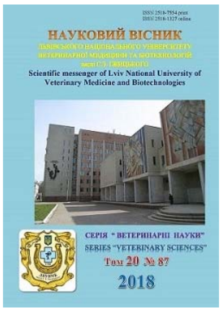

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The principles of rational chemotherapy of bacterial infections in poultry

B. Tykałowski, A. Koncicki

University of Warmia and Mazury in Olsztyn, Polska

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Department of Poultry Diseases, Faculty of Veterinary Medicine, University of Warmia and Mazury in Olsztyn, ul. Oczapowskiego 13, 10-716 Olsztyn, Polska.
E-mail: koncicki@uwm.edu.pl
bartlomiej.tykalowski@uwm.edu.pl

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Growing levels of microbial resistance to chemotherapeutic agents pose a threat to public health and constitute a global problem. The above can be often attributed to improper and excessive use of antibacterial drugs in veterinary and human medicine, animal breeding, agriculture and industry. To address this problem, veterinary and human health practitioners, animal breeders and the public have to be made aware of the consequences and threats associated with the uncontrolled use of antibacterial preparations. In recent years, many countries have implemented programs for monitoring antibiotic resistance which provide valuable information about the applied antibiotics and the resistance of various bacterial species colonizing livestock, poultry and the environment. Special attention should be paid to the sources and transmission routes of antibiotic resistance. There are no easy solutions to this highly complex problem. The relevant measures should address multiple factors, beginning from rational and controlled use of chemotherapeutic agents in veterinary practice, to biosecurity in animal farms, food production hygiene, and sanitary and veterinary inspections in the food chain. The tissues of treated birds should not contain antibiotic residues upon slaughter. Rational use of antibiotics should minimize the risk of drug resistance and decrease treatment costs without compromising the efficacy of treatment. Therefore, the key principles of antibiotic therapy of bacterial infections in poultry should be the adequate selection and dosage of the administered drug, a sound knowledge of the drug's pharmacokinetic and pharmacodynamic properties, as well as a knowledge of the differences between bacteriostatic and bactericidal drugs and between time-dependent and concentration-dependent drugs. There is an urgent need to revise the existing approach to the use of chemotherapeutic agents in the treatment of poultry diseases, and to increase the awareness that antibiotics cannot compensate for the failure to observe the fundamental principles of biosecurity in all stages of poultry farming.

Key words: *bacterial infections in poultry, principles of chemotherapy, antibiotic resistance.*

In view of the growing levels of antimicrobial resistance in poultry pathogens, veterinary practitioners are faced with the difficult task of selecting the most effective therapeutic method, including the drug and its dosage. Antibiotic resistance in microorganisms can be largely attributed to improper and excessive use of antibacterial drugs in veterinary and human medicine, animal breeding, agriculture and industry. This problem poses a serious public health hazard, and it has been addressed by the World Organization for Animal Health, the Food and Agriculture Organization of the United Nations, the World Health Organization and the European Parliament (Truszczyński and Pejsak, 2013a). Efforts are being made to develop an EU-wide plan for combating bacterial resistance to antimicrobial drugs. Veterinary and human health practitioners, animal breeders and the public have to be made aware of the consequences and threats associated with the uncontrolled use of antibacterial preparations and effective methods of preventing drug resistance. It should be stressed that irrational antibiotic use without prior identification of the etiological factor and its sensitivity to chemotherapeutic agents exerts an adverse effect on the immune system, eliminates healthy gut bacteria and often leads to treatment failure. In treated birds, recovery is largely determined by effective immune responses which are often compromised by previous or ongoing infections with immunosuppressive pathogens, errors in production technology, absence of biosecurity or the use of antibiotics with strong immunosuppressive effects (Tykałowski et al. 2013a).

