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HAZARDS TO HUMANS AND ANIMALS ASSOCIATED WITH ANTIBIOTIC MISUSE

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Abstract

The increasing resistance of community and hospital acquired bacterial strains has become a challenge to the current health policy in Poland. Although some bacteria are known to have a peculiar resistance towards a given agent, antibiotics have a well-established position in clinical practice and are broadly available in our lives. The universal access to antimicrobial therapy and its overuse have created an issue of previously susceptible bacteria now presenting antibiotic resistance. All bacteria that survive antibiotic treatment, continue growth and reproduction. This phenomenon is also observed in livestock rearing. An inadequate implementation of antibiotic therapy leads to the transfer of resistant bacterial strains into the environment of people, who eat products of animal and plant origin. Moreover, the non-compliance to law in terms of antibiotics added to animal fodder or negligence of withdrawal periods seems to further exacerbate the situation. Various research projects conducted in Poland and elsewhere have demonstrated that antibiotics produce an immunosuppressive effect, which exposes both humans and animals to different infections. Antibiotics also interfere with the growth of many microorganisms, recognized as part of the human and animal physiological microflora, as a result of which dysbacteriosis may develop. In order to limit the use of antibiotics in animal husbandry, research should be focus on finding alternative agents based on plant extracts that undergo biodegradation.

Keywords: antibiotics, antibiotic resistance, dysbacteriosis, plant extracts, microflora, animal husbandry, viral infections, staphylococcusstrain.

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INTRODUCTION

Antibiotics are either products of metabolism of microorganisms, such as bacteria, fungi and embryophyta or they are obtained synthetically. Their bactericidal, bacteriostatic and antifungal properties against pathogenic bacteria and fungi (WEBBER, PIDDOCK 2003) are widely employed in treatment of bacterial infections in humans, animals and plants (SURTEES 2006). Antibiotics are also used as additives in fodder for some groups of livestock in countries where this practice has not been prohibited yet.

There are various mechanisms of action of antibiotics: inhibition of bacterial cell wall synthesis (e.g. bacitracin, penicillin, cephalosporin), inhibition of protein synthesis (e.g. chloramphenicol, tetracycline), RNA (e.g. rifampicin) or DNA (quinolones) (KHACHATOURIANS 1998).

Penicillin was discovered by Alexander Fleming in 1928 (CRAUGHWELL 2008). With time, it was discovered that under the influence of penicillin, the bacterium *Staphylococcus aureus* synthesized a cell wall that was less permeable to penicillin. This indicated that the bacteria started to develop resistance, in this case to penicillin (ZHANG et al. 2006, PAKULA 2014). In the 1950s, a new antibiotic called methicillin appeared on the market and as soon as the 1960s methicillin-resistant *Staphylococcus aureus* (MRSA) began to spread, being responsible for a significant percentage of all hospital infections. In 1996, another antibiotic, vancomycin, became marketable, leading to the rise of the vancomycin-resistant *Staphylococcus aureus* (VRSA) strain. The introduction of the successive antibiotic, linezolid, gave rise to a resistant bacteria in the first year of its use in clinical practice. Research conducted in USA revealed that 70% of hospital acquired bacterial strains exhibit resistance to antibiotics used previously in patients treated for the same disease (MARCINIAK 2008). Currently it has become more challenging than ever before to treat tuberculosis, pneumonia, sepsis, and even otitis in children. In order to combat infection, experimental agents have to be used, often toxic ones (KARWICKA et al. 2008, TODAR 2009, MARCZEWSKA et al. 2013).

PURPOSE

The aim of this paper is to emphasize the issue of antibiotic misuse in people and animals, to outline the most threatening habits associated with antibiotic therapy and to present innovative and environment-friendly alternatives in infection control.

