



## Risk of Resistance Due to Incorrect Use of Antibiotics in Children

**Bahodirov Behruz Shavkat Ogli**

Bukhara state medical institute after named Abu Ali ibn Sino  
bahodirov.behruz@bsmi.uz

**Abstract:** The problems of irrational antibiotic therapy are also observed in children who received treatment for community-acquired pneumonia. This is because pediatricians prescribe antibiotics that are not recommended in clinical guidelines. According to American colleagues who analyzed the medical records of more than 10,000 children treated in outpatient clinics in Pennsylvania and New Jersey, only slightly more than one-third (40.7%) received the recommended amoxicillin. On the other hand, macrolides were prescribed in 42.5% of cases, and broad-spectrum antibiotics were used in 16.8% of cases.

**Key words:** anti-bacterial agents, antibiotic resistance, microbiome, children.

Clinical guidelines do, in fact, influence the physician's choice of treatment. For instance, prior to the implementation of joint clinical guidelines from the Society of Infectious Diseases and the American Society for Pediatric Infectious Diseases in 2011, fewer than 10% of children hospitalized with a pneumonia diagnosis received treatment with penicillin-based antibiotics. However, after these guidelines were introduced (from 2012 to 2015), the figure rose to 27.6%. In hospitals where physician education was provided, the correct choice was made in 29.5% of cases, while in those without educational programs, it was only 20.1%. A similar study was conducted in Russia, showing a stronger impact of medical professionals' education on rational antibiotic therapy. According to Russian researchers, prior to educational programs, incorrect antibiotic prescriptions occurred in 78–90% of clinical situations. After training sessions for both medical and nursing staff, this figure dropped to 20–30%. Interestingly, Americans prescribe antibiotics for viral infections in 30% of cases, whereas in Russia and other post-Soviet countries, this figure reaches up to 90%.

It is especially concerning that children are often treated with antibiotics at an early stage. A study conducted by a team of researchers in 8 countries examined antibiotic use in children under two years of age. Over a 5-year period (from 2009 to 2014), the authors tracked 2,134 children from Bangladesh, Brazil, India, Nepal, Pakistan, Peru, Tanzania, and South Africa. On average, children were prescribed 4.9 courses of antibiotics per year, with the highest frequency observed in South Asian countries. Antibiotics were also prescribed for viral infections, with 44.2% of cases of viral gastroenteritis and 39.5% of upper respiratory infections receiving antibiotic treatment, which was not in accordance with treatment protocols.

Irrational use of antibiotics always leads to increased antibiotic resistance. Israeli scientists highlighted in their publication that antibiotic resistance closely follows antibiotic prescription patterns and can even be predicted. Over a 5-year period, they observed two communities of Israeli citizens (Jewish and Arab) and documented seasonal increases and decreases in antibiotic prescriptions, with antibiotic resistance following these patterns with a three-month delay. They developed a mathematical model capable of predicting future resistance to various antibiotic groups.

An interesting but lesser-known fact is that antibiotic-resistant bacteria are spread globally by travelers. Swedish students who studied abroad in India and Central Africa, despite not being ill or



using antibiotics during their travels, returned home with increased resistance in their gut microbiome to various antibiotics. Metagenomic analysis of their feces revealed a 2.6-fold increase in resistance genes to sulfonamides and beta-lactams, and a 7.7-fold increase in resistance to trimethoprim after their return, compared to levels before their trip. Prior to the trip, only one student carried beta-lactamase genes; after returning, 12 students had them. This phenomenon is likely due to the introduction of antibiotic-resistant bacteria into the human body via food or water.

A recent study by Indian colleagues highlighted regional differences in resistance genes within the human gut microbiome. They analyzed the gut microbiomes and antibiotic resistance genes for 240 antibiotics in 275 individuals from the USA, Europe (Denmark, Spain, Italy, France), and Asia (China, Japan). They identified four distinct "resistotypes" specific to the residents of each region, each with its own pattern of resistance to different antibiotics. These findings could form the basis for national strategies to control antibiotic resistance.

The topic of the gut microbiome and its impact on human health is actively discussed today. Interestingly, when Harvard scientists sequenced the human gut microbiome, they discovered thousands of new bacteria and other organisms, most of which were previously unknown. The microbiome changes not only with age but also depending on the mode of birth (natural delivery or cesarean section), breastfeeding or formula feeding, and whether the child received antibiotics, especially in early childhood. Changes in the microbiome are now understood to underlie not just physical diseases, but also many mental health issues.

For example, Finnish researchers concluded that an altered gut microbiome in infancy can contribute to an increased risk of excess weight in preschool children, which can lead to rapid obesity development. By studying two cohorts of healthy Finnish and Dutch infants born via natural delivery, they found a direct link between early antibiotic use and increased body mass index (BMI) at ages 5–6. Bifidobacteria and streptococci affect body weight positively and negatively, respectively, and can serve as early prognostic markers for future health issues. Thus, antibiotics prescribed in the first months of life can dramatically alter a child's developmental trajectory, leading to obesity, type 2 diabetes, early hypertension, and other modern health problems. Therefore, preventing early antibiotic use in children may help preserve their long-term health.

Lastly, one might ask: should prevention efforts for various health problems start earlier, even during fetal development? What is known about the effects of antibiotics administered to pregnant women?