In recent years, many countries have implemented programs for monitoring antibiotic resistance which provide valuable information about the applied antibiotics and the resistance of various bacterial species colonizing livestock, poultry and the environment (EFSA, 2010, 2012, 2013; Truszczyński and Pejsak, 2013b). The alarming rise in bacterial resistance to drugs has been described extensively by (Truszczyński and Pejsak, 2011;

Truszczyński and Pejsak, 2013a; Truszczyński and Pejsak, 2013b), with special emphasis on the source and transmission routes of antibiotic resistance. There are no easy solutions to this highly complex problem. The relevant measures should address multiple factors, beginning from rational and responsible use of antibiotics and chemotherapeutic agents in human and veterinary medicine, to biosecurity in animal farms, food production hygiene, and sanitary and veterinary inspections in the food chain.

Recent research points to a steady increase in the number of resistant strains in pathogenic microorganisms that are most frequently isolated from birds and require treatment with veterinary drugs (Koncicki, 2013). The above also applies to zoonotic bacteria, including Campylobacter *spp*. (Woźniak and Wieliczko, 2009; Woźniak et al., 2013; Wieczorek and Osek, 2013; Koncicki et al., 2015) and Salmonella *spp*. (Threlfall et al., 2006). These zoonotic bacteria are pathogenic for humans, and poultry and poultry meat are the main reservoirs of these microorganisms. *Escherichia coli* causes the greatest losses in poultry production, and *E. coli* infections are mostly commonly treated with fluoroquinolones, polymyxins and β-lactam antibiotics (Kuczkowski et al., 2013).

An analysis of the latest research findings indicates that bacteria isolated from poultry are characterized by growing levels to resistance to chemotherapeutic agents and that selected strains of resistant bacteria can be a source of resistance genes for other strains, which poses a threat to human and animal health. These problems stem from long-term use of antibacterial chemotherapeutic agents in poultry and the presence of antibiotic resistant bacteria and/or bacterial genes encoding antibiotic resistance in human and animal habitats.

Natural resistance is conferred by genetically conditioned phenotypic traits in bacteria, such as the width of protein channels in cell membranes which determines an antibiotic molecule's ability to penetrate a bacterial cell (Quinn et al., 2002). The second type of resistance is acquired resistance which is linked with one or more point mutations in chromosome or plasmid genes and the transfer of genes encoding antibiotic resistance to drug-sensitive bacteria. Most importantly, genetic material is transferred between bacterial cells in microorganisms that are pathogenic for humans and animals as well as between saprophytic bacteria (Bywater et al., 2004). Humans, animals, raw materials and food products of plant and animal origin, human and animal feces, wastewater, soil and water bodies as well as cafeterias, kitchens, food storage facilities and grocery shops can all act as vectors for the transmission of antibiotic-resistant bacteria and genes encoding antibiotic resistance (Woźniak and Wieliczko, 2009; Truszczyński and Pejsak, 2011; Truszczyński and Pejsak, 2013b). The presence of genes encoding resistance to several antibiotics in genetic material transferred from the donor to the recipient of bacteria leads to multiple drug resistance (MDR) (Bywater et al., 2004; Woźniak and Wieliczko, 2009; Truszczyński and Pejsak, 2013b). It should also be noted that the use of antibiotics as growth promoters has been banned in the EU, including in Poland, since 1 January 2006. However, antibiotics can still be used as growth promoters in animal production in non-EU countries (Przeniosło-Siwczyńska and Kwiatek, 2013). Therefore, food products imported from third countries can be a source of antibiotic-resistant bacteria and genes encoding antibiotic resistance.

In view of the growing levels of antibiotic resistance in bacteria, veterinary practitioners should be made increasingly aware of the need to administer chemotherapeutic agents to poultry in a safe and rational manner and in strict observance of legal regulations.

It is of utmost importance that antibiotics are administered based on the results of an antibiogram test performed on correctly sampled biological material. Antibiotics should be applied in early stages of disease, and their effectiveness should be closely monitored. However, it should be stressed that antibiotic therapy may involve initial therapy and alternating therapy (Pejsak and Truszczyński, 2013). The initial therapy is usually administered empirically before determining the drug sensitivity profile of bacteria, although veterinary practitioners often rely only on empirically selected antibiotics. This approach requires clinical, anatomopathological and microbiological knowledge (bacterial species, i.e. potential etiological agents of disease), experience with poultry diseases and access to the results of screening studies analyzing the antibiotic susceptibility of bacteria encountered in turkey farms and turkey farming regions. In many cases, the isolated bacterial strains are resistant to antibiotics that have never been applied in the examined farm. The above can be attributed to various sources and transmission routes of antibiotic resistance.