DISCUSSION

Some bacteria are naturally insensitive to a given antibiotic, i.e. they are characterized by a peculiar, internal antibiotic resistance. The situation becomes dangerous when previously susceptible bacteria suddenly present with antibiotic resistance. Two main mechanisms exist through which microorganisms obtain resistance, i.e. present acquired resistance. One mechanism is associated with mutation, a phenomenon that occurs in bacterial genes and stems from DNA replication errors, which lead to a change in DNA, enabling bacteria to acquire new traits. As a result, microorganisms accommodate to unfavourable environments, such as the presence of antibiotic. The action of the other mechanism relies on the transfer of antibiotic resistance associated genes between two bacteria in a process of genetic material exchange, i.e. conjugation, transformation and transduction (WEBBER, PIDDOCK 2003, PURDOM 2007). Conjugation is the most threatening process because it is quick and very efficient. Transformation and transduction processes require the presence of special conditions, thus making them less dangerous than conjugation (MARCINIAK 2008).

Treatment of infections caused by antibiotic resistant bacteria usually requires an alternative approach, with costly antibiotics that are often characterized by a longer list of adverse effects. It often involves inpatient administration of intravenous preparations instead of oral administration of medications, which can be done in a more convenient home setting. High antibiotic consumption in inpatient and outpatient populations fosters the dissemination of those bacteria (TRUSZYŃSKI et al. 2012).

Hospitals are where resistant bacterial strains are most prevalent. Apart from the main use of antibiotics in infection treatment, they are also used in operating theatres for disinfection (GENEREUX, BERGSTROM 2005). After antibiotic therapy, an organism loses its physiological bacterial flora. This creates a potential space to be colonized by new resistant strains of bacteria. Microorganisms are spread by direct contact, therefore negligence of hand hygiene and frequent travel of carriers further contribute to the quick distribution of resistant bacteria.

The situation is analogous in animal treatment (BRADLEY et al. 2010). The first antibiotic resistance case on a farm was documented in Great Britain in 1963, when a resistant strain of *Salmonella typhimurium* was discovered (KHACHATOURIANS 1998). In the 1950s, the problem of antibiotic resistant bacteria in livestock did not exist. At that time, a recommended dose for infection treatment was 5-10 ppm, being ten- or even twenty-fold higher in the late 1990s. Strains resistant to antibiotics originating from farms are transferred to the human environment via animal excrements. It has been estimated that 80-90% of antibiotics administered to animals is not fully digested and reach the environment (www.sustainabletable.org) and surface water with animal excreta. Water is than used in cultivation of vegetable consumed

by people or animals. Strains of those microorganisms can also reach human organisms through the ingestion of meat from animals fed antibiotics and colonized by resistant bacteria. Most consumers who eat products of animal origin value their health safety and want to buy high quality products characterized by health-promoting properties in order to live healthy and long lives (MICIŃSKI et al. 2012, POGORZELSKA et al. 2013, MICIŃSKI et al. 2013). Ideally, such products should be free of any antibiotic residue. Therefore, it is absolutely necessary to instigate a detailed control over antibiotic therapy in human and veterinary medicine and veterinary (HRYNIEWICZ, MAZIŃSKA 2009).

The development of large scale production in animal husbandry together with the dense stocking of animals on farms encouraged the addition of antibiotics into animal fodder, which began in the late 1940s. Research conducted between 1950-1960 in the USA and the UK showed many positive aspects of antibiotics added to fodder for livestock, including poultry. Significant improvement in animals' gain, their health and fodder conversion was observed. In Poland, antibiotics in fodder were used for the first time in 1968-1970 (www.sustainabletable.org). Antibiotic Growth Promoters (AGP) or Antimicrobial Growth Promoters were mixed with animal feed (KHACHATOURIANS 1998). The concept of such antibiotic use became very popular in the agriculture environment owing to the achieved fodder consumption decrease, increase in animals' weight gain with a simultaneous decrease in feed rations, as well as the improvement in animals' health with decreased mortality. Antibiotics then played a key role in health prophylaxis policy in large farms, as an agent inhibiting the growth of microorganisms which colonize the gastrointestinal tract of livestock animals. In some part of the world, antibiotics are also used on a large scale on salmon farms (50-60 kg per acre) or on fruit trees against bacteria present on fruit surfaces (WISE et al. 1998).