Today, when children frequently experience episodes of bronchial obstruction (including in the context of respiratory infections), which can sometimes be the first signs of bronchial asthma, scientists are particularly concerned with the origins of these conditions. Researchers who observed 4,000 newborns found that antibiotic use by their mothers during the third trimester of pregnancy, for treating urinary tract infections, was directly correlated with the frequency of respiratory infections in the children and the appearance of wheezing during the first 18 months of life. The researchers believe that this phenomenon is due to the disruption of the mothers' intestinal microbiota caused by antibiotics, which in turn affects the health of their offspring. This study supports earlier findings from Denmark. By analyzing national registers, which included more than 910,000 children born in Denmark between 1997 and 2010, the authors concluded that, firstly, maternal antibiotic use (for various infections, primarily respiratory) is linked to an increased risk of asthma in their children. Secondly, the relationship between antibiotic use and the development of asthma is dose-dependent and extends beyond the pregnancy period. In other words, by disrupting their microbiota through antibiotic therapy, mothers inadvertently increase the risk of many diseases in their children. This highlights the importance of having a specialized team, including not only obstetricians and gynecologists but also pediatricians, involved in the care of mothers and children to ensure that antibiotics are not prescribed without specific indications.

Interestingly, there is also data suggesting a link between antibiotic use and an increased risk of spontaneous miscarriage. A study found that antibiotic use increased the risk of spontaneous abortion:



macrolides by 67%, quinolones, tetracyclines, sulfonamides by 65%, and metronidazole by 70%. These scientific findings clearly indicate that while antibiotics can save millions of lives, their misuse can also be harmful, even to future generations! This raises the question of the rational use of antibiotics and underscores the fact that, despite all efforts, there is a lack of knowledge in the global medical community regarding the potentially harmful side effects of antibiotic therapy. Some researchers report on the irrational use of antibiotics, far from recommended guidelines, and mainly in injectable form. According to their data, antibiotics were prescribed empirically, primarily for diagnoses of pneumonia, sepsis, and meningitis. Pediatricians in certain regions report a significantly higher frequency of antibiotic prescriptions for young children compared to other countries. Similar data is available for Russia and other CIS countries. One can only guess at the scale of antibiotic prescriptions. In Ukraine, given that the official vaccination rate for children is much lower than necessary, the situation is even more concerning.

To be fair, it should also be noted that there is a lack of awareness about the problems associated with excessive antibiotic use among the parent community. For example, in a study by researchers using anonymous surveys of parents, it was highlighted that around 40% of mothers and fathers still believe that antibiotics are useful for common colds, and another 36.2% expect them to speed up recovery in such cases. Additionally, 37.9% are confident that antibiotics can treat viral infections, and one in five parents reduces the dosage if the child feels better. Interesting data has been provided in a systematic review regarding parental knowledge from multiple countries over the past 20 years on the use of antibiotics in children with lower respiratory tract infections. It was noted that people living in countries with developed economies and higher socioeconomic groups demonstrated the best knowledge of the issue. Furthermore, detailed explanations from doctors significantly improved family adherence to recommendations (including those related to "prescribing antibiotics"). These conclusions are indirectly confirmed by another systematic review, which showed that written recommendations for parents have a higher effect.

The facts described raise the question of personal responsibility, especially since more and more people in both Russia and around the world are turning to "natural medicine." Sociologists who surveyed people in various settlements across Russia found that more than half of Russians trust "folk medicine." However, many respondents have difficulty understanding the differences between treatments used in traditional Chinese medicine, homeopathic remedies, and "phytomedicine" (herbal medicines). The desire to use "natural remedies" is also expressed by people in other countries. This trend has become so popular that both the American Medical Association and the American Academy of Pediatrics felt it necessary to publish their own statements on the matter. In fact, the American Academy of Pediatrics updated its clinical guidelines on integrative pediatrics, replacing the earlier version. This change is due to the fact that patient knowledge on the subject often exceeds the awareness of pediatricians. For example, over 10% of children in the U.S., including those with chronic diseases, have used various complementary or alternative medicine methods (ranging from dietary supplements to yoga). Pediatricians need documents summarizing these practices and providing evidence of their scientific basis.

In fact, there is evidence supporting the effectiveness of some interventions in specific clinical situations, particularly when carried out by well-trained specialists. For instance, yoga has been shown to improve the psychological condition and reduce symptoms in children with attention deficit hyperactivity disorder, inflammatory bowel disease, and juvenile idiopathic arthritis. However, there is another side to this issue: many complementary treatments, including those presented as safe "folk or natural remedies," are difficult to evaluate due to minimal regulation of their circulation. For biologically active supplements or "natural medicines" registered as food products, the regulatory process is much weaker, which is why they are not registered as medicines. Consequently, they do not undergo clinical trials for safety and effectiveness before being released to the market. Manufacturers often mislead consumers, highlighting only the positive effects and "forgetting" to mention the potential severe side effects that may occur with these supplements. For example, there





are known cases of serious interactions between St. John's Wort supplements and therapeutic doses of anticoagulants, calcium channel blockers, digoxin, benzodiazepines, etc. In official analyses of Ayurvedic medicine products, toxins and even heavy metals are often found, while "natural" homeopathic remedies have been shown to contain toxic doses of belladonna, causing severe poisoning in children.

Documents that explain the potential risks of these so-called "folk medicine" products are urgently needed for modern pediatricians, as they must be able to convincingly explain to parents, who believe that plant-based remedies are completely harmless, that "phytomedicines" vary greatly and that careful selection of proven effective and safe "natural" remedies for children is essential. The American Academy of Pediatrics and the National Center for Complementary and Integrative Health echo this concern, reminding consumers that some "natural" plant-based products can mistakenly be perceived as safe. All of them have potential side effects, including allergic reactions, up to asthma, as well as hepatotoxicity, increased bleeding risks, and interference with contraceptive medications, antidepressants, and HIV treatment drugs when using St. John's Wort supplements. The document even includes a recommendation to avoid such "herbal products" in children and pregnant women due to the lack of safety studies. This should once again prompt reflection on the need for evidence-based research on the safety and effectiveness of phytomedicines that are registered as pharmaceuticals, which is something modern pediatricians lack.

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