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Modern View of the Problem of Antibiotic Resistance in Children before and after Liver Transplantation, Causes of Antibiotic Resistance

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Introduction

Antibiotic resistance is a topic of concern to all mankind today. These days, the "craze" for antibiotics has become like an epidemic and today, antibiotic resistance is a global problem. The words of the new WHO Secretary-General echo the earlier concerns of the European Commissioner for Health, Vytenis Andriukaitis: "Antibiotic resistance is one of the most pressing public health problems of our time, and if it is not addressed, we may return to a time when even the simplest medical operations were impossible, especially organ transplants, chemotherapy for oncology or intensive care."

Purpose

The aim of this work is to study antibiotic resistance in children before and after surgery.

Materials and Methods

Since March 2016, 32 liver transplants from a living related donor have been performed in children. The age of the patients ranged from 6 months to 8 years. Of these, 23 (78.1%) patients with biliary atresia, 2 (6.2%) with cirrhosis of the liver in the outcome of autoimmune hepatitis, 1 (3.1%) with primary hyperoxaluria, 1 (3.1%) with cholangiocarcinoma, 1 (3,1%), 1 (3,1%) with inoperable hepatoblastoma, 1 (3.1%) cirrhosis of the liver in the outcome of viral hepatitis C on the background of Langerhans cell histiocytosis. The number of girls was 17 (53.1%) and boys 15 (46.9%). The 5-year liver transplant survival rate was 75%. There was a 100% antibiotic intake in the preoperative period, including the primary health care level, district and city hospitals. 5 (15.6%) children with Klebsiella sepsis and with a fatal outcome were resistant to all groups of antibacterial drugs.

According to the treatment protocol No. 33, approved by the Joint Commission on the Quality of Medical Services of the Ministry of Health of the Republic of Kazakhstan dated November 28, 2017, from the day of the surgical treatment, all children received three-component antimicrobial therapy - a group of broad-spectrum penicillins with a beta-lactamase inhibitor (piperacillin tazobactam), an antibiotic of the chloramphenicol group (chloramphenicol) and an antiprotozoal drug with antibacterial activity (metronidazole). Antifungal therapy was carried out according to the results of microbiological studies. During the analysis, we obtained the following data:

Klebsiella (pneumonie, species, ozaenae, oxytoxa)- 8 cases (25%) before surgical treatment, after 10 cases (31.25%). Resistant to a large number of drugs - to amoxiclav, levofloxacin, meropenem, pefloxacin, cefazolin, cefepime, ceftriaxone, cefuroxime, cefotaxime, ertapenem, ciprofloxacin, amoxclave, levofloxacin, meropenem, piperacillin, cefazolin, cefepime, cefotaxime, ceftriaxone, ertapenem, gentamicin, imipenem, ciprofloxacin.

There are 5 (15.6%) cases of Staphylococcus aureus before surgery and 5 (15.6%) cases after surgery. Also they are resistant to amoxiclav, levofloxacin. meropenem, cefazolin, ceftriaxone, cefuroxime, azithromycin, gentamicin, ciprofloxacin, erythromycin-clindamycin.

There are 11 (34.3%) cases of Staphylococcus epidermiditis before surgery and 2 (6.25%) cases after surgery. They are resistant to azithromycin, amoxiclav, erythromycin, cefazolin, ceftriaxone, cefuroxime, cefotaxime, pefloxacin, gentamycin, azithromycin, clindamycin.

There are 4 (12.5%) cases of Streptococcus viridans before surgery and 2 (6.25%) cases after surgery. They are resistant to azithromycin, clindamycin, cefotaxime, azithromycin, clindamycin, erythromycin, vancomycin, ceftriaxone, cefuroxime, cefazolin, amoxiclav, azithromycin, erythromycin, pefloxacin.

There are 4 cases (12.5%) of E. Coli and 1 (3.1%) case after surgery. They are resistant to tobramycin, cefuroxime, cephazoline, cefotaxime, ceftriaxone, norfloxacin, pefloxacin, cefazolin, ceftriaxone, cefepime, cefotaxime, ciprofloxacin.

There are 4 (12.5%) cases of Enterobacter cloacae, aerogenes before surgery and 1 (3.1%) case after surgery. They are resistant to cefazolin, cefepime, cefotaxime, ceftriaxone, cefuroxime, gentamicin, cefotaxime, ceftriaxone, levofloxacin, ertapenem, pefloxacin, cefuroxime, ciprofloxacin.

There are 7 (21.8%) cases of Streptococcus pyogenes before surgery and 3 (9.3%) cases after surgery. They are resistant to ciprofloxacin, levofloxacin, erythromycin, azithromycin, pefloxacin, clindamycin, amoxiclav, amikacin, imipenem, meropenem, cefuroxime, ceftriaxone, cefazolin, cefepim, pseflamypotaximemu.

There is 1 case (3.1%) of Pseudomonas aeruginosa before surgical treatment. They are resistant to cefuroxime, pefloxacin, cefazolin.