Unfortunately, from the very beginning, most of antibiotics administered to animals, and later on also sulfonamides, were simultaneously used in humans. This has led to a significant acceleration of the resistance acquisition process by many bacteria. Due to the introduction of a wide range of universally accessible and misused antibiotics, a sudden increase in pathologic fungal, viral and chlamydia infections has been observed. Moreover, bacterial enzymes that can inactivate antibiotics have come to play.

Since 1980, it has been observed that antibiotics have an immunosuppressive action. Most antibiotics (except cephalosporins and lincosamides) have an inhibitory effect on the immune system's functions and predispose both animals and humans to infections. Antibiotics inhibit the growth of many microorganisms, also saprophytes, which belong to the physiological microflora of animals and humans. The harmful effect of antibiotics on symbiotic microflora has been described as dysbacteriosis. Dysbacteriosis leads to pathologic changes of mucosa, superinfections and hypovitaminosis. Signs of dysbacteriosis are the inflammation of esophageal, gastric and intestinal mucosa, as well as diarrhoea. Superinfection is an infection caused by micro-

organisms insensitive to the administered antibiotic, usually fungi, penicillin-resistant *Staphylococcus aureus* or Gram negative bacilli (e.g. *Pseudomonas aeruginosa*). An example of antibiotic resistance dissemination that has been caused by the overuse of an antibiotic in agriculture is the resistance to glycopeptides, including vancomycin. An inappropriate use of vancomycin in therapeutics and avoparcin (antibiotic from group of glycopeptides) as a fodder additive has resulted in the rise of enterococci resistant to vancomycin (VRE). In response to this fact, Because of this fac, Denmark in 1995 and the EU in 1997 withdrew avoparcin from use. In 1998, the European Commission banned the use of fodder additives such as tylosin, spiramycin and bacitracin in the whole European Union. It was also recommended to use these antibiotics rationally and modestly for therapeutic purposes in veterinary medicine. In contrast, in Sweden the use of antibacterial agents in animal breeding was prohibited as early as 1986. Antibiotics are allowed to be used only in recommended doses and only for therapeutic and prophylactic purposes. Following this step, the antibiotic consumption has dropped by 55%. Additionally, it has been proven that good and competitive results in animal production cab be achieved even without the use of antibiotics.

The pressure by consumer, ecologist and medical organizations has led to a gradual withdrawal of antibiotics from animal fodder. It was allowed to use registered antibiotic growth stimulators in the European Union only until 31 December 2005. This decision forced pharmaceutical and feed manufacturing companies to do research on innovative, more modern and promising alternatives to antibiotic growth stimulators that will not accumulate in animal tissues. Ideally, they should be safe to people's health and ought to undergo biodegradation. Both previous and current research results from chemotaxonomy, phytopharmacology and pharmacognosy have provided essential knowledge that enables the introduction of preparations replacing antibiotic growth stimulators.

In 2004-2007, preparations based on pure phytoncides linked with plant-based enzymes were formulated. They can be used as an alternative to growth stimulators and in prophylaxis of parasitic (*coccidiosis*), bacterial and fungal diseases. Some are also characterized by antiviral properties. Phytoncides can be considered together with phytoalexins, which are antibiotics produced by embryophytes (bryophytes, pteridophytes, gymnosperms, angiosperms) that show potent bactericidal and bacteriostatic action. Phytoncides are additionally characterized by fungistatic and fungicidal properties. Some of them inhibit viral proliferation or significantly damage structure of viruses. The earliest recognized phytoncides are glucosinolates, black mustard oils, isosulphurcyanogen glycosides and garlic oils. Those substances are organic compounds, often glycosidic compounds of sulphur and isosulphurcyanogenic acid.

Sulphuric and isosulphurcyanogenic phytoncides are characterized by a stronger and more rapid antibacterial action on Gram-positive and Gram-negative bacteria than other known antibiotics (e.g. bacitracin, neomy-

cin). They contribute to myorelaxation, bile flow stimulation, bile production, blood circulation stimulation, increased nutrient absorption by intestines. They inhibit the growth of putrefactive bacteria or pathogenic fungi, and they produce a protozoacidal effect. They stimulate gastric acid production, increase appetite, decrease blood cholesterol and glucose concentration. Ajoenes (garlic oils) inhibit erythrocyte aggregation, preventing vein thrombosis. Volatile phytoncides of *Asarum europaeum*, inula, tagetes, *Chelidonium majus*, garlic and tropaeolum kills tuberculosis bacilli in 3-5 minutes, which is faster than carbolic acid (phenol) (KARWICKA et al. 2008, MARCZEWSKA et al. 2013).

