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Solutions to the Antibiotic Resistance Crisis

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Abstract: Irrational antibiotic therapy is not just about "excessive," unnecessary antibiotics. It also involves the wrong choice of medication, dosage, and/or duration of treatment. The benefits of such "treatment" are questionable, while the harm is evident. An incorrectly chosen drug will not ensure the eradication of the pathogen and/or may increase the risk of side effects for the patient.

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Irrational antibiotic therapy is not just about "excessive," unnecessary antibiotics. It also involves the wrong choice of medication, dosage, and/or treatment duration. The benefits of such "treatment" are questionable, while the harm is evident. An incorrectly chosen drug will not ensure the eradication of the pathogen and/or may increase the risk of side effects for the patient. Subinhibitory concentrations of antibiotics will not have a therapeutic effect, but will contribute to mutagenesis, horizontal gene transfer, and changes in gene expression. Induced gene expression by antibiotics may affect the virulence of the infectious agent, while increased mutagenesis and horizontal gene transfer lead to the emergence of antibiotic-resistant strains. Thus, suboptimal dosing of antibacterial drugs and non-compliance with treatment regimens create the conditions necessary for the circulation of superpathogens—highly virulent and multi-resistant organisms.

As for the duration of antibiotic courses, unfortunately, in pediatrics, it is rarely based on evidence (from studies), and more often on expert opinions. In the publication with the intriguing title "5, 7, 10, or 14 days: the appropriate duration of bacteremia treatment, or an example of 'antimicrobial bingo'?" the author analyzes studies on antibiotic therapy for bacteremia associated with urinary tract infections in infants. The author points out that the duration of parenteral antibiotic therapy for this disease depends on the protocols adopted in specific clinics, ranging from 7 to 14 days. The duration does not depend on the severity of symptoms (which are related to host factors and the microorganism type), nor on the risk of relapse (mainly determined by the presence of anatomical defects). Since organizing comparative studies on this rare pathology is extremely difficult, the author suggests aiming for shorter antibiotic courses, reducing the so-called standard durations on an individual basis. The basis for shortening the course is proposed to be the child's clinical response to treatment and levels of bacterial infection biomarkers—C-reactive protein and procalcitonin.

Several studies have shown that short courses of high-dose antibiotics for certain conditions are more effective than prolonged courses with low doses. Short courses minimize the risk of antibiotic resistance development and also offer benefits such as reduced treatment costs and improved patient adherence.

Are individual incorrect antibiotic prescriptions harmless? Where are we headed by prescribing amoxicillin-clavulanate for sudden exanthema, cefixime for catarrhal otitis, and ceftriaxone for rotavirus diarrhea?

The situation is tense, with publications about antibiotic resistance problem filled with terms like "crisis," "catastrophic consequences," and "nightmare scenario." Antibiotic-resistant bacteria have earned the ominous name "superbugs." Antibiotics have saved many lives and continue to do so, but whether they will continue to save lives tomorrow is uncertain. The trend is unfavorable: in all countries of the World Health Organization, there is a steady increase in the detection of resistant flora, both gram-positive and gram-negative. This issue particularly affects hospital-acquired infections. In 2008, L. Rice identified a group of pathogens with high antibiotic resistance responsible for most hospital-acquired infections in the USA and named it ESKAPE* (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter species). These microorganisms are highly resistant to virtually all available antibiotics, leaving doctors helpless and posing a life-threatening risk to patients.

Multidrug-resistant gram-negative bacteria are a problem not only for adult patients but also in the pediatric population. For example, a cohort study conducted in 48 children's hospitals in the USA showed an increase in the number of patients with infections caused by multidrug-resistant Enterobacteriaceae isolates. In 2007, their share was 0.2% of all patients with infections caused by gram-negative enterobacteria, while in 2015, it had risen to 1.5%. These children were much harder to treat, with longer hospital stays and higher mortality rates than those with infections caused by susceptible strains. They did not respond to treatment with antibiotics from the first-line or second-line groups. The severity of their condition required the use of drugs not intended for pediatric practice and unsafe for children, increasing the risk of serious side effects. This study is the first to demonstrate the prevalence of diseases caused by multidrug-resistant bacteria in children, and its results are concerning.

It’s not just ESKAPE group pathogens that show high antibiotic resistance. In different regions, multidrug-resistant strains of Mycobacterium tuberculosis, Streptococcus pneumoniae, and Neisseria gonorrhoeae, as well as highly virulent fluoroquinolone-resistant Clostridium difficile, are being discovered. Even the frequency of resistant isolates of microorganisms that are genetically less prone to variability and acquire resistance slowly, such as Neisseria meningitidis, is increasing. Although penicillin remains the drug of choice for treating invasive meningococcal infections, the increasing prevalence of penicillin-resistant isolates is prompting clinicians to use third-generation cephalosporins for initial therapy.

