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MODERN CHALLNGES IN ANTIBIOTIC TREATMENT OF MASTITIS IN DAIRY COWS

Інфекційні агенти є основними етіологічними факторами маститу у молочних корів. Тим не менш, контроль за маститу на молочних фермах має ґрунтуватися на низці заходів, включаючи вибір препарату та режим застосування, удосконалення методів утримання та годівлі, процедури гігієни ферми, стан здоров'я корів та їх вік тощо. Основна мета цього огляду полягає у висвітленні сучасних проблем антибіотикотерапії молочних корів за маститу.

Було встановлено, що дослідження щодо застосування антибіотиків за маститу у молочних корів є численними. Домінуючими ізольованими збудниками маститу є стафілококи та стрептококи, Escherichia coli та інші грамнегативні ентеральні бактерії. Антибіотики є найбільш поширеною групою препаратів, які використовуються за маститів у молочних корів. Резистентність та життєва здатність збудників маститу змінюються і цей факт слід враховувати. Ефективність лікування маститу залежить від групи факторів. Ці фактори включають напрацювання належної схеми лікування (тривалість, спосіб введення лікарського засобу, вибір лікарського засобу) та врахування факторів ризику для корів (вік тварини, задні чи передні долі вимені, перебіг інфекції) та на фермі (алгоритм гігієни).

Подальше дослідження необхідно спрямовувати на оцінку віддаленого впливу лікування (коротке або тривале, дозування, частота використання) на резистентність патогенів та кількість рецидивів.

Ключові слова: корова, мастит, лікування, антибіотик, режим, резистентність.

The infection agents are the major ethiological factors of mastitis in dairy cows. Yet, the control of mastitis on dairy farms has to be grounded in a number of measures including drug choice and application regime, keeping and feeding systems, farm hygiene procedures, cows' health status and parity etc. Petzer I.M. et al. [1] also emphasize the importance of economic considerations.

The number of mastitis pathogens is quite numerous. Birhanu M. et al. [2] used California mastitis test (CMT) to examine 1048 quarters of 262 cows. They found that 105 (40.1%) of cows and 170 (16.1%) of udder quarters were positive for sub-clinical mastitis. Out of all 170 samples cultured, 153 were positive for subclinical mastitis pathogens. The dominant bacteria isolated were Staphylococcus species (out of them Staphylococcus aureus − 44.9%), Streptococcus spp. (25.3%), other gram negative enteric bacteria and Escherichia coli (8.8%). The obtained data also allowed the authors to affirm that age, body condition score, milk yield and number of parity may be considered as potential risk factors for the occurrence of subclinical mastitis in cows.

That is why the mastitis is considered as the most common reason for the use of antimicrobials on dairy farms. The importance of responsible use of antimicrobials was strengthened by O. Samson et al. [3]. To assess what information could be used as a predictors for cure the authors invited farmers to submit milk samples from mastitis cases to their veterinary practice for bacteriological culture. It was found that among 624 culture-positive samples, 251 were positive for Streptococcus uberis. Additional data were collected at the cow level (somatic cell count (SCC), parity, lactation stage, milk yield, fat and protein contents, treatment) and at the herd level (housing, bedding, premilking teat disinfection, postmilking teat disinfection). There was established that probability of cure was higher among first- and second-parity animals than among older cows, and in animals with a single elevated SCC than in animals with multiple high SCC records. In overall the authors concluded that routinely available cow-level information can help to predict the outcome of antimicrobial treatment of the most common causes of gram-positive mastitis. This conclusion is supported by the Griffioen K. et al.[4]. They found out the need for microbiological mastitis diagnostic tests

among Dutch dairy farmers. The farmers are willing to do the tests that would result in a treatment advice. The availability of a reliable diagnostic test, with a suitable time-to-result period, on an authors' opinion, will likely increase the use of microbiological mastitis diagnostics and eventually optimize antibiotic usage.

The results of the other study [5] indicated that overall positive population level effect of lactation antibiotic therapy is acceptable for herds with successfully implemented practices that reduce the transmission rate of pathogens. In herds with high transmission rates, treatment of chronically infected quarters have little impact on the proportion of infected quarters and no positive population level effect in reducing the force of infection and new infection rates. The authors suggested that field trials to evaluate efficacy of antimicrobial treatment should include estimates on indirect treatment effects.

At the same time recent study showed emerging trend of the development of antibiotic-resistant microbes associated with subclinical mastitis in dairy cows [6], the risk of milk contamination substantially endanger the use of antibiotics [7].

That is why the purpose of this paper was to identify main challenges of antimicrobial therapy while dealing with mastitis in the modern dairy farms.

The most common isolated microorganism in cows with clinical or subclinical mastitis is Staphylococcus aureus. Xavier A.R. et al. [8] studying the S. aureus isolates from affected milk found out that they were divided into two groups with 26 distinct subgroups. The analysis of RAPD-PCR showed no genetic diversity among them, heterogeneous profile and absence of clonality.

E. Coli was also identified as a major pathogen in cows with mastitis [9]. The pathogen showed resistance to ampicillin, carbenicillin and sulfamethoxazole-trimethoprim. The authors found that E. coli isolated from the water samples on the farm possessed ESBL phenotype and carried antibiotic resistance genes,blaTEM and blaCMY-2. They also suggested that pathogenic E. coli exposed to antibiotics on dairy farms can potentially transfer these resistance genes to other pathogenic bacteria under certain conditions.

While known mastitis pathogen may have changed their resistance properties a new bacteria may step in. The results obtained by M. Sun et al. [10] indicate that A. viridans could be considered as an emerging aetiological agent of bovine subclinical mastitis as soon as it exerts an effect on SCC, milk yield and composition.

Analysis done by L. Fox [11, 12] shows that mycoplasma mastitis is infecting about one-fifth to one-quarter of all large dairy herds annually. The author affirms that the U.S. Pacific Northwest experienced a 5-fold increase in clinical mycoplasma mastitis over a 2 to 3-year period in the mid-2000s and, more recent data indicate that mycoplasma mastitis has also emerged in Canada, England and others countries.

With the arising problems of antibiotics usage the effectiveness of alternative methods have been studied. Thus I. Orjales et al. [13] aimed to compare SCC in organic farms not using antibiotics (O, n = 6), organic farms using antibiotics (OA, n = 7) and conventional farms (CA, n = 5) using antibiotic treatments. SCC was statistically significantly higher in O (173780) compared to CA (93325) and OA (107152). Their data also indicated that there were no difference in udder health in the primiparous heifers from the three groups of farms, but it deteriorates in older cows because of chronic infections in udder. The authors concluded that the non-use of antibiotics had a worsening effect on udder health in cows.

The other research team have been studied the effectiveness of live culture of Lactococcus lactis in ruminants with staphylococcal mastitis [14]. The authors found out that intramammary infusions with L. lactis led to a transient clearance of the pathogen in the gland. But it also caused mild to moderate clinical cases of mastitis. The authors believe that it is still early to recommend bacterial formulations as alternatives for treating mastitis in ruminants.

Wu J. et al. [7] studied the efficacy of antimicrobial peptide, nisin, used for the treