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Influence of antibiotic treatment duration on the development of antibiotic resistance

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Avoidance of unnecessary antimicrobial administration is a key point of antimicrobial stewardship; knowing the optimal duration of therapy obviates over-treatment. In this article we have highlighted the results of modern research on the influence of the duration of antibiotic use on the success of treatment and the development of resistance of microorganisms. Foreign literary sources and the results of scientific research by experts in this field are analyzed. Based on the research results, the following conclusions were made. The results of modern studies on the duration of antibiotic use show that short-course antibiotic therapy is superior to usual long-course antimicrobial treatment. A short course of antibiotic therapy usually leads to the same positive clinical outcomes, a lower rate of antibiotic resistance and the number of clinical relapses. The two most important potential complications associated with the duration of antibiotic therapy are incomplete treatment and the emergence of antibiotic resistance. The time points used for antibiotic treatment (clinical or bacteriological cure, relapses, etc.) are subjective, complex and unreliable. The effectiveness of procalcitonin or other blood parameters for use in monitoring antibiotic treatment requires more focused studies.

Despite the high relevance and publicity of various aspects of antibiotic therapy in the practice of human and animal healthcare, research on the efficacy and consequences of short-term antibiotic therapy in veterinary medicine is limited. More attention should be paid to this issue, especially in the field of animal husbandry.

Key words: antibiotic resistance, antibiotic, microorganisms, treatment scheme, animals, duration of antibiotic therapy, clinical result, relapses.

Problem statement and analysis of recent research. It is known that antibiotic use is the main reason for the increasing problems with resistant bacteria. The therapeutic value of antimicrobials has been amply demonstrated over the past century in saving lives and alleviating suffering in both humans and animals. However, the continued success of antimicrobial therapy now hangs in the unstable balance due to developing antimicrobial resistance (AMR). Antimicrobial resistance is an emergent global health problem. AMR reduces the therapeutic efficacy of antimicrobial treatment in both human and veterinary medicine [1]. As companion animals are able to acquire and exchange pathogens with humans, and many of the same antimicrobial agents are used in human and veterinary medicine, companion animals can serve as a reservoir of AMR for in-contact people [2–5]. This highlights the importance of appropriate antimicrobial usage in companion animal practice and increases the imperative to adopt strategies that mitigate AMR in small animal veterinary clinics.

The use of optimal antibiotic regimen is an important factor in preventing of antibiotic resistance

development. Haidar R. et al. [6] claim that there is no solid evidence to support that the prolonged use of antibiotics guaranties the successful treatment the chronic bone infections in animals. Authors emphasized that the older types of surgical procedures practiced in the past in treating chronic osteomyelitis might have contributed to the decisions to proceed with the prolonged antibiotic treatment. They noted that nowadays, despite the surgical approach to the treatment of bone infections has advanced markedly, still the same long duration of antibiotic regimens is mostly being used.

Major advances are also being made in the field of antibiotic prescription. Bacterial cultures are usually obtained from the infected animals, and, in the case of failure of empiric antibiotic therapy, antibiotic selection is based on the results of culture and sensitivity testing [7].

That is why, a range of medical studies, including those in animals and humans' field, is being done to advance the prescription regimen for the antibiotic usage.

However only few randomized, controlled trials in which scientists compared the effectiveness of a short course (5 days) of antibiotics to a longer course (more than 7 days) for treatment of pneumonia, and also assessed whether the length of the course of antibiotics affects the development of resistant bacteria. Research conclusions were based on clinical outcome, microbiological efficacy, patient safety, and antibiotic resistance in both courses of treatment [8]. The clinical success rate was 87-95% in patients receiving a short course of antibiotics and 88-94% in patients receiving a longer course. The studies also noted the lack of influence of the duration of treatment on the development of resistance to antibiotics. So the high need for the study seeking for optimal treatment durations for patients with various infection diseases are still existing in veterinary as well as in human medicine.

Results of meta-analysis done by Li Q. et al. [9] suggest that a shorter course (3–5 days) of antibiotics was non inferior to a longer course (5-10 days) in patients with non-severe community-acquired pneumonia. In addition, fewer reports of gastroenteritis were recorded with a shorter course of antibiotics. The authors concluded that clinicians should consider prescribing a shorter course of antibiotics for the management of pediatric non severe pneumonia.

The data obtained by Holm A.E. et al. [10] showed that short-course (up to 5 days) antibiotic treatment was as effective as long-course (more than 7 days) antibiotic treatment for early clinical cure. Yet, the subgroup analysis showed that short-course penicillin was less effective for early clinical cure and bacteriological eradication in comparison to long-course penicillin. It was also found that short-course macrolides were equally effective, compared to long-course penicillin. And finally, short-course cephalosporin was more effective for early clinical and microbiological cure in comparison to long-course penicillin.

The other authors [11] found that short-course (up to 4 weeks) antibiotics are safe and effective in patients with acute osteomyelitis, but long-course (more than 6 weeks) antibiotics treatment may still be preferred in vertebral osteomyelitis, especially those caused by *S. aureus* infection.

Not having enough consistent and numerous data on the matter Cooper L. et al. [12] indicated the need for further research to determine the optimum length of antimicrobial treatment. Proper analysis of the available information and further randomized clinical trials are required to investigate if short-duration courses of antibiotics are effective and to provide scientific evidence to elaborate the standard operative procedure for veterinary and medical practitioners.

The aim of the study. The aim of the study was to analyze scientific publications and compare the possibility of antibiotic resistance development depending on the duration of the course of antibiotic therapy.

Materials and methods. The search, selection and analysis of the last 15 years publications according to the research topic were carried out according to the methodology for systematic literature reviews [13]. To search for foreign scientific articles, the Web of Science Core Collection (http://apps.webofknowledge.com) and PubMed (https://pubmed.ncbi.nlm.nih.gov) databases were used. The following keywords were used to search for materials: antibiotic resistance, treatment scheme, antibiotics, animals, duration of antibiotic therapy, microorganisms. We studied scientific articles in magazines from the following categories: veterinary sciences, animal sciences.

Results. Resistance of pathogens to drugs used to fight infection is a long-standing problem. This applies to microbial organisms in humans [14, 15], as well as in veterinary [16–20] medicine.

One of the main reasons for the development of resistance of microorganisms to antibiotics is a violation of the treatment regimen. Dinh A. et al. [21] emphasized that comparative efficacy of long-course antibiotic treatment is not yet sufficiently studied. The authors point to some objective and subjective reasons that make it difficult to conduct relevant studies for a better assessment of the options for the treatment scheme.

One of the main indicators of the antibiotic regimen is the duration of treatment. In this article, we highlighted the results of modern research on the influence of the duration of antibiotic use on the success of treatment and the development of resistance.

Meta-analysis done by Jia Y. et al. [22] showed no difference between short and long courses of antibiotic agents. The results of the subgroup analysis of the same authors showed no differences between the failure rates of patients with joint infection treated with short and long courses of antibiotic agents during different treatment modalities, and different joints. The authors concluded that patients with joint infections may not require long-term or lifelong antibiotic agents after surgical treatment, but in such cases, short-term antibiotic therapy (4–6 weeks) may be usually effective enough. However, scientists focus attention on the fact that the choice of antimicrobial drugs as a whole should be consistent with the recommendations of methodological recommendations. The authors note that an insufficient dose of antimicrobial drugs is also one of the reasons for ineffectiveness achieving an adequate minimum inhibitory concentration of antibiotics that promotes AMR [23].

Lee R.A. et al. [24] also confirm that the overuse of antimicrobial drugs is a serious public health problem that contributes to the resistance of microorganisms to antibiotics. Such overuse includes unnecessarily prolonged antibiotic therapy in patients with common bacterial infections such as acute bronchitis, urinary tract infections, and others. A short course (5–7 days) was as effective as a long (more than 7 days) course of antibiotic therapy in patients with cystitis and chronic bronchitis. Research done by Li X. et al. [25] showed that a 7-day course of antibiotics is not inferior to a 14-day course in patients with uncomplicated gram-negative bacteremia. Considering the drug-related side effects and cost-effectiveness the both authors claim that a shorter duration of antibiotic treatment may be more preferable [24, 25].

The results obtained by C. Olmos et al. [26] suggested further investigation whether a two weeks short-course of intravenous antibiotics in patients with infectious endocarditis caused by gram-positive microorganisms, is not inferior in safety and efficacy to conventional antibiotic treatment that usually last 4-6 weeks. While treating the patients with bacterial sepsis N. Takahashi et al. [27] found that the 28-day mortality was significantly lower in the short-course (to 7 days) group, comparing to long-course treatment (more than 8 days), even though there was a higher rate of re-initiated antibiotics in the short course.

Most studies evaluating short-term antibiotic use in human with tuberculosis [28–33] show that shorter (9–11 month) comparing to a longer (20 month and more) regimens can reduce the transmission of resistant strains. Shorter regimens are highly effective and well tolerated by patients. They are more often associated with a decrease in the prevalence of second line drugs-resistant and extensively drug-resistant pathogens, are effective at preventing the acquisition of MDR-tuberculosis pathogens. At the same time, Gao J. et al. [34] showed that standard chemotherapy of a short (6-8 month) course subsequently leads to the development of acquired drug resistance of the causative agent of tuberculosis, which may be the cause of treatment inefficiency.

Some scientists have demonstrated the advantage of tuberculosis therapy under direct observation compared to independent therapy in reducing acquired drug resistance, microbiological failure, and disease relapse rates [35]. They found that directly observed therapy was not significantly better than self-administered therapy in preventing microbiological failure, relapse, or acquired drug resistance, and pointed to the need for research to identify other causes of poor microbiological outcomes.

Chotiprasitsakul D. et al. [36] compared the results of patients who received a short course (6–10 days) and a long course (11–16 days) of antibiotic therapy for Enterobacteriaceae bacteremia. It has been established that a short course of antibiotic therapy gives the same clinical results as a long course. The authors suggested that a short course of antibiotic therapy may prevent further emergence of multi resistant gram-negative bacteria.

Pugh R. et al. [37] used a short-course (6–8 days) antibiotic regimen for the treatment of pneumonia (not caused by non-fermenting gram-negative bacteria). The authors concluded that such therapy is unlikely to increase the risk of adverse clinical outcomes and may even reduce the emergence of resistant pathogens compared to antibiotic therapy over a longer period (10–15 days). However, they indicate that there is a higher risk of recurrence of pneumonia caused by non-fermenting gram-negative bacteria after short-course antibiotic therapy. The results of similar experiments [38–40] basically lead to the same conclusion, but the authors emphasize the importance of using an individual approach to treatment to be sure of reducing the duration of antibiotic therapy for pneumonia. Higher efficiency of short-course chemotherapy in lung diseases was also confirmed by D. Deshpande et al. [41].

Pinzon M.R. et al. [42] compared the clinical efficacy of short-term antimicrobial therapy with long-

term therapy in randomized controlled trials. There were no differences in clinical success, bacterial eradication, side effects, or mortality rates. Analysis of similar studies by Sutijono D. et al. [43] found that there were no significant differences in treatment failure or relapse rates between a 3-day and a 5-day course of antibiotics in three of four studies representing two-thirds of the observed patients.

Until the end of the 20th century, multidrug-resistant strains of Salmonella enterica were a major problem in human and veterinary medicine. Research conducted by H.M. Cheat et al. [44] showed that short-course (3–5 days) therapy by ceftriaxone promotes faster clinical recovery in patients with severe gastroenteritis.

Khariwala S.S. et al. [45] showed that antibiotic application during three and more days after reconstruction of head and neck soft tissue defects did not prevent postoperative infection better than a short-course antibiotic regimen with duration of two and less days. In addition, the authors observed that long-term antibiotic treatment was associated with a higher risk of pneumonia development.

To prevent the development of postoperative infections in clean orthopedic practices, Mathur P. et al. [46] evaluated the effectiveness of a short (24 hours, 3 doses of 1 g of intravenous cefuroxime with an interval of 12 hours) perioperative prophylactic treatment with antibiotics compared with 5 days of intravenous antibiotic (cefuroxime 1 g 2 times a day together with amikacin 15 mg/kg in 2 doses) followed by oral cefuroxime 500 mg 2 times a day until the sutures are removed. The authors found that there was no significant difference in rates of postoperative wound infection between the two groups in the study. They also suggested that the introduction of a short-term perioperative regimen may be more likely to help reduce antimicrobial resistance, treatment costs and side effects.

Oliva A. et al. [47] reported a case of bloodstream infection caused by pan-resistant K. pneumonia. The disease was insecure due to the high mortality rate and lack of effective antimicrobial combinations, especially when the strain was resistant to colistin. An innovative regimen of short-course colistin combined with carbapenems has been used in patients with apparent success. The authors noted the synergistic and bactericidal effects of this treatment regimen.