The strong bactericidal effect of many other phytoncides has also been established. Phytoncides contained within *Heracleum sphondylium* fruits, in just a few minutes, completely eliminate putrefactive bacteria, which mediate the putrefication process in animal tissues. Volatile phytoncides of garlic kill *Mycobacterium tuberculosis* in 3-5 minutes. Fresh mush of garlic kept close to a drop containing *Vibrio cholerae* bacteria causes an immediate inhibition of the movement of this microorganisms due to its sudden death. Phytoncides contained in garlic and onion eliminate streptococci, staphylococci, *Salmonella typhi* or *Corynebacterium diphtheriae* in a few minutes. The inhibitory effect of phytoncides has also been established in the case of *Influenza viruses* and rods of Flexner type dysentery.

More and more often, antibiotics are used in veterinary sciences. They coincide with the same antibiotics used in human therapy, which is reflected by their low efficacy (NOUWS et al. 1983, NAIDONG et al. 2003, LARSEN et al. 2010). The most popular antibiotics used in treatment of dairy cows are amoxicillin (AML), enrofloxacin (ENR), gentamicin (GN), tetracycline (T), chloramphenicol (C), Kanamycin (K), Lincomycin (MY), tetra-delta (NPSN), colistin (CT), cloxacillin (OB), enrobiofloxacin (ENB), cefalexin (CL), streptomycin (S), erythromycin (ERT), and penicillin (P). These antibiotics are subdivided into three fundamental groups. The first group encompasses agents necessary in veterinary medicine (aminoglycosides, cephalosporins, macrolides, penicillins, phenicols, quinolones, and tetracyclins); the second group of antibiotics includes highly important agents (fosfomycin, ionophores, lincosamides), while the third group of agents comprises pharmaceuticals that are the least significant in veterinary practice (ortosomycins, novobiocins, chinoxalins) (TRUSZYŃSKI, PEJSAK 2012, 2013). It has been shown that resistant microorganisms are *Enterococcus faecalis*, *Staphylococcus aureus*, and *Streptococcus pyogenes*. *Enterococcus faecalis* is resistant to vancomycin (GENEREUX, BERGSTROM 2005). There are three genes determining bacterial resistance, which code for protein variants that decrease the potential of voncomycin binding to bacterial cell surface. The source of these genes turned out to be *Amycolatopsis orientalis*, a non-pathogenic microorganism in soil, which naturally produces vancomycin.

Staphylococcus aureus is a Gram-positive bacteria that is abundant in air, soil, on skin surface, in sebaceous glands, sweat glands, hair follicles,

and all mucosa exposed to the outside environment (eyes, lips, nose, throat), both in humans and animals (www.gronkowiec.eu). When the tissue continuity is disrupted, a foreign body is present within tissues, concomitant diseases or other immunosuppressive factors occur, *Staphylococcus aureus* can induce suppurative infection of the skin, mucosa, connective tissue and bones. Once the bacteria enter blood circulation, they can cause sepsis with multi-organ failure. The ubiquitous presence of this microorganism is especially threatening because of its resistance to meticillin (ENRIGHT et al. 2002). MRSA has been first detected in the United Kingdom, and later also in Japan, Australia and the USA. In 2005, the MRSA strain was associated with about 94 000 infections in the USA, accounting for 19 000 of deaths, which is a higher mortality rate than that due to AIDS at the same time (KUBIAK 2008). The resistance to meticillin relies on the presence of MecA gene, which codes for new protein synthesis that repossesses the function of proteins inactivated by β -lactam antibiotics that are responsible for the synthesis of the peptidoglycan layer of bacterial cell walls (STEFANŃSKA 2003). The rise of the vancomycin resistant *Staphylococcus aureus* (VRSA) strain is another threat to people since there is no effective agent to suppress this microorganism.

