrophilic chain of amphotericin B molecule (C1-C15) is represented by several hydroxyl groups, hydrophobic part of it (C20- C33) is located parallel to it. The cholesterol molecule is 19 angstroms long. The hydroxyl group in the 3-beta position is on the surface of the membrane. Thanks to this group, antibiotics interact with sterin. According to the ion channel model, two semiforms are required to form this conductive structure, each formed from an equal amount of antibiotics and cholesterol. Stoichiometrically, one amphotericin molecule interacts with only one cholesterol molecule. The hydrophobic side of the amphotericin B molecule binds to cholesterol, forming the amphotericin B-cholesterol complex. From the inside, the ion channel is lined with hydroxyl groups localized to carbon C1-C15 atoms (Finkelstein and Holz, 1973; DeKruyff and Demel, 1974). The pore diameter

inside is 8 angstroms. Two semi-carriers gather on different sides of the membrane. Hydroxyl groups in the amphotericin B molecule at carbon atom C35 form hydrogen bonds with the corresponding groups of the other half. So a full conductive time is formed. At the channel entrance, the hydroxyl group in the antibiotic molecule localizes at the C15 carbon atom. The hydroxyl group C35 reacts with the OH-corresponding amphotericin B molecule located on the opposite side of the membrane (DeKruyff and Demel, 1974). A cholesterol molecule binds to two amphotericin B Polopore molecules on each side of the membrane is formed from 8 amphotericin B molecules and 8 cholesterol molecules. The formation of a pore channel in such stoichiometry results in one hundred hydrophilic sides of the molecules forming a hydrophobic part of the membrane. Stabilization of the channel complex in the cell membrane is carried out by molecules of sterol and polar groups of PA. Functionally, the sterol component molecule interacts with the PA molecule to form a conductive port in the membrane. In this case, amphotericin B is a model of PA, as the antibiotic most studied in this direction (Samedova, 2016).

A great step in the treatment of mycoses was the creation of the polyene antibiotic AMB in 1955 - an antifungal antibiotic from several polyene macrolides, having a wide spectrum of antimicrobial action. Unlike other drugs in this group, AMB is administered intravenously, so it is effective in systemic lesions. AMB is one of the main drugs recommended for the treatment of systemic mycoses (Deray, 2002). The drug, in relatively small concentrations, acts on many opportunistic and pathogenic fungi and is effective in diseases such as aspergillosis, blastomycosis, candidiasis, cryptococcosis, coccidiosis, histoplasmosis, zygomycosis, etc. Bacteria from the genera Actinomyces, Nocardia and others (protozoa and viruses) are insensitive to this antibiotic. AMB in therapeutic concentrations acts fungistatically; *In vitro,* the fungicidal effect is exhibited by prolonged exposure to high concentrations. AMB irreversibly binds to the ergosterol of the fungal cell membrane, which results in disruption of its permeability, and also causes peroxidation reactions in the cell membrane. Intravenously administered AMB is still the drug of choice for most deep mycoses, especially life-threatening mycoses with definitively outstanding etiology (Sergeev and Sergeev, 2003). At intravenous administration of medium doses sufficient therapeutic concentration of preparation in plasma is maintained for 6-8 hours, and then for the next 20 hours smoothly decreases by half. The half-life with slow drip administration is 24-48 hours AmB is metabolized in the liver and excreted with urine. In the first 24 hours after administration only 5% of the administered dose is output, and in 7 days - 20-40%, so it is possible to cumulate the preparation and increase side reactions. In the case of kidney function disorder, the elimination of the drug is further delayed. Therefore, it is very difficult to predict pharmacodynamics by multiple administration of AMB without monitoring its plasma concentration. The preparation is usually administered intravenously drop-wise at a dose of 0.5-0.8-1.0-1.5 mg/kg/day. It should be remembered that AMB practically does not pass through the blood-brain barrier and is found in the spinal fluid at a minimum concentration insufficient for antifungal action, so intravenous administration of the preparation for the treatment of mycotic CNS lesions is almost ineffective. AMB can be administered intrathecally (in brain shells), intrapleural, subconjunctivally, and within the vitreous body, and it can also be administered during lumbal, cistern, or ventricular puncture. In general, it is desirable to achieve an optimal concentration of the preparation in the blood by gradually increasing the dose to the target level. Unfortunately, the possibilities for effective AMB treatment are limited due to its toxicity. Side effects of the preparation include fever, chills, headache, nausea and vomiting, thrombophlebitis at the place of administration, erythropoiesis suppression, hepatotoxic and neurotoxic effects in intrathecal antibiotic administration, neurotoxic reactions in the form of paresis, tremor, and convulsions are possible. The most severe consequence of the use of the drug is due to its toxic effect on the kidneys, as a criterion of which some researchers consider an increase in the level of creatinine in blood serum compared to the initial level on 100% (Shevyakov et al., 2012), others - the achievement of this value > 0.12 mmol/l (3). The most serious complication due to AMB use is acute renal injury (ARI). The preparation has a direct toxic effect leading to acute tubular necrosis, causes pronounced vasoconstriction and reduced renal blood flow. These lesions are responsible for decreased tangle filtration and tubular dysfunction (Deray, 2002). The damage of the canals leads to hypokalemia, hypomagnesemia, hypostenuria, reduction of uric acid excretion, so careful monitoring of nitemia and water-electrolyte balance is necessary. The rate of development of kidney function disorders during AMB treatment is high and, according to various researchers, is 49-65% (1). According to J. R. Wingard et al. (1999), a doubling of creatinine levels compared to the baseline was observed in more than 50% of patients in the study group, 29% showed an excess of creatinine of 0.25 mmol/L with a decrease in renal function of at least 70%. 15% of patients needed dialysis. Analysis of treatment results 707 patients treated parenterally with AmB found that ARI (creatinine increase peak > 0.2 mmol/L) developed in 212 patients (30%), with 89 (13%) having a severe form (creatinine peak > 0.3 mmol/L). The average duration of therapy in the tested group was 14.8 days, the average dose of AmB was 1.2 g (Bates D.W., et al., 2001). According to the scientific literature, the main risk factors for kidney function disorder due to amphotericin B use are 1. Daily dose. A nephrotoxic dose exceeding 35 mg (Harbarth S., et al., 2001) or 0.5 mg/kg (Richardson M. D., et al., 1997) is