There are 7 cases (21.8%) of Candida albicans before surgery and 4 cases (12.5%) after surgery. They are resistant to ketocanazole, flucanazole, clotrimazole.

Thus, the problem of resistance is largely due to the widespread and often irrational use of these drugs. Infections caused by resistant strains of microorganisms are characterized by a more severe course, more often require hospitalization of the patient, increase the duration of his hospital stay, and requires the use of combined antimicrobial therapy using reserve drugs. All this leads to an increase in treatment costs, worsens the prognosis for the health and life of patients, and also creates conditions for the emergence of epidemics.

Everyone knows that the unjustified use of antibiotics not only increases the cost of treatment and creates the risk of side effects, but also leads to an increase in the resistance of microorganisms. This problem is global and it depends on its solution whether humanity will be able to effectively fight bacterial infection in the future. Unfortunately, today there are many cases of inappropriate use of antibiotics in pediatrics and the reasons why doctors prescribe antibiotics when they are not needed.

According to the European Centre for Disease Control (ECDC, 2016), the resistance of Klebsiella pneumoniae, the causative agent of the most severe bacterial lung lesions in humans, increased from 6.2 to 8.1%, in just three years (from 2012 to 2015) and this resistance is noted at once to several groups of antibiotics. In this case, we are talking specifically about combined resistance, for example, to carbapenems and colistin, which is an extremely alarming signal, meaning that doctors have practically no money left to actually save the patient. In addition, an unpleasant tendency is observed in the antibiotic resistance of E. coli, which is also a common cause of various infectious complications. This is evidenced by the results of public opinion polls conducted recently in 12 countries (Barbados, Vietnam, Egypt, India, Indonesia, China, Mexico, Nigeria, Russian Federation, Serbia, Sudan, South Africa), published on the WHO website [1,2]. Having interviewed about 10,000 people in order to reveal their knowledge of antibiotic therapy, antibiotic resistance and their possible consequences for humans, the authors received unexpected results. It turned out that humanity is dominated by myths: 2/3 of the respondents have generally heard about antibiotic resistance, but 76% of them believe that it develops as an individual "addiction" of the body of a particular patient to a particular antibiotic; another 66% - that if the patient follows the doctor's instructions, then he is immune to insensitive microbes, 44% associate the problem of antibiotic resistance only with those patients who take antimicrobial drugs on a regular basis. Of course, these facts are very clear evidence of how important and relevant educational work with the population regarding compliance with the rules for taking antibiotics and curbing antibiotic resistance. By the way, the infectious morbidity in the CIS countries with many infectious diseases continues to increase. In 2016, the incidence of rubella significantly increased (in 2.8 times compared to the previous year), mumps (1.9 times), whooping cough (1.9 times) and Q fever (4 times). The incidence of salmonellosis increased by 14.7%, intestinal infections of unknown etiology by 5%, Siberian tick-borne typhus by 4.7% and trichinosis by 6 times. Last year, there were 50 new cases of malaria and 79 cases of Dengue fever. And most of these diseases require antibiotic treatment. As, however, we see same situation in other countries. In a recent study published in the Journal of the Society of Pediatric Infectious Diseases, American scientists, having analyzed the medical data of 94,000 children under the age of 18, hospitalized in 48 hospitals in different states of America with a diagnosis of enterobacterial infection, found a 700-fold (!) increase in these infections due to antibiotic resistance . The researchers described that the proportion of antibiotic-resistant pathogens increased from 0.2% in 2007 to 1.5% in 2015. Moreover, more than 75% of these resistant microbes were already present at the time of hospitalization, that is, the infection was not nosocomial. At the same time, the duration of hospitalization among patients with resistant pathogens was 20% longer. By the way, antibiotics cannot cope with about 1/4 of pneumonia in adults today, as evidenced by an analysis of data from 252,000 patients treated on an outpatient basis in the United States in 2011–2015 from community-acquired pneumonia [3-5]. Unfortunately, the problems of inappropriate antibiotic therapy are also observed in children receiving therapy for community-acquired pneumonia. And all because pediatricians do not prescribe the antibiotics prescribed in clinical guidelines. So, according to American colleagues, who analyzed the medical history of more than 10,000 children treated in outpatient clinics in Pennsylvania and New Jersey, only slightly more than 1/3 (40.7%) received the recommended amoxicillin. But macrolides were prescribed in 42.5% of cases, and broad-spectrum antibiotics - in another 16.8%. Clinical guidelines still influence the choice of a doctor [6,7]. So, before the introduction in 2011 into pediatric practice of the joint clinical guidelines of the Society of Infectious Diseases and the Society of Pediatric Infectious Diseases of America in 2009–2011. less than 10% of children hospitalized with a diagnosis of pneumonia received treatment with penicillin antibiotics, and after their introduction (in 2012–2015) - already 27.6%. At the same time, in hospitals where doctors were educated, this was the right choice in 29.5% of cases and where they did not study - in 20.1%.

According to the study, Americans prescribe antibiotics for the treatment of viral infections in 30% of cases; in the post-Soviet countries this level reaches 90%. It is especially sad that children are being treated with antibiotics very early. A study conducted by a team of scientists in 8 countries examined the use of antibiotics in children in the first two years of life. Over 5 years (from 2009 to 2014), the authors followed 2,134 children in Bangladesh, Brazil, India, Nepal, Pakistan, Peru, Tanzania and South Africa. Over the years, children received an average of 4.9 antibiotic courses per child per year, with the highest frequency of prescriptions for patients in South Asian countries. Including antibacterial agents were prescribed for viral infections: in 44.2% of cases of viral gastroenteritis and 39.5% of upper respiratory tract infections, that is, the treatment was not carried out in accordance with patient management protocols. Inappropriate use of antibiotics always leads to increased antibiotic resistance. The fact that antibiotic resistance literally "follows on the heels" of the prescription of antibiotics, and that it can be predicted was well highlighted in their publication by Israeli scientists [8-10]. After observing two communities of Israelis of Jewish and Arab origin for 5 years, fixing seasonal increases and decreases in antibiotic prescription and antibiotic resistance following them with a three-month lag, the authors created a mathematical model capable of predicting future resistance to different groups of antibacterial agents. An interesting fact from a scientific point of view, but little known to the general medical and non-medical community, is that that resistant bacteria are spreading around the world by travelers. Swedish exchange students who studied in India and Central Africa, did not get sick during the trip and were not treated with antibiotics, returned home with the resistance of the intestinal

microbiome to various antibiotics. A metagenomic analysis of the feces of students revealed a 2.6-fold increase in the number of genes for resistance to sulfonamides and beta-lactams and a 7.7-fold increase in the number of resistance genes to trimethoprim after returning compared to the level before the trip. Before studying abroad, only 1 student had genes for beta-lactamases, and then already in 12. This phenomenon is most likely the result of the ingestion of antibiotic-resistant bacteria with food or water into our bodies. Now it becomes clear that there are differences in resistance genes in the intestinal microbiome of people living in different geographic regions of the world, described in an article by Indian colleagues [11,12]. After analyzing the features of the intestinal microbiome and genes for antibiotic resistance to 240 antibacterial drugs in 275 individuals from America (USA), Europe (Denmark, Spain, Italy, France) and Asia (China and Japan), the scientists described 4 clusters (called by them resistotypes) characteristic of residents of different countries. So, resistotype 1a was mainly characteristic of Europeans and Japanese, 1b - was equally common among residents of America and Europe and more often than in Asia, resistance type 1c was more typical for Americans, and 2 - for Chinese and did not spread among residents of others regions. Each resistance type has its own sensitivity/resistance to each of the analyzed antibacterial drugs, what could be the basis for the adoption of national strategies to contain antibiotic resistance at the country level. In general, the topic of intestinal microbiota and its effect on human health is being discussed very actively today. When Harvard scientists deciphered the genome of the microbes that inhabit the human intestines, they discovered thousands of new bacteria and other representatives of this "fauna", the vast majority of which are still unknown to mankind. It is noteworthy that the microbiome changes not only with age, it depends on how a person was born - during natural childbirth or by caesarean section, how he was fed (with breast milk or formula), and also whether he received antibiotics, especially in the early childhood. But it is precisely the change in the microbiome that is today the basis of not only somatic diseases, but also many mental problems. The tendency to overweight in preschool children (which threatens the subsequent rapid development of obesity) may be a consequence of the intestinal microbiota changed in infancy: this is the conclusion made by Finnish scientists. By observing two cohorts of healthy Finnish and Dutch babies born naturally, and analyzing the relationship between the microbiota at 3 months and body mass index at the age of 5-6 years, scientists have shown that there is a direct relationship between changes in the composition of intestinal bacteria under the influence of antibiotic therapy and weight bodies of preschoolers. Bifidobacteria and streptococci affect, respectively, positively and negatively on the body weight of the child and can be early predictive markers of future problems. Thus, antibiotics prescribed to a child in the very first months of life dramatically change the entire trajectory of its subsequent development, often and quickly lead to the development of overweight, and then obesity, diabetes mellitus, early arterial hypertension and the rest of the bunch of problems of modern people. This means that by preventing the early use of antibiotics in children, you can preserve his health for many years [13].

Conclusion

Antibiotic resistance is a major threat to global health and sustainable development, the principles of which were defined in the 2030 Agenda and the Sustainable Development Goals. It is estimated that, in the absence of effective interventions, the development of antimicrobial resistance could lead to a global death's will increase by about 10 million cases annually. Growing concerns about antibiotic resistance have led to the adoption of a number of national, regional and global action plans in recent years to raise awareness, promote research and optimize antimicrobial use and access. Global initiatives also highlight the importance of more effective and sustainable investment in technology development and intersectoral action.

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