According to Codex Alimentarius, each factor, be it biological, chemical or physical one, can be a direct threat to the human race, creating a potential source of negative effects on the human health. There are various sources of danger, for example milk or meat consumption (SPEARS, WEISS 2008). Possible threats are caused by the lack of compliance with withdrawal periods during dairy cows' treatment, an inappropriate drug dosing, deliberate addition of antibiotic to raw milk, addition of antibiotic to animal fodder or negligence of a veterinary doctor's recommendations. ROŻAŃSKA and LEWTAK-PILAT (2011) state that the gravest and most common adverse effect associated with the presence of antibiotic residue in milk is the increase of allergic reactions among people (ALLORE et al. 1998). In particular, β -lactam antibiotics contribute to this phenomenon, which appear to be unaffected by sterilization or pasteurization processes. The hazard gradually increases because antibiotics remain active despite the fact that a food product does not show any microbiological changes, and they exert their action on the delicate human intestine microflora. Abnormalities within functions of tissues or organs that have carcinogenic and mutagenic potential are also being noted by scientists (POSYNIAK 2005, BABAKI et al. 2005).

Food products are an exclusive source of nutrients necessary for the development and proper functioning of the human organism (KŁOBUKOWSKI et al. 2014). Maintaining the nutritional balance is an essential component of a healthy growth of children and adolescents (MEŠKAITE et al. 2013). A growing interest in the nutritional value and health benefits of food products of animal origin has been witnessed in recent years (MICIŃSKI et al. 2012). Among other products, milk and its quality appear to be significantly affected by the presence of antibiotics. Afflictions associated with milk consumption and dairy products containing antibiotic residue depend on the involvement of a

specific antibiotic (SMOCZYŃSKI et al. 1986, HERTLI et al. 2010). Tetracyclines cause numerous adverse effects characterized by gastrointestinal disturbances, provoked by the irritation of mucosa. Nausea, vomiting and abdominal pain are not uncommon. Damage to the intestinal epithelium is characterized by atrophy and an overall decrease in the number of intestinal villi (MŁODECKI 2014). These developments are most dangerous to children (SEŃCZUK 2002). The effect of undesirable macrolides is limited to atopic dermatitis, nausea, vomiting and diarrhoea. In rare cases, an injury to hepatic tissues could present with jaundice. Above all, aminoglycosides are characterized by strong toxicity, which leads to the vestibular and cochlear nerve damage, balance disturbance and hearing impairment (KOPYTKO, KOWALSKI 2014). Also renal tubules are damaged as a result of the drug's toxicity. Chloramphenicol is another agent, whose main adverse effect is seen in bone marrow. After addition of large doses of the antibiotic, anaemia and leucopenia develop, most probably due to the inhibition of mitochondrial protein synthesis (NIKONOROW 1979).

CONCLUSIONS

1. Since the revolutionary discovery of antibiotics and the beginning of their widespread use, a significant number of originally sensitive bacteria has developed various protective mechanisms that provide them with resistance to various chemical agents. Because the scope of microbial resistance continues to increase gradually, it has become a serious issue and a grave threat to the public health.

2. Simultaneously, significant differences exist among countries in their approach to legal regulations of antibiotic prescription, sale and application. Nevertheless, in 2001, European Union Council urged the EU member states to undertake action directed towards the assurance of rational antibiotic use (Council Recommendation of 15.11.2001 on the prudent use of antimicrobial agents in human medicine (2002/77/EC)). Owing to this initiative, antibiotic use in livestock rearing has been subjected to rigorous surveillance. However, the problem still exists in relation to the addition of antibiotics to animal fodder in non-EU countries, where antibiotic resistance does not seem to worry local authorities.

3. Uncontrolled administration of antibiotics to farm animals creates a chance for opportunistic and pathogenic bacteria to acquire antibiotic resistance and to reach the human environment.

4. Formulation of preparations based on phytoncides bound with plant-based enzymes should be encouraged, perceived as an alternative to growth stimulators and an innovative solution in prophylaxis of parasitic, bacterial and fungal diseases.

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