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Current Views on the Problem of Antibiotic Resistance and its Negotiation in Clinical Pediatrics

Authors: A.P. VOLOSOVETS, S.P. KRIVOPUSTOV, E.I. YULISH, Bogomolets National Medical University, Kiev, Donetsk National Medical University of Maxim Gorky
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It is known that resistance to antibiotics has always existed. So far, no antibiotic, effective to all pathogenic bacteria, have been created (and probably will never be).

Resistance of microorganisms to antibiotics can be intrinsic and acquired. The intrinsic (spontaneous) stability is characterized by absence in microorganisms of action target of antibiotic or inaccessibility of target owing to initially low permeability or an enzymatic inactivation. When bacteria have natural stability, antibiotics are clinically inefficient.

Acquired resistance is an ability of particular strains of bacteria to keep viability at those concentrations of antibiotics, which suppress the major part of microbial population. Appearance of the acquired resistance in bacteria is not necessarily followed by the decrease in clinical effectiveness of antibiotic. Formation of resistance in all cases is associated with genetics — the acquisition of new genetic information or the change of expression level of own genes.

The following biochemical mechanisms of resistance of bacteria to antibiotics are known: modification of action target, antibiotic inactivation, active excretion of antibiotic from microbial cell (efflux), damage of permeability of external structures of microbial cage, formation of the metabolic shunt.

The reasons for development of resistance of microorganisms to antibiotics are different; a significant place among them belongs to irrationality, and occasionally inaccuracy in application of preparations.

1. Unreasonable prescription of antibacterial agents.

The indication for prescription of antibacterial preparation is a recorded or suspected bacterial infection. The most widespread error in ambulance situation, which is observed in 30–70% of cases, is indication of antibacterial preparations in case of viral infections.

2. Errors in selection of anti-infective drug.

Antibiotic should be selected with regard to the following basic criteria: a range of antimicrobial activity of preparation in vitro, regional level of resistance of activators to antibiotic, established effectiveness in controlled clinical trials.

3. Errors in selection of dosage regimen of anti-infective drug.

Errors in selection of an optimal dose of an anti-infective drug can lie both in insufficient and in surplus dose of the indicated preparation, as well as a wrong selection of intervals between administration. If a dose of antibiotic is insufficient and doesn't create concentrations exceeding minimum depressive concentration of the basic infectious agents in blood and tissues of airways, that is a condition of eradication of the corresponding activator, it becomes not only one of the reasons of therapy inefficiency, but also creates actual background for formation of resistance of microorganisms.

The wrong selection of intervals between administrations of anti-infective drugs is usually associated not so much with the difficulties of parenteral administration of preparations under outpatient treatment or a negative attitude of patients, but with lack of knowledge in practical doctors on some pharmacodynamic and pharmacokinetic characteristics of preparations which have to define their dosage regimen.

4. Errors of co-administration of antibiotics.

One of the errors of antibacterial therapy of community acquired respiratory tract infections is an unreasonable indication of a combination of antibiotics. In the modern situation in the presence of a wide range of high-efficiency antibacterial preparations of a wide range of indication to the combined antibacterial therapy are considerably narrowed, and the priority in treatment of many infections still belongs to monotherapy.

5. Errors connected with duration of antibacterial therapy.

In particular, at the present time unreasonably long antibacterial therapy is conducted in children in some cases. Such wrong tactics is associated first of all with insufficient understanding of the purpose of antibacterial therapy itself, which is resulted in the first instance to eradication of activator or suppression of its further growth, i.e. is focused on suppression of microbial aggression.

Except the specified errors of prescription of antibacterial preparations, the development of antibiotic resistance is promoted by the social problem of inadequate access to drugs that causes appearance in the market of low-quality, but cheap preparations, fast development of resistance to them and, as a result, prolongation of disease time.

In general, the development of antibiotic resistance of microorganisms is associated with the biochemical mechanisms developed during evolution. The following ways of realization of antibiotic resistance in bacteria are distinguished: modification of a target of antibiotic action, inactivation of antibiotic, decrease of permeability of external structures of bacterial cells, formation of new metabolic pathways and active extraction of antibiotic from bacterial cell. Their own mechanisms of resistance development are peculiar to various bacteria.

The resistance of bacteria to beta-lactam antibiotics is developed during the change of normal penicillin-associated proteins (PAP); gaining of an ability to develop additional PAP with low affinity to beta lactams; excessive development of normal PAP (PAP -4 and-5) with lower affinity to beta-lactam antibiotics, than in PAP -1,-2,-3. In gram-positive microorganisms, a cytoplasmatic membrane concerning is relatively porous and belongs to a peptidoglycan matrix directly, therefore, cephalosporins reach PAP rather easily. By contrast, the external membrane of gram-negative microorganisms has essentially more composite construction: it consists of lipids, polysaccharides and proteins that is a barrier for penetration of cephalosporins into periplasmatic space of a microbial cell.

Decrease in affinity of PAP for beta-lactam antibiotics is considered as the leading mechanism of formation of resistance of *Neisseria gonorrhea* and *S treptococcus pneumoniae* to penicillin. Methicillin-resistant *Staphylococcus aureus* (MRSA) produce PAP-2 (PAP-2a) which are characterized by considerable reduction of affinity for penicillin-resistant penicillins and cephalosporins. The ability of these "new" PAP-2a to replace essential PAP (with higher affinity for beta lactams) eventually leads to formation of resistance of MRSA to all cephalosporins.

By all means, objectively the most clinically significant mechanism of resistance development of gram-negative bacteria to cephalosporins is production of *betalactamases*.

Betalactamases are widespread among gram-negative microorganisms, and they are also produced by a number of gram-positive bacteria (staphilococci). Today, more than 200 types of enzymes are known. Recently, up to 90% of resistant strains of bacteria, isolated in humans, are capable to produce betalactamases, that defines their resistance.

Not long ago so-called extended-spectrum betalactamases, coded by plasmids (ESBL), were found. ESBL come from TEM-1, TEM-2 or SHV-1 owing to a point mutation in the active site of enzymes, and are produced mainly by Klebsiella pneumoniae. Production of ESBL is associated with a high level of resistance to aztreonam and cephalosporins of the III generation — to ceftazidime, and etc..

Production of betalactamases is under control of chromosomal or plasmid genes and their development can be induced by antibiotics or is mediated by constitutional factors in body height and distribution of bacterial resistance with which plasmids transfer genetic material. Genes, coding the resistance to antibiotics, are caused by mutations or get into the microbes from outside. For example, in case of conjugation of stable and sensitive bacteria, the genes of resistance can be transmitted wit plasmids. Plasmids are small genetic elements in the form of DNA fibres enclosed in a

ring, capable to transfer from one to several genes of resistance not only among bacteria of one species, but also among epy microbes of different species.

Besides plasmids, the genes of resistance can get in bacteria by means of bacteriophages or be captured by microbes from surrounding medium. In the latter case, the genetic carriers of resistance are the free DNA of the dead bacteria. However, mole of resistance genes by means of bacteriophages, or capture of free DNA containing such genes, does not mean yet that their new host became resistant to antibiotics. The genes coding it should be obligatory incorporated in plasmids or in chromosomes of bacteria to acquire resistance.

The molecular-level inactivation of beta-lactam antibiotics by betalactamase is represented as follows. There are stable bounds of amino acids in betalactamases. These groups of amino acids form a lacuna which beta-lactam enters in such a way that serine in the center cuts a beta-lactam link. As a result of reaction of free hydroxyl group of serine amino acid entering the active site of enzyme, with beta-lactam ring, an unstable acyl-ether complex which is quickly exposed to hydrolysis. As a result of hydrolysis, an active molecule of enzyme and a destroyed antibiotic molecule are released.

From the practical point of view, while characterizing betalactamases it is necessary to take into account several parameters: substrate specificity (ability to hydrolyze separate beta-lactam antibiotics), sensitivity to action of inhibitors, localization of gene.

The standard classification of Richmond and Sykes divides betalactamases into 5 classes depending on the effect on antibiotics (according to Y.B. Belousov, there are 6 types). The I class includes the enzymes resolving cephalosporins the II — penicillin, the III and the IV — various antibiotics of broad spectrum. The enzymes which resolve isoxazolyl penicillins, belong to the V class. Betalactamases, associated with chromosomes (I, II, V), resolve penicillin, cephalosporins, and plasmid-associated (III and IV) — penicillins of broad spectrum. Table 1 shows classification of betalactamases according to K. Bush.

Table 1. Classification of betalactamases according to Bush (1995)

Group	Class	Predominant substrate	Inhibition Clav/EDTEA		Typical representatives
1	C	Cephalosporins	-	-	AmpC enzymes of gram-negative bacteria; MIR-1
2a	A	Penicillins	+	-	Penicillinase of gram-positive bacteria
2b	A	Penicillins, Cephalosporins	+	-	TEM-1, TEM-2, SHV-1
2be	C	Penicillins, Cephalosporins of narrow and wide	+	-	TEM-3 – TEM-26, SHV-2 – SHV-6,
		spectra, monobactams			*Klebsiella*oxytoca K1
2br	A	Penicillins	+/-	-	TEM-30 – TEM-36, TRC-1
2c	A	Penicillins, Carbenecillin	+	-	PSE-1, PSE-3, PSE-4
2d	D	Penicillins, Cloxacillin	+/-	-	OXA-1 – OXA-11, PSE-2 (OXA-10)
2e	A	Cephalosporins	+	-	Inducible cephalosporinases from *Proteus*
2f	A	Penicillins, Cephalosporins, Car-	+	-	NMC-A from *Enterobacter cloacae*, Sme-1 from Serratia

		bapenems			
3	B	Majority of betalactams, including Carbapenems	-	+	L1 from Xanthomonas maltophilia, CcrA from *Bacteroides fragilis*
4	ND	Penicillins	-	-	Penicillinases from *Pseudomonas*cepacia

Several representatives of *Enterobacteriaceae* family *(Enterobacter spp., Citrobacter freundii, Morganella morganii, Serratia marcescens, Providencia spp*.), as well as *Pseudomonas aeruginosa*, show ability to produce the inducible chromosomal cephalosporinases, characterized by high affinity to cephamycins and cephalosporins of III generation. The induction or stable "depression" of these chromosomal betalactamases in the period of "pressure" (administration) of cephamycins or cephalosporins of III generation results in formation of resistance to all available cephalosporins. Distribution of this form of resistance is increased in cases of treatment of infections, first of all caused by *Enterobacter cloaceae* and *Pseudomonas aeruginosa*, cephalosporins of broad spectrum.

Chromosomal betalactamases, produced by the gram-negative bacteria, are divided into 4 groups. Chromosomal cephalosporinases belong to the 1st group (the I class of enzymes according to Richmond — Sykes), the 2nd group of enzymes resolves cephalosporins, in particular cefuroxime (cefuroximase), betalactamases of broad spectrum belong to the 3rd group, the 4th group includes the enzymes produced by anaerobes.

Chromosomal cephalosporinase are divided into two subtypes. Betalactamases, produced by *E.coli, Shigella, P.mirabilis* belong to the first subtype; in presence of beta-lactam antibiotics they do not increase production of betalactamases. At the same time, *P.aeruginosae, P.rettgeri, Morganella morganii, E.cloaceae, E.aerogenes, Citrobacter, Serratia spp.* can produce a large amount of enzymes in presence of beta-lactam antibiotics (the second subtype).

For the infection caused by *P.aeruginosae*, the development of betalactamases is not the main mechanism of resistance, i.e. only 4-5% of resistant forms are associated with production of plasmid-associated and chromosome-associated betalactamases. Generally, resistance is connected with violation of permeability of bacterial wall and abnormal structure of PSP.

Chromosomal cefuroximases are low-molecular weight compounds, active in vitro against cefuroxime and are partially inactivated by clavulanic acid. Cefuroximases are produced by *P.vulgaris, P.cepali, P.pseudomallei.* Unstable cephalosporins of the first generation stimulate production of this betalactamase type. The induction of cefuroximases and stable cephalosporins is possible. Klebsiella synthesize chromosomally determined betalactamases of the IV class which destroy penicillin, ampicillin, cephalosporins of the first generation (broad-spectrum betalactamases), as well as other cephalosporins.

Chromosomal betalactamases of gram-negative bacteria (*Morganella, Enterobacter, Pseudomonas*) are more intensively formed in the presence of ampicillin and cefoxitin. However, their production and activity are suppressed with clavulanic acid and especially sulbactam.

Plasmid-associated betalactamases, produced by gram-negative bacteria, first of all, by Escherichia coli and *P.aeruginosae*, determine overwhelming number of hospital-acquired strains, resistant to modern antibiotics. Many enzymes of betalactamases inactivate not only penicillin, but also peroral cephalosporins and preparations of the first generation, as well as cefamandole, cefazolin and cefoperazone. Such enzymes as PSE-2, OXA-3, hydrolyze and determine low activity of ceftriaxone and ceftazidime. Stability of cefoxitin, cefotetan and lactamocef to the enzymes of SHV-2 and CTX-1 types is described.

As betalactamases play an important role in ecology of the range of microorganisms, they are widely distributed in nature. So, in chromosomes of many types of gram-negative microorganisms, the genes of betalactamases are found in vivo. It is evident, that introduction of antibiotics in medical practice has changed biology of microorganisms fundamentally. Though details of this process are unknown, it can be expected that some of chromosomal betalactamases appeared mobilized in the structure of mobile genetic elements (plasmids and transposons). The selection advantages

which provided possession of these enzymes to microorganisms, led to fast spreading of the latter among clinically significant pathogens.

Betalactamases of class C (group 1 according to Bush) belong to the most widespread enzymes with chromosomal localization of genes. Genes of these enzymes are found in chromosomes practically of all gram-negative bacteria. Particular features of expression are characteristic for betalactamases of class C with chromosomal localization of genes. In some microorganisms (for example, *E.coli*), chromosomal betalactamases are expressed constantly, but on a very low level, insufficient even for ampicillin hydrolysis.

The inducible type of expression is characteristic for microorganisms of *Enterobacter, Serratia, Morganella*, etc. group. In the absence of antibiotics in the environment, enzyme is practically not produced, but after contact with some beta lactams, synthesis speed is risen sharply. Upon violation of regulatory mechanisms, a constant hyperproduction of enzyme is possible.

Whereas at the present time more than 20 betalactamases of class C, localized on plasmids, have already been described, these enzymes have not widely spread yet, however already in the near future they can become a real clinical problem.

Chromosomal betalactamases *K.pneumoniae, K.oxytoca*, with *C.diversus* and *P.vulgaris* belong to class A, distinctions in expression are characteristic for them as well. However, even in case of hyperproduction of these enzymes, microorganisms keep sensitivity to some cephalosporins of the III generation. Chromosomal betalactamases Klebsiella belong to the group 2be according to Bush, and betalactamases *C.diversus* and *P.vulgaris* — to the group 2e.

For reasons not well understood, mobilization of betalactamases of class A on mobile genetic elements, happens more effectively, than of class C enzymes. So, there is every reason to believe that plasmid betalactamases SHV1 and their derivants, widespread among gram-negative microorganisms, derived from chromosomal betalactamases *K.pneumoniae*.

Historically, the first betalactamases, which caused serious clinical problems, were staphylococcal betalactamases (group 2a according to Bush). These enzymes efficiently hydrolyze natural and semi-synthetic penicillin, also partial hydrolysis of cephalosporins of the I generation is possible; they show sensitivity to action of inhibitors (clavulanate, sulbactam and tazobactam).

Genes of enzymes are localized on plasmids that support their fast intra- and interspecific disctribution among gram-positive microorganisms. As early as at the middle of the 50th years, in some regions more than 50% of strains of staphilococci produced betalactamases that led to fall-off of penicillin effectiveness. By the end of the 1990th, the frequency of betalactamases production among staphilococci practically everywhere exceeded 70–80%.

The first plasmid betalactamase of class A (TEM-1) in gram-negative bacteria was described in the early sixties, soon after introduction of aminopenicillins in medical practice. Thanks to plasmid localization of genes, TEM-1 and two others betalactamases of class A (TEM-2, SHV-1) spread among representatives of *Enterobacteriaceae* family and other gram-negative microorganisms practically everywhere within a short period of time.

The listed enzymes were named broad-spectrum betalactamases. According to classification of Bush, broad-spectrum betalactamases belong to the group 2b. Practically important characteristics of broad-spectrum are the following:

— cephalosporins of the III–IV generation and carbapenems are resistant to them;

— an ability to hydrolyze natural and semisynthetic penicillins, cephalosporins of the I generation, partially cefoperazone and cefamandole;

— sensitivity to action of inhibitors;

— plasmid localization of genes.

The period since the end of the 1960th and to the middle of the 1980th was noted by intensive development of beta lactam antibiotics; carboxy- and ureidopenicillins, as well as cephalosporins of three generations, were implemented in practice. These preparations significantly excelled aminopenicillins, according to the level and the range of antimicrobial activity, as well as according to

pharmacokinetic characteristics. The majority of cephalosporins of the II and the III generations, in addition, were resistant against broad-spectrum betalactamases.

During some time after practical application of cephalosporins of the II-III generations, the acquired resistance to them practically was not noted among enterobacteria. However, already in the early 1980th there were first reports on the strains with plasmid localization of resistance determinants to these antibiotics. It was found out quickly enough that this resistance was associated with production by microorganisms of the enzymes which were genetically related with broad-spectrum betalactamases (TEM 1 and SHV-1); new enzymes were named extended-spectrum betalactamases (ESBL).

The first identified enzyme of an expanded spectrum was betalactamase TEM-3. By now, about 100 derivants of TEM-1 enzyme are known. Most often, betalactamases of TEM-type are met among *E.coli* and *K.pneumoniae*, however, their detection is possible practically among all representatives of *Enterobacteriaceae* and some other gram-negative microorganisms.

According to Bush classification, betalactamases of TEM- and SHV-type belong to the 2be group. Practically important properties of ESBL are the following:

— an ability to hydrolyze cephalosporins of the I–III and to a lesser extent of the IV generation;

— carbapenems are resistant to hydrolysis;

— cephamycins (cefoxitin, cefotetan and cefmetazole) are resistant to hydrolysis;

— sensitivity to action of inhibitors;

— plasmid localization of genes.

Among betalactamases of TEM-and SHV type, the enzymes with a peculiar phenotype, are described. They are not sensitive to the action of inhibitors (a clavulanate and a sulbactam, but not tazobactam), however, their hydrolytic activity, in regard to the majority of beta lactams, is lower, than in precoursor enzymes. The enzymes which were named "inhibitor-resistant TEM" (IRT) were included in the group 2br according to the classification of Bush. In practice, the microorganisms, which have these enzymes, show a high resistance to the protected beta lactams, but they are only moderately resistant to cephalosporins of the I-II generation and are sensitive to cephalosporins of the III-IV generation. It should be noted, however, that in separate betalactamases, the resistance to inhibitors and an expanded spectrum of hydrolytic activity are combined.

The enzymes which amount is rather quickly increasing in recent years, belong to CTX-like betalactamases (cefotaximase), which represent a sharply defined group different from other enzymes of class A. The preferable substratum of the indicated enzymes, in contrast to TEM- and SHV derivants, is not ceftazidime or cefpodoxime, but cefotaxime. Cefotaximase was found in various representatives of *Enterobacteriaceae* (mainly in *E.coli* and *Salmonella enterica*) in geographically outlying regions of the world. At the same time, in Eastern Europe, the distribution of clonal and relative strains of Salmonella typhimurium, which produce CTX-M4 enzyme, is described. According to the classification of Bush, betalactamases of STH-type belong to the group 2be. Origin of the enzymes of STH-type is not clear. The considerable degree of homology is found with chromosomal betalactamases *K.oxytoca, C.diversus, P.vulgaris, S.fonticola*. Lately, a high degree of homology has been established with chromosomal betalactamase *Kluyvera ascorbata*.

Also, there is a number of rarely found enzymes, which belong to the class A and has the phenotype, specific for ESBL (ability to hydrolyze cephalosporins of the III generation and sensitivity to inhibitors). These enzymes (BES-1, FEC-1, GES-1, CME-1, PER-1, PER-2, SFO-1, TLA-1 and VEB-1) have been isolated in a limited number of strains of different types of microorganisms in various regions of the world from South America to Japan. The listed enzymes differ according to preferable substrata (single representatives of cephalosporins of the III generation). The majority of these enzymes have been described after the publication of the work of Bush et al., in this connection, their position in classification is not determined.

Class D enzymes belong to ESBL as well. Their precursors, broad-spectrum betalactamases, hydrolyzing mainly penicillin and oxacillinum, are poorly sensitive to inhibitors, are common basically in Turkey and France among *P.aeruginosa*. The genes of these enzymes are, as a rule, localized on plasmids. The majority of the enzymes showing an extended spectrum phenotype (preferred

hydrolysis of cefotaxime and ceftriaxone — OXA-11,-13,-14,-15,-16,-17,-8,-19,-28), derive from betalactamase OXA-10. According to the classification of Bush, betalactamases of OXA-type belong to the 2d group.

Bush provides some more groups of enzymes, which significantly differ according to the characteristics (including according to action spectrum), but usually not considered as extended-spectrum betalactamases. The preferred substrata for the enzymes from the group 2c is penicillin and carbenicillin, they meet among P.*aeruginosa, Aeromonas hydrophilia, Vibrio cholerae, Acinetobacter calcoaceticus* and some other gram-negative and gram-positive microorganisms, the genes are more often localized on chromosomes.

The preferred substratum for enzymes of the group 2e is cephalosporins; chromosome inducible cephalosporinase *P.vulgaris* is considered as a typical example. Betalactamases of this group are described also in *Bacteroides fragilis* and, less frequently, in other microorganisms.