A review of systematic studies comparing the effectiveness of short and long courses of oral antibiotics for infections treated in an outpatient setting was conducted by E.E. Dawson-Hahn et al. [48]. The authors concluded that a short course of antibiotics is no less effective than a long course for most common infections treated in an outpatient setting. At the same time, they emphasized that the impact of a short course of antibiotic therapy on antibiotic resistance and related treatment complications require further research.

Two major potential drawbacks of antibiotic regimens are under-treatment and possible antibiotic resistance. De Santis V. et al. [49] retrospectively analyzed data on all hospitalized patients with bacteremia over a 6-month period. Pathogens, forms of resistance, use and duration of monotherapy or combination therapy, rates of breakthroughs and relapses, and patient outcomes were evaluated. The authors found that the use of a short course of antibiotic therapy was effective in achieving good clinical outcomes, reducing rates of antibiotic resistance and clinical relapses. They emphasized the need for further study of short-course treatment regimens to assess its clinical efficacy and antimicrobial resistance potential.

Many experts argue that the usual long course of antibiotic therapy does not live up to expectations, possibly because of its ability to promote the development of antibiotic resistance [50]. This is supported by data obtained by Crotty M.P. et al. [51], which indicate that long-term (3–10 days) compared to short term (3 days and less) use of antibacterial drugs in viral pneumonia did not affect clinical outcomes, but, in addition, it increased the frequency of subsequent infection/colonization with microorganisms resistant to various drugs.

Therefore, the number of scientific works indicates that, according to clinical results, treatment regimens with short-term antibiotic therapy may be more justified comparing to long-term antibiotic therapy regimens. The main advantages of short-course therapy are its ability to reduce the development of antimicrobial resistance, better patient compliance and cost-effectiveness.

Nevertheless, some anecdotal data must be considered when expectations of short-term treatment have not been met. For example, in the study of D.S.Y. Ong et al. [52], the use of empiric short-course (1-3 days) gentamicin therapy in patients with sepsis was associated with an increased incidence of renal failure, but not with faster resolution of shock or improved survival in a setting with a low prevalence of antimicrobial resistance.

In another study, Sartelli M. et al. [53] highlighted the conditions under which a short course of antibiotic treatment can be applied. The authors suggest that short-term antimicrobial therapy (3–5 days) can be used in stable patients with adequate source, fever, and leukocytosis control. Critically ill patients always need an individual approach, and the patient's inflammatory reaction should be regularly monitored. The authors suggest using the procalcitonin level as a guideline for antibiotic treatment in critically ill surgical patients.

Research results of M.R. Pinzone et al. [54] indicated that in cases where non-fermenting Gram-negative bacilli were not causative agents, short-term therapy was as effective as long-term therapy in patients with pneumonia. The authors also emphasized the importance of using common antibiotic endpoints, clinical signs, or biomarkers such as procalcitonin. According to the authors, this approach allows to reduce the impact of antibiotics and the risk of developing antimicrobial resistance without a negative impact on the clinical outcome.

In general, the treatment of infectious diseases, in particular assigning the antibiotic therapy regimens, remains difficult. Development of an appropriate regimen and its application are limited by deficiencies in pathogen isolation and susceptibility testing, availability of antimicrobials, and economic concerns. As noted by M.R. Pinzone et al. [42] this often leads to empirical selection of antimicrobials using only clinical judgment, assuming possible local patterns of antimicrobial resistance, etc. According to the authors, these problems can significantly contribute to long and ineffective courses of antimicrobial therapy. A review of the literature related to the problem S. Esposito et al. [55] also observed that, despite the large amount of data available, the optimal duration of antibiotic treatment remains an individual decision, mainly based on clinical criteria. The authors believe that shorter antimicrobial therapy may be equally effective compared to longer antibiotic regimens, and that shorter exposure to antibiotics will reduce antibiotic resistance, drug costs, and other side effects.

Discussion. Antibiotic resistance is raising problem in all parts of the world. New resistant microbial species are emerging and spreading globally, threatening the ability of veterinary and human practitioners to treat even common infectious diseases. In cases when antibiotics can be brought for human or animal consumption without a prescription, the emergence and spread of resistant microbes constitute a major hazard. It also relates to the situations where the care is provided without standard treatment guidelines, antibiotics are over-prescribed by human doctors and veterinarians or over-used by the public. One more important component of the problem is lack of research support for proper treatment duration regimen for antimicrobial drugs. The solution of antibiotic resistance problem demands an urgent action as soon as we may easily go back to the time when even common infections or minor injuries may kill people or animals again.