considered. A daily dose increase of 0.1 mg/kg was accompanied by a 1.8-time increase in the risk of nephrotoxicity (Fisher M. A., et al., 1989). 2. Dehydration. Simultaneous administration of AMB and the diuretic drug significantly (12.5 times) enhances the toxic effect of AMB on the kidneys (Fisher M. A., et al., 1989). 3. Cumulative dose. The likelihood of ARI development in patients receiving AMB depends to a large extent on the total dose of the drug. If it is less than 0.5 g, then ARI occurs in 23% of patients, if the dose of AMB is in the range of 0.5 g to 0.9 g, then ARI develops in 30%. At a dose of 1.0 g to 1.4 g, kidney function is impaired in approximately 37% of patients. In the group of patients receiving AMB from 1.5 g to 1.9 g, ARI was observed in 40%, more than 2 g in 43% of patients (Bates D.W., et al., 2001). At a dose of more than 5 g, the development of ARI was observed in almost 100% of patients. If the cumulative dose is more than 4 g, the kidney function disorder can be irreversible (Deray, 2002). 4. Initial kidney function disorder. ARI occurs more often in patients having elevated creatinine levels and/or reduced tangle filtration before AMB therapy (9). 5. Combination of AMB with potentially nephrotoxic preparations (cyclosporin A, aminoglycosides, vancomycin, platinum preparations, acyclovir, non-steroidal anti-inflammatory agents, cardiac glycosides (especially against the background of hypokalemia) and current-like myorelaxants. The most aggressive is the combination of AmB with cyclosporin A (Gubbins et al., 2002; Filatov, 2003). The probability of developing complications caused by the nephrotoxic effect of AMB depends on the number of nephrotoxic preparations produced simultaneously with it (Walsh J.W., et al., 1999): in monotherapy of AMB (0.6 mg/kg) or in case of its combination with one nephrotoxic preparation, complications develop in 15.2% of patients; In the course of treatment including, together with AMB, more than 2 nephrotoxic agents - in 40.5% of patients; At simultaneous administration of more than 3 drugs with a toxic effect on kidneys, and AMB - in 45.4%. 6. Nature of the concomitant disease (e.g. type of transplantation). A group of a high risk of developing ARI, as a result of AMB treatment, refers primarily to patients after autologous and allogeneic bone marrow transplantation (auto BMT and Allo BMT). Kidney function disorder due to AMB nephrotoxicity is somewhat less common in patients with neutropenia (without transplantation) and after organ transplantation. According to J.R. Wingard with coauthors (1999), the frequency of the dysfunction of kidneys (increase twice in comparison with initial creatinine level) caused by AMB nephrotoxicity in the group of patients after alloBMT (the I group) reaches 61%, after autoBMT (the II group) - 80%, after transplantation of solid bodies (the III group) - 35%, at neutropenia without transplantation (the IV group) - 54%. The creatinine concentration was also found to exceed 0.25 mmol/l in group I - 33% of patients, in II - 47%, in III - 36%, in IV – 40%. The authors note that replacement renal therapy (hemodialysis) was required: in group I - 20% of patients, in group II - 19%, in group III - 18%, in group IV - 7%. The fatality in the groups was: after alloBMT - 71%, after auto BMT - 88%, after transplantation of solid organs - 36%, in neutropenia without transplantation - 62%. 7. Male Sex As one of the risk factors in AMB treatment, several authors consider the male sex of the patient (Bates D.W., et al., 2001; Harbarth S., et al., 2001). 8. Patient weight > 90 kg (Harbarth S., et al., 2001).

