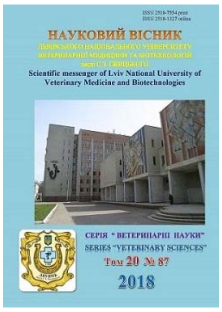

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Consumption of antimicrobials in the European Union and indications for their rational administration

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Antimicrobials are essential for the medical care and health of animals and livestock populations. On the other hand it is generally accepted that the increase in prevalence of antimicrobial resistance is a worldwide problem. Therefore, in many countries of the world, the consumption of antibiotics and the resistance of pathogens isolated from humans and animals are monitored. Collected data indicate the need to reduce antimicrobial use in humans and in food-producing animals. This goal can only be achieved if antimicrobials will be used rationally and in accordance with the latest knowledge.

Key words: *antibiotic consumption, antimicrobial resistance, rational antimicrobial treatment.*

Introduction

In the pre-antibiotic era, infectious diseases accounted for significant morbidity and mortality, and invasive medical procedures were fraught with the risk of infection. All this changed after the discovery of antimicrobials. The introduction of antibiotic therapy in the treatment of bacterial infections is considered to be the greatest scientific achievement of the twentieth century (Gupta et al., 2015). The importance of this fact can provide the award of the Nobel Prize (in 1945) in the field of physiology or medicine to Alexander Fleming, Howard Florey and Ernst Chain for the discovery of penicillin and its curative effect in various infectious diseases (The Nobel Prize in Physiology or Medicine 1945). In 1952, Selman Waksman was awarded the Nobel Prize for discovery of streptomycin, the first antibiotic effective against tuberculosis (The Nobel Prize in Physiology or Medicine 1952). Due to the fact that currently synthetic antimicrobial drugs are also called antibiotics, we should remember about the Nobel Prize awarded to Gerhard Domagk in 1939 for the discovery of the antibacterial effects of prontosil (The Nobel Prize in Physiology or Medicine 1939), a red dyestuff which is a derivative of sulphanilamide. Thus, within ten years (in 1940–1942 the prize was not awarded) scientists engaged in research related to antibacterial therapy have been awarded three times. However, the discoverer of the first antibiotic, Alexander Fleming, warned against the imprudent use of penicillin, which could lead to resistance to this drug. Currently it has been generally accepted that bacterial resistance to antibiotics is primarily a consequence of their consumption. Where they are rarely used resistant bacteria is less or appear sporadically.

At the moment, antibiotic resistance is one of the most important global public health threat because it reduces the effectiveness of the therapy, extends its duration, increases mortality due to bacterial infections and generates huge costs resulting from it. The importance of this phenomenon is noticed all over the world (and especially in Europe) by strategic institutions for public health such as: World Health Organization (WHO), European Center for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA) and European Medicines Agency (EMA). The last three European agencies published in 2017 (at the request of the European Commission) (European Commission, 2016) «Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) Report» showing consumption of antibiotics in Europe in the period 2013–2015 and the occurrence of drug resistance among bacteria isolated from humans and in food-producing animals (ECDC…, 2017). In 2013 the consumption of antimicrobials in 26 European countries amounted to 11872 tons of which 3809 tons were used in humans and 8063 tons in food-producing animals. In the same year in Poland 819 tons of antibiotics were used of which 242 tons in humans and 577 tons in food-producing animals. In 2014, in 28 European countries 3821 tons of antibiotics were used in humans and 8927 tons in animals; in Poland 263 and 578 tons of antibiotics were used in humans and food-producing animals, respectively. The above data indicate that both in Europe and in Poland, the total consumption of antibiotics was higher in food-producing animals than in humans. Also, the average total consumption of antimicrobials in 2014 expressed in milligrams of active substance per kilogram of estimated biomass (calculated on the basis of the number of inhabitants/individuals multiplied by body weight) was higher in animals (152 mg/kg) than in humans (124 mg/kg), however, there were large differences between individual countries (ECDC…, 2017). The consumption of antibiotics was lower in food-producing animals than in humans in 18 of 28 countries, in two it was similar, and in eight was higher or much higher in food-producing animals than in humans (including Poland were 110.7 mg/kg and 140.8 mg/kg antimicrobials were used in humans and food-producing animals, respectively). Analysis of the consumption and antibiotic resistance of drugs from individual therapeutic groups showed that third and fourth generation cephalosporins were used mainly in humans (especially hospitalized), which was significantly associated with the resistance of *Escherichia* (*E.*) *coli* isolated from humans to the third generation of cephalosporins. Furthermore, a significant relationship was found between consumption of the new-generation cephalosporins and resistance of *E. coli* and *Salmonella spp*. isolated from animals to the third-generation cephalosporins (ECDC…, 2017). In the case of carbapenems, which in Europe are not registered for use in food-producing animals, a significant correlation has been observed between their consumption in humans and resistance of *K. pneumoniae* isolated from patients. In food-producing animals, only very rare isolates of *E. coli* and *Salmonella spp.* resistant to carbapenems were found (ECDC…, 2017). The consumption of tetracyclines in most countries was significantly higher in food-producing animals than in humans, with significant fluctuations in their use in food-producing animals in individual countries. Significant correlations between the consumption of tetracyclines in humans and resistance to these drugs have been found in *Salmonella spp*. and *Campylobacter spp*. isolated from patients. Significant dependence was also found between the consumption of tetracyclines in food-producing animals and the resistance of *E. coli*, *Salmonella spp*. and *C. jejuni* isolated from them in years 2013–2015. In addition, a significant relationship was found between the consumption of tetracyclines in food-producing animals and *C. jejuni* resistance isolated from humans (ECDC…, 2017). The consumption of macrolides was similar in food-producing animals and humans, although there were differences in individual countries. In humans, macrolides were used mainly in the community and there were no significant relationships between their intake and resistance of *Campylobacter spp.* isolated from patients. However, a significant relationship was found between the consumption of macrolides in food-producing animals and the resistance of *C. coli* isolated from them in the years 2014–2015. In addition, there was a significant relationship between the consumption of macrolides in food-producing animals and resistance of *C. jejuni* and *C. coli* isolated from humans (ECDC…, 2017). In the case of polymyxins (mainly colistin), their consumption was significantly higher in food-producing animals than in humans, but there were large differences in the use of this group of drugs in animals in individual countries (polymyxins are not used in several countries). At the same time, a significant correlation was found between the use of polymyxins and the resistance occurring in *E. coli* isolated from food-producing animals, despite the fact that resistance to polymyxins in animals is usually low. In the case of humans, a significant relationship was found between the use of polymyxins in hospitals and *Klebsiella* (*K.*) *pneumoniae* resistance, while no relationship was found for polymyxins used in the community (ECDC…, 2017). Also, consumption of fluoroquinolones in most countries was higher in humans than in food-producing animals, and the differences were smaller than in the case of cephalosporins. The use of fluoroquinolones in humans (which mostly occurs in the community) was significantly associated with human-isolated *E. coli* resistance, but this relationship was not found for *Salmonella spp.* and *Campylobacter* (*C.*) *spp*. An important relationship was found between the use of quinolones in food-producing animals and the resistance of *E. coli*, *Salmonella spp*., *C. jejuni* and *C. coli* in years 2013–2015. An important relationship was also found between the use of quinolones in food-producing animals and the resistance of *E. coli*, *C. jejuni* and *C. coli* isolated from humans (ECDC…, 2017). The obtained data indicate a greater correlation between the consumption of antibiotics and resistance occurring in *E. coli* than *Salmonella spp.* Moreover, they also confirmed the occurrence of *E.coli* resistance to tetracyclines and third and fourth generation cephalosporins in food-producing animals. In order to further knowledge of the current situation the data on the occurrence of resistance in *E. coli* isolated from healthy people would probably be a good indicator showing the relative exposure to drug-resistant bacteria resulting from food intake and direct consumption of antibiotics in the community. Moreover, the ability to compare commensal *E. coli* in humans and and food-producing animals might be useful in a multivariate analysis approach the results of which would be important for the «One Health» concept.