Alternating therapy may be proposed if the initial therapy was ineffective. The treatment may be empirical (if the results of an antibiogram test are not yet available) or targeted if the isolated bacteria's antibiotic susceptibility profile has been reliably determined. However, the results of *in vitro* tests can differ from the *in vivo* performance of an antibiotic, and not all targeted treatments are effective. The risk of failure should be minimized in antibiotic treatments addressing serious problems and large flocks of infected poultry.

Veterinary practitioners should select medicinal products that most effectively target a given ailment, preferably based on the results of an antibiogram test (but bearing in mind that *in vitro* results can differ from the drug's performance *in vivo*). The determination of the drug's most effective dose is a very important consideration in antibacterial chemotherapy. The adequate dose should be set based on three key criteria to minimize the spread of drug resistance in poultry pathogens: the drug has to be administered at a sufficiently high concentration, at the appropriate time intervals and over a sufficiently long period of time (Dzierżawski and Cybulski, 2012; Świtała, 2013). The failure to observe the above principles contributes not only to a rapid increase in antibiotic resistance, but also to non-observance of the appropriate withdrawal (waiting) period. A change in the drug dosage recommended by the manufacturer could improve the efficacy of treatment, but it could also prolong the withdrawal period. In poultry, the administered dose plays the key role in drug kinetics, and it influences the time (in days) after which the concentration of the drug decreases below the maximum residue limit (MRL). In the EU, the

MRL is the maximum concentration of residue that is deemed as safe for consumers by the European Medicines Agency (EMA).

Veterinary practitioners have to be familiar with the pharmacokinetic and pharmacodynamic properties of the prescribed drug to determine its effective dose and minimum inhibitory concentration (MIC). Based on those two indicators, chemotherapeutic agents for poultry can be divided into two groups: concentration-dependent drugs (enrofloxacin, flumequine, neomycin, colistin) and time-dependent drugs (β-lactam antibiotics (amoxicillin), macrolides (erythromycin, spiramycin, tilmicosin), lincosamides (lincomycin), pleuromutillins (tiamulin), tetracyclines (doxycycline, oxytetracycline), phenicols (florfenicol, thiamphenicol) and sulfonamides (Świtała, 2013). The efficacy of concentration-dependent drugs is determined by their concentration in the body, and these antibiotics generally deliver rapid bactericidal effects regardless of the phase of bacterial growth (although treatment is always more effective in the initial stage of infection characterized by the log phase of bacterial growth). This group of chemotherapeutic drugs is most effective when administered in a single daily dose within a relatively short period of time. Time-dependent chemotherapeutic drugs are most effective when the daily dose is administered over a prolonged period of time to maintain effective plasma concentration (MIC) during the dosing interval.

Antibiotics can also be classified as bacteriostatic (plasma and tissue concentrations of the drug are maintained above the MIC to merely inhibit the growth of pathogenic bacteria which are ultimately eliminated by the immune system) and bactericidal antibiotics (drug concentration can drop below the MIC). Bacteriostatic agents include tetracyclines, macrolides, lincosamides, phenicols and sulfonamides. Examples of bactericidal antibiotics include β-lactams, aminoglycosides, fluoroquinolones and polymyxins.

Combination antibiotic therapy, where two or more products are used simultaneously, is yet another form of chemotherapy. Medical practitioners must be aware of the possible interactions between the prescribed combination of antibiotics. The administered drugs should deliver synergistic effects (combined antibiotics exert stronger effects than individual drugs). Bactericidal antibiotics generally exhibit synergistic effects in combined therapy, whereas bacteriostatic antibiotics can disrupt the bactericidal effects of an antibiotic by inhibiting microbial growth (bacteriostasis). Examples of combination antibiotic therapy include β-lactams with aminoglycosides, quinolones or clavulanic acid, and fluoroquinolones with polymyxins. Combination therapy is recommended for severe infections, infections with a high mortality rate and infections without a fully known etiology (antibiotic monotherapy is recommended once the infectious agent has been identified and subjected to an antibiogram test). In principle, chemotherapeutic agents with the narrowest possible spectrum of action that selectively target one type of bacteria should be used.