Meanwhile the research data accumulate on the matter. Many of them relate to the duration of antibiotic regimen. Wayne A. et al. [56] conducted a prospective, observational investigation to evaluate the resolution rate of pneumonia when using 14 days or less of antibiotic therapy compared to longer therapy in dogs. It was found that there was no significant difference in radiographic resolution or relapse rates between the two treatment groups. Kaushik A. et al. [57] using mouse model for tuberculosis treatment concluded that injectable preparations have significant potential for shortening tuberculosis therapy.

It is also noted today that many studies [58–60] concentrate on finding the shortest course duration that is non-inferior to the standard antibiotic regimen duration in terms of clinical outcomes for human and animals with various microbial infections.

Conclusions. The analysis of the given data allows us to draw the following conclusions:

1. The duration of treatment is one of the important indicators of the use of antibiotics, which affects the results of treatment.

2. Schemes of antibiotic therapy should take into account the clinical status, kind of isolated pathogens and their sensitivity to antimicrobials, adherence to treatment and economic issues.

3. The results of current studies on the duration of antibiotic use show that short-term antibiotic therapy is usually superior to conventional long-term antimicrobial therapy.

4. A short course of antibiotic treatment usually shows equally good clinical results, lower rates of antibiotic resistance and clinical relapses.

5. The two most important potential complications associated with the duration of antibiotic treatment are incomplete treatment and the emergence of antibiotic resistance. Both require careful consideration in clinical and research settings.

6. The cut-off indicators used for antibiotic therapy (clinical or bacteriological cure, recurrence rate, etc.) are subjective, complex and often unreliable. The effectiveness of procalcitonin or other blood parameters for their use in monitoring antibiotic therapy should be better defined and studied.

Despite the high relevance and publicity of various aspects of antibiotic therapy in the practice of human and animal health care, research on the effectiveness and consequences of short-term antibiotic therapy in veterinary medicine is limited. This issue should be given more attention, especially in the field of animal husbandry.

Information on compliance with bioethical norms. For our review there were chosen only the articles where the use of animals was approved by the relevant Ethical Committee.

Conflict of interest statement. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Вплив тривалості курсу антибіотикотерапії на розвиток атибіотикорезистентності

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Уникнення зайвого введення антимікробних препаратів є головним принципом антибіотикотерапії. Знання оптимальної тривалості лікування запобігає тривалому курсу застосування антибіотиків та попереджує появу стійкості мікроорганізмів до них. Висвітлено результати сучасних досліджень щодо впливу тривалості застосування антибіотиків на успішність лікування та розвиток резистентності мікроорганізмів. Проаналізовано зарубіжні літературні джерела та результати наукових досліджень фахівців у цій галузі. Результати сучасних досліджень щодо тривалості застосування антибіотиків показують, що короткий курс антибіотикотерапії перевершує звичайне довготривале антимікробне лікування. Короткий курс антибіотикотерапії зазвичай приводить до таких же позитивних клінічних результатів, нижчого рівня антибіотикорезистентності та кількості клінічних рецидивів. Двома найважливішими потенційними ускладненнями, пов'язаними з тривалістю антибіотикотерапії, є незавершене лікування та поява резистентності до антибіотиків. Часові точки, які використовують для лікування антибіотиками (клінічна картина, бактеріологічний контроль ефективності лікуван-

ня, рецидиви тощо), є суб'єктивними, складними та ненадійними. Ефективним маркером в моніторингу лікування антибіотиками може бути рівень показника прокальцитоніну або інші параметри крові, однак, це потребує подальших більш цілеспрямованих досліджень.

Незважаючи на високу актуальність і публічність різних аспектів антибіотикотерапії в практиці охорони здоров'я людей і тварин, дослідження ефективності та наслідків короткочасної антибіотикотерапії у ветеринарії обмежені. Цьому питанню слід приділяти більше уваги, особливо в галузі тваринництва.

Ключові слова: антибіотикорезистентність, антибіотик, мікроорганізми, схема лікування, тварини, тривалість антибіотикотерапії, клінічний результат, рецидиви.

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