Development of resistance is a complex phenomenon and is associated not only with the consumption of antibiotics but also includes a number of other factors (Cheng et al., 2015). Therefore, factors such as people traveling, transfer of patients between hospitals, intra-and inter-animal trade, import and trade of food, food of non-animal origin or exposure of humans and animals to environmental factors should be taken into account in the drug resistance analysis. Another extremely important factor contributing to the emergence of drug resistance is the interaction between a pathogen (which may produce a different type of resistance), a drug (which may have different pharmacokinetic parameters) and an infected organism (who can have a differently functioning immune system, organ failure and can be treated with other drugs at the same time). Each of these elements reflects a dynamic system that can affect the effectiveness of therapy.

Equally important in rational antibiotic therapy is the current knowledge of the veterinarian, who decides about antibacterial treatment. The optimal antibiotic should be characterized by: a) a narrow spectrum of action, b) a high therapeutic index and c) if necessary, good penetration into the tissues (Hansen and Kietzmann, 2012). Unfortunately, antimicrobials are not always used appropriately (wrong indication or choice of the antibiotics, inadequate dose and/or duration time). Therefore, for implementation a rational antimicrobial treatment regimen, practitioners should answer themselves for the following questions: 1) Does the diagnosis indicate that antimicrobial therapy is required? 2) What criteria should be considered when choosing an antibiotic (e.g. type and spectrum of activity)? 3) What pathogens are responsible for the infection? 4) What is the sensitivity of pathogens to antibiotics? 5) In what part of the body or tissue is the infection located? 6) What interactions may be expected? 7) What adverse drug reactions or toxicities can be expected? 8) How long the antibiotic should be administered? (Jaroszewski, 2014). In rational antibiotic therapy, the use of antimicrobials is only justified in cases in which they are actually necessary and when a careful choice of the active substance to achieve the purpose of treatment has been made. In 2015, the European Commission published «Guidelines for the use of antimicrobials in veterinary medicine», which indicates that prudent use of antimicrobials should lead to more rational and targeted use, thereby maximising the therapeutic effect and minimising the development of antimicrobial resistance (Commission notice, 2015). This effect will be possible to obtain through an overall reduction of antimicrobials consumption, predominantly by limiting their use only to situations where they are necessary. It follows that antimicrobials should be used as targeted treatment and according to best practices, i.e. based on clinical diagnosis and, whenever possible, on the results of microbiological susceptibility tests, and using an antimicrobial agent of as narrow-spectrum as possible. The document also indicates that antimicrobial metaphylaxis should be prescribed only when there is a real need for treatment and routine prophylaxis must be avoided. Also the off-label use (cascade) should be avoided and strictly limited to very exceptional cases. When possible, alternative strategies for controlling the development of diseases (e.g. vaccinations) should be preferred over antimicrobial treatment.

In summary, the available data confirm the link with the occurrence of antibiotic consumption and antimicrobial resistance of pathogens isolated both from humans and animals. Therefore, activities leading to limited and rational use of antibiotics from all therapeutic groups may reduce the spread of resistance of human and animal pathogens.

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