In infected poultry, drugs are usually administered *per os* with water (less commonly with feed) or are delivered by injections or aerosols. Interactions with metal ions can significantly influence the efficacy of chemotherapeutic agents. For this reason, the quality of water administered with drugs should be closely inspected. Metal ions in hard water (calcium, magnesium, zinc, iron, copper, aluminum) are capable of chelating drugs, such as fluoroquinolones, which impairs the drug's absorption from the gastrointestinal tract, decreases its bioavailability, renders the treatment ineffective, and may have serious clinical implications. The produced chelates are larger and have a different molecular structure than unchelated drugs. Chelated drugs may be unable to bind to the carrier and penetrate cells (Turel, 2002). Tetracyclines are very often used to treat infections in poultry, and their efficacy and stability decrease when dissolved in hard water. The pH of water also significantly influences a drug's solubility and stability; for example, amoxicillin is inactivated in an acidic environment. When drugs are supplied with drinking water in animal farms, the water supply system should be clean and disinfected (free of biofilm) and dosing pumps should be in working order.

Regardless of the route of drug administration, veterinary practitioners should be familiar with the pharmacokinetics of various chemotherapeutic agents, and should be able to distinguish between drugs that are poorly absorbed (colistin, neomycin, lincomycin) and well absorbed (doxycycline, tiamulin) from the gastrointestinal system. Veterinarians should also be aware that tetracyclines and tiamulin are accumulated in joints, which is a very important consideration in the treatment of leg disorders in birds, in particular turkeys.

Diseases caused by a single bacterial species are becoming increasingly rare in commercial poultry farms. In large-scale poultry farming, birds are commonly affected by syndromes that are caused by several pathogens, such as viruses and bacteria, under the adverse influence of non-infectious factors (housing and management conditions, diet, stress). These types of infections are severe and difficult to treat. Chronic and recurring bacterial infections in poultry, such as ornithobacteriosis, pose a considerable therapeutic problem which is difficult to resolve with the use of antibiotics and chemotherapeutic agents due to growing levels of antimicrobial resistance. Irrational and excessive antibiotic use without the identification of the etiological factor and its sensitivity to chemotherapeutic agents adversely influences the immune system, leads to the elimination of healthy gut flora and often results in treatment failure (Tykałowski et al., 2013a; Tykałowski et al., 2013b). Birds infected with bacterial strains resistant to chemotherapeutic agents can benefit from immunomodulation as supplementary treatment because their recovery is largely determined by immune system health (Tykałowski, 2012).

According to current knowledge, selected antibacterial drugs, in particular aminoglycosides, tetracyclines and sulfonamides, can significantly inhibit the key immune mechanisms and lead to secondary immunodeficiencies during repeated antibiotic therapy, which increases the patient's susceptibility to other infections (Tykałowski et al., 2013b). For this reason, antibacterial chemotherapeutic agents are often used with immunomodulators to increase the efficacy of treatment. Effective natural immunomodulators include β-glucans extracted from the cell walls of *Saccharomyces cerevisiae* yeast, and lysozyme dimers (lysozyme extracted from chicken egg white and subjected to dimerization). Synthetic immunomodulators are also used, including levamisole (antiparasitic drug) and methisoprinol (isoprinosine) (Andrzejewski, 2007; Stenzel, 2009; Tykałowski, 2012).

In view of the above, there is an urgent need to revise the existing approach to the use of chemotherapeutic agents in the treatment of poultry diseases. The awareness that antibiotics cannot compensate for the failure to observe the fundamental principles of biosecurity in all stages of poultry farming should be spread among veterinary practitioners and poultry breeders.

The 20th century will undoubtedly be remembered as the era of antibiotics. However, the rapid increase in antibiotic resistance and the risk of veterinary drug residues in meat and eggs could contribute to the biologization of poultry production in the 21st century by encouraging the use of beneficial microorganisms that inhibit the growth of pathogens, immunomodulation, immunotherapy, phage therapy and phytotherapy (Koncicki et al., 2015).

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