Diagnosis of drug nephrotoxicity based on a 50% increase in creatinine compared to baseline. But it should be remembered that in some cases, urinary disorders occur long before obvious biochemical abnormalities. With AKI level changes serum creatinine is known to lag behind the time of renal damage for 24-48 hours. It is now recognized that it is better others contribute to the early diagnosis of AKI-determination of serum cystatin C, lipocalin - a substance associated with the hydrolase activity of leukocytes (NGAL, Neutrophil Gelatinase-Associated Lipocalin), IL-18 in urine (Ermolenko and Nikolaev, 2010). Serum cystatin C is a marker of kidney function, which after 6 hours begins to increase in blood with a decrease in glomerular filtration rate (“fast creatinine”), the appearance in the urine of lipocalin, IL-18 - products of pathological processes that indicate the phase of active renal damage ("renal troponin") (Safdar et al., 2010). Decreased nephrotoxicity allows the use of this drug in higher doses than the deoxycholate complex AmB, in particular, in kidney transplant recipients, who are at the highest risk of developing AKI during treatment with polyene antibiotics (Rocamora et al., 2004).

CONCLUSION

In the mid-1950s, the first antimicrobial agents, polyene antibiotics, were obtained. These drugs are active against several agents of systemic mycosis. The mechanism of their antifungal action is based on interaction with ergosterol of the cytoplasmic membrane of the fungus, causing its damage, which leads to disruption of the life of the fungi and their death. However, it is also possible to cross-interact polyene antibiotics with cholesterol, which is part of the cytoplasmic membranes of animal cells, including human cells. As a result, damage to these cells occurs, which is the cause of numerous side reactions. So, the use of amphotericin B on the kidney is also a risk.

REFERENCES

Asselieau J, Lederer E (1960). Lipide metabolism. New York: John Wiley and Sons, p.337

Baginski M, Resat H, Borowski E (2002). Comparative molecular dynamics simulations of amphotericin B-cholesterol/ergosterol membrane channels. Biochim. Biophys. Acta, 1567: 63-78.

Bittman R, Clejan S, Rottem S (1983). Transbilayer distribution of sterols in mycoplasma membranes, Yale J.Biol.Med., 56:397-403.

Bolard J, Cleary JD, Kramer RE (2009). Evidence that impurities contribute to the fluorescence of the polyene antibiotic amphotericin B. J. Antimicrob. Chemoth, 63:921-927.