NO NEW ANTIBIOTICS?!

It is naive to hope that the creation of new antibiotics will be the solution to the antibiotic resistance crisis. The number of new antibiotics currently in development is quite small, and even fewer are truly novel compounds. Several drugs targeting methicillin-resistant Staphylococcus aureus (MRSA) are in clinical trials, but no fundamentally new treatments are being developed for several gram-negative pathogens, such as Acinetobacter baumannii and Pseudomonas aeruginosa. For pharmaceutical companies, developing new antibiotics is not economically viable. It is a complex process that requires significant financial investment, while the market for the final product is limited: antibiotics are needed by only a small number of people, and treatment courses are short. Moreover, the growing antibiotic resistance of bacteria leads to a policy of restraint in the use of new antibiotics. Leading specialists in microbiology and infectious diseases recommend using "old" drugs as first-line treatments and reserving new ones for therapy-resistant cases. This generally sound approach further restricts the use of new antibiotics, making investment in their development and production economically unjustifiable. Pharmaceutical companies find it more profitable to produce drugs for treating chronic diseases such as diabetes, asthma, and neurological disorders.

Limiting Prescription to Preserve Effectiveness

Since we cannot expect new antibiotics in the near future, it is crucial to preserve the effectiveness of old antibiotics by limiting their use. A recent Cochrane review provided strong evidence that limiting the use of antibiotics in hospitalized patients is an effective strategy. And not just in the context of combating antibiotic resistance: hospitals that restricted antibiotic therapy saw reduced patient stays, without an increase in mortality rates.

Another effective strategy is to delay the initiation of antibiotic therapy. Cochrane Collaboration experts studied the effect of this approach in treating acute respiratory infections, including patients with cough (bronchitis) and sore throat, as well as middle ear infections. Eleven studies involving 3,555 patients (children and adults) compared three treatment approaches: immediate antibiotic therapy, delayed therapy, and no antibiotics. Delayed therapy meant prescribing antibiotics with the recommendation to wait for a while before starting treatment, hoping that symptoms would improve without antibiotics. The analysis showed no significant differences in the duration of the main respiratory infection symptoms (fever, pain, malaise, cough, runny nose) among the three patient groups. There was also no difference in complication rates. In other words, whether the patient received antibiotics immediately, delayed, or not at all, the disease lasted the same amount of time, and the number of complications was the same. Immediate antibiotic therapy only had a slight advantage over delayed therapy in reducing symptoms of otitis media and sore throat. It is important to note that only 31% of patients with delayed therapy ultimately required antibiotics. Based on these results, the authors of the review recommend delaying antibiotic therapy when the diagnosis is uncertain—this is an acceptable compromise that can significantly reduce unnecessary antibiotic consumption.

What Else Can Be Done?

Limiting or delaying the prescription of antibiotics are undoubtedly effective strategies. However, as mentioned earlier, they are often associated with reduced patient satisfaction. This means doctors are less likely to apply them—who wants conflicts and complaints? To avoid reducing patient satisfaction, communication with the patient/parents is essential, but doctors often lack time for this.

Various techniques have been developed to address this problem. For example, making comments during the examination such as "There is slight redness in the throat," or "The lungs are clear, no wheezing." This doesn’t require additional time but reassures the parent, conveying the idea that nothing serious is wrong with the child and that the doctor is knowledgeable and attentive. Another strategy is to emphasize the viral nature of the illness to justify the lack of antibiotics, saying things like, "Your child has viral nasopharyngitis," or "A viral cold can last up to three weeks."

Providing written (printed) information helps doctors save time and limit the prescription of antibiotics without reducing patient satisfaction. This could include leaflets with information about the disease, the medication, or a standardized "symptomatic prescription" with general advice (drink more fluids, ventilate the room) and medications prescribed by the doctor for symptoms like "cough" or "runny nose."

The accuracy of decisions to prescribe (or withhold) antibiotics is significantly improved by using rapid diagnostic methods. A rapid test to detect Group A Streptococcus allows clinicians to identify patients with streptococcal pharyngotonsillitis and provide targeted antibiotic therapy. As mentioned earlier, biomarkers of bacterial infections (C-reactive protein and procalcitonin) are useful in deciding when to start or stop antibiotic therapy, such as for the differential diagnosis of viral versus bacterial pneumonia. However, further research is needed to apply these tests to other infections, including as a reliable marker for safely discontinuing antibiotics in bloodstream infections.

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