The group 2f includes the rare enzymes of class A, which are capable to hydrolyze the majority of beta lactams, including carbapenems. Livermore relates these enzymes to extended-spectrum betalactamases, other authors don't.

Except the listed betalactamases, it is necessary to mention the two last groups of enzymes included in the classification of Bush. Rare, but potentially critical metal-betalactamases of B class, as a natural result, found among *Stenotrophomonas maltophilia* and rarely met in other microorganisms (*B.fragilis, A.hydrophila, P.aeruginosa*, etc.), belong to the enzymes of the group 3. The differential characteristic of these enzymes is an ability to hydrolyze carbapenems. The group 4 includes under-studied P.aeruginosa penicillinases suppressed by clavulanic acid.

The rate of ESBL distribution varies considerably in certain geographical regions. For example, according to the data of multicenter research MYSTIC, in Europe, the highest rate of ESBL distribution is noted steadily in Russia and Poland (more than 30% among all studied strains of enterobacteria). In some medical institutions of the Russian Federation, the rate of ESBL production among *Klebsiella spp*. exceeds 90%. Depending on specifics of the medical institution, various mechanisms of resistance (methicillin-resistance, resistance to fluoroquinolones, hyperproduction of chromosomal betalactamases, and etc., can be the most common in it).

As articulated earlier, ESBL has a wide range of activity; more or less they hydrolyze practically all beta-lactam antibiotics, apart from cephamycins and carbapenems.

However, the presence of resistance determinants to any antibiotic in microorganism not always means clinical failure in treatment with this preparation. For example, there are reports on high efficiency of cephalosporins of the III generation in the treatment of infections caused by the strains producing ESBL.

In the whole world, for the purpose of improvement of effectiveness and safety of antibacterial and antiviral agents and prevention of development of antibiotic resistance, the societies and associations have been created, the declarations have been adopted, the educational programs for rational antibiotic therapy have been developed. The most important of them include:

— «Copenhagen Recommendations», introduced by the countries of the European Union, 1998;

— «Action Plan of Public Health Care on Combat against Antibiotic Resistance», suggested by American Society for Microbiology and a number of US departments, 2000;

— «Global WHO Strategy on suppression of resistance to antimicrobial agents», 2001.

Besides, in Canada (2002), the World declaration to combat antimicrobial resistance has been introduced, in which it is specified that resistance to antibiotics correlates with their clinical inefficiency; it is created by a person, and only the person can solve this problem, and unreasonable administration of antibiotics by population, wrong application and undervaluation of the problem of resistance by doctors and pharmacists prescribing antibiotics, can lead to resistance distribution.

In 2002, according to the order of MH of Ukraine No. 489/111 of 24.12.2002, the commission on control of rational use of antibacterial and antiviral agents was created in our country.

The main goals when studying an antibiotic susceptibility and antibiotic resistance are the following:

— development of local and regional standards of prevention and therapy of hospital-acquired and community-acquired infections;

— justification of measures on restriction of distribution of antibiotic resistance in hospital conditions;

— identification of initial signs of formation of new resistance mechanisms;

— detection of regularities of global distribution of separate resistance determinants and development of measures on its restriction.

— carrying out of a long-term prognosis of distribution of separate resistance mechanisms and justification of development trends of new antibacterial preparations.

Antibiotic resistance and antibiotic susceptibility are studied both with point contact methods (within one institution, district, state), and by means of case follow-up on resistance spreading.

It is rather difficult to compare the data obtained with the use of commercial systems of antibiotic susceptibility assessment of different manufacturers. The existence of various national criteria of sensitivity makes the situation even more complicated. So, among the countries of Europe alone, the national criteria of sensitivity exists in France, the United Kingdom, Germany and some other. In separate institutions and laboratories, the techniques of material sampling and assessment of clinical significance of isolates often differ considerably.

However it is necessary to notice that the use of antibiotic not always leads to antibiotic resistance (the evidence of it is the sensitivity of *Enterococcus faecalis* to ampicillin, which has been not changing for decades) and, moreover, it does not depend on administration duration (resistance can develop within the first two years of its administration or even at the stage of clinical trials).