Bolard J, Seigneuret M, Boudet G (1980). Interaction between phospholipid bilayer membranes and the polyene antibiotics amphotericin B. Lipid state and cholesterol content dependence. Biochem. Biophys.Acta, 599(1): 280-293.

DeKruyff B, Demel R (1974). Polyene antibioticsterol interact ions in membranes of Acholeplasmalaidlawii cells and lecithin lyposomes. III Molecular structure of the polyene antibioticcholesterol complexes. Biochim. Biophys. Acta, 339: 57-70

Deray G (2002). Amphotericin B nephrotoxicity // J. Antimicrob. Chemoth. - Vol. 49, Suppl. S1. - P. 37-41.

Dowling A., JO' Dwyer, CC Adley (2017). Antibiotics: Mode of action and mechanisms of resistance, in book: Antimicrobial research: Novel bioknowledge and educational programs (A. Méndez-Vilas, Ed.)Publisher: Formatex Research Center, August

Ermolenko VM, Nikolaev AY (2010). Acute renal failure: a guide - M.: GEOTAR-Media, - 240s

Filatov LV (2003). Strategy and tactics of minimizing the risk of developing acute renal failure as a result of treatment with amphotericin B // Successes in medical mycology: Mat. I All-Russian Congress of Medical Mycology. - M., - T. 2. - C. 230-233 (in Russian)

Finkelstein A, Holz R (1973). Aqueouspores created in thin lipid membranes by polyene antibioticnystatin and amphotericin B. In: Membranes. Ed. G.Eisenman. NewYork: Marcell Dekker Inc., 2: 377-407.

Ghosh BK, Chattergee AN (1963). Action of an antifungal antibiotic, nystatin on the Protozoa Leishmania donovani. Ann. Biochem. Explt.Med., 23: 309-318.

Gubbins PO, Penzak SR, Polston S., et al. (2002). Characterizing and predicting amphotericin B - associated nephrotoxicity in bone marrow or peripheral blood stemcell transplant recipients // Pharmacotherapy. Vol. 22, №8. - P. 961-971.

Kasumov Kh.M (1971). The mechanism of action of polyene antibiotics.Abstract of Cand.dissertation. Moscow-Pushchino,(in Russian)

Kasumov Kh.M, Liberman EA (1974). The role of cholesterol in increasing the conductivity of bimolecular membranes by polyene antibiotics. Biophysics, 19: 71-74(in Russian)

Lampen JO (1966). Interference by polyene antifungal antibiotics (especially nystatin and filipinwith specific membranes functions. Simposium Soc.Gen. Microbiol., 16:111-130.

Neumann A, Czub J, Baginski M (2009). On the possibility of the amphotericin B –sterol complexformation in cholesterol-and-ergosterol-containing lipid bilayers: a molecular dynamic study. J.Phys. Chem.Biol., 113: 15875-15885.

Rocamora N, Tormo AM, Franco A, et al. (2004). Fever and cavitary infiltrate in a renal transplant recipient // Nefrologia. - Vol. 24, Suppl. 3. - P. 16-20.

Safdar A, M a J, Saliba F., et al. (2010). Drug-induced nephrotoxicity caused by Amphotericin B lipid complex and liposomal Amphotericin B. A Review and Meta-Analysis // Medicine. - Vol. 89, №4. - P. 236-244.

Samedova AA (1984). The effect of philipine and individual components of nystatin on the conductivity of bilayer membranes, News of Acad.Sci.ofAzerb., a series of biological sciences, 6: (in Russian)

Samedova AA (2016). Structural and Functional Dependence of Macrolide Polyene Antibiotics in Plasma and Bilayer Lipid Membranes, The news of Azerbaijan National Academy of Sciences (biological and medical sciences), 71, No. 1, p. 37-46 (in Russian)

Sergeev AY, Sergeev YV (2003). Fungal infections: A guide for doctors. - M .: Binom-press- 440 p. (in Russian)

Shevyakovм A, Kolmakova Ye.V, Rakhmatullina LN (2012). Nephrotoxicityofantimycotics (Review), Problems Of Medical Mycology, T.14, №4

Andreoli T (1973). On the anatomy of amphotericin B-cholesterol poresin lipid bilayer membranes. Kidney International, 4: 337-345.