There are several ways of overcoming of resistance of bacteria to antibiotics. One of them is protection of well-known antibiotics from degradation by enzymes of bacteria or from removal from a cell by means of membrane pumps. In such a way, "protected" penicillins — combinations of semisynthetic penicillins with inhibitors of bacterial betalactamases - appeared. There is a number of compounds which suppress production of betalactamases; part of them are applied in clinical practice:

— clavulanic acid;

— penicillanic acids;

— sulbactam (sulfone of penicillanic acid);

— 6-chlorpenicillanic acid;

— 6- iodinepenicillanic acid;

— 6- brominepenicillanic acid;

— 6- acetylpenicillanic acid.

There are two types of betalactamase inhibitors. Antibiotics resistant to the action of enzymes belong to the first group. Such antibiotics in addition to antibacterial activity possess inhibition characteristics in regard to betalactamases, which are evident at the high concentration of antibiotics. They include methicillin and isoxazoline penicillins, monocyclic beta-lactams like carbapenems (tienamicin).

The second group includes inhibitors of betalactamases, which show inhibitory activity at low concentration, and at high concentration they have antibacterial characteristics. Clavulanic acid, halogenated penicillanic acids, sulfone of penicillanic acid (sulbactam) may serve as an example. Clavulanic acid and sulbactam block penicillin hydrolysis by staphilococci.

Clavulanic acid and sulbactam, which have hydrolytic activity, are most widely used as inhibitors of betalactamases. Sulbactam blocks betalactamases of the II, III, IV and V classes, as well as chromosome-mediated I class of cephalosporinases. Clavulanic acid has similar characteristics. The difference between preparations is that in much smaller concentration, sulbactam blocks formation of chromosome-mediated betalactamases, and clavulanic acid — of plasmid-associated enzymes. Moreover, sulbactam has irreversible inhibitory effect on a number of lactamases. Inclusion in the

environment of betalactamases inhibitor of clavulanic acid increases sensitivity the penicillin-resistant staphilococci from 4 to 0.12 μg/ml.

Perspective approaches to overcoming of resistance of bacteria to antibiotics appear also administration of combinations of antibiotics; carrying out a specific and focused antibacterial therapy; synthesis of new compounds which are belong to the known classes of antibiotics; search of basically new classes of antibacterial preparations.

For the purpose of prevention of resistance development in microorganisms to medicinal preparations, the following principles should be followed:

1. To carry our therapy using anti-infective drugs in maximum doses until the complete overcoming of disease (especially in severe cases); the preferable mode of preparation administration is parenteral (taking into account process localization).

2. To replace periodically widely used preparations by recently created or rarely prescribed (reserve).

3. Combined use of a number of preparations is theoretically reasonable.

4. Preparations, to which the resistance of streptomycin type is developed in microorganisms, should be not prescribed ad monotherapy.

5. One antibacterial preparation should not be replaced by the other, to which there is a crossed resistance.

6. Resistance is quicker developed to antibacterial preparations for preventive and outward application (especially in aerosol form), than for their parenteral administration or ingestion. Topical administration of antibacterial preparations should be minimized. Thus, the agents which are not used for systemic medication and with low risk of fast development of resistance to them are used, as a rule.

7. To carry out an assessment of the type of antibacterial preparation (approximately once a year), which was most often administered for medical purposes and analysis of treatment results. It is necessary to distinguish antibacterial preparations, which are administered most often and in severe cases, reserve and of a deep reserve.

8. To systematize diseases depending on localization of focus of inflammation and severity of patient's condition; to isolate antibacterial preparations for administration in the corresponding area (organ or tissue) and for use in exceptionally severe cases, moreover, a permission of the competent persons who are specifically engaged in antibacterial therapy, on their administration is obligatory.

9. To assess periodically the type of activator and resistance of strains of microorganisms circulating in hospital environment, to plan control measures for prevention of hospital-acquired infection.

10. Upon uncontrolled administration of anti-infective drugs, virulence of infectious agents is strengthened, and the forms resistant to pharmaceuticals appear.

11. To limit administration in food industry and veterinary medicine of those preparations, which are used for the treatment of people.

12. Administration of preparations with narrow spectrum is recommended as the way of resistance reduction of microorganisms.

DECLARATION

to combat antimicrobial resistance, accepted on the World Day of resistibility (September 16, 2000, Toronto, Ontario, Canada)

We have met the enemy and he is us.

Poge

Considerations:

1. Antimicrobial Agents (AA) are nonrecoverable resources.

2. Resistibility is correlated with clinical inefficiency.

3. Resistibility is created by a man, and only a man can solve this problem.

4. Antibiotics are social preparations.

5. Polypharmacy of AA by population, wrong presentation and undervaluation of resistibility problem by doctors and pharmacists, prescribing AA, lead to resistibility.

6. Administration of AA in agriculture and veterinary medicine contributes accumulation of resistibility in environment.

Actions:

1. Monitoring of resistibility and epidemiological surveillance should become routine both in polyclinic and at hospital.

2. In the whole world application of antibiotics as growth promoters in animal breeding should be stopped.

3. Rational administration of AA is the main measure for resistibility lowering.

4. Creation of educational programs for doctors and pharmacists, prescribing AA.

5. Development of new AA.

Suggestions:

1. There is a need in creation of specialized institutions for introduction of new AP and control action of resistance development.

2. The committees on AP control should be created both in all medical treatment facilities, in which AP are prescribed, and in the countries and regions for development and introduction of policy of its administration.

3. Treatment time and AP dosage regimen should be reviewed in accordance with structural resistance.

4. It is advisably to carry out researches for determination of the most active preparation in the groups of antibiotics for control of resistance development.

5. The approaches to AP administration with the prevention and therapeutic purpose in veterinary medicine should be reviewed.

6. Creation of biorecycled AP is recommended.

7. Development of antibiotics, specifically affecting pathogens or tropic to various organs and systems of human body.

8. It is recommended to consider the possibility of cyclic AP administration.

9. More attention should be paid to health communication across the population.

Global WHO strategy on suppression of resistance to antimicrobial agents

On September 11, 2001 World Health Organization published a Global strategy on suppression of resistance to antimicrobial agents. This program is focused on assurance of efficiency of such life-saving medications, as antibiotics, not only for the current people generation, but also in future. Without coordinated actions of all countries many great findings, made by medical scientists for the last 50 years, can lose their significance due to antibiotic resistance spreading.

Antibiotics are one of the most significant findings of the XX century. Owing to them, it is now possible to treat and cure those diseases, which have been earlier fatal (tuberculosis, meningitis, scarlatina, pneumonia). If humanity fail to protect this greatest achievement of medical science, it will enter a postantibiotical age.

For the last 5 years more than 17 mln. dollars have been spent for pharmaceutical industry on research and development of medicinal preparations, used for treatment infectious diseases. If resistance of microorganisms to medicinal preparations develops quickly, the majority of these investments could be lost.

The WHO strategy on suppression of resistance to antimicrobial agents concerns everyone who, to some extent, is associated with administration or prescription of antibiotics — from patients to doctors, from administrative employees of hospitals to the Ministers of Healthcare. This strategy is the result of a 3-year work of WHO experts and cooperating organizations. It is focused on assistance to reasonable administration of antibiotics with the purpose to minimize resistance and to give an opportunity to the next generations to administer efficient antimicrobial agents.

The informed patients will be able not to press upon the doctors to make them prescribe antibiotics. The educated doctors will prescribe only those medicinal preparations, which are really necessary for the treatment of patient. the administrative employees of hospitals will be able to carry out a detailed on-site monitoring of effectiveness of medicinal preparations. The Ministers of Health will be able to make the majority of really necessary preparations available for use, while inefficient preparations would not be administered.

Use of antibiotics in the food industry also promotes growth of antibiotic resistance. Today 50% of all produced antibiotics are used in agriculture not only in the treatment of sick animals, but also as growth promoters of cattle and birds. Steady microorganisms can be transferred from animals to human. To prevent it, WHO recommends a sequence of actions, including obligatory prescription of the recipe for all antibiotics used in the treatment of animals, and phasing out of the antibiotics which are used as growth promoters.

Antibiotic resistance is an essential biological process. Today we live in the world where antibiotic resistance is quickly spreading, and the number of vital preparations which become inefficient, is growing. At the moment the resistance of microorganisms is registered to the antibiotics used in the treatment of meningitis, sexually transmittable diseases, hospital infections, and even for a new class of the antiretroviral preparations used in the treatment of HIV infection. In many countries, mycobacteria of tuberculosis are resistant to at least two among the most efficient preparations used in the treatment of tuberculosis.

This problem concerns to the same extent advanced and industrial, as well as developing countries. Polypharmacy of antibiotics in many developed countries, insufficient duration of course of treatment in the poor eventually create identical threat for mankind in general.

Antibiotic resistance is a global problem. There is no country, which could allow ignoring it, and there is no country, which couldn't respond to it. Only simultaneously conducted actions on growth suppression of antibiotic resistance in each particular country can give positive results all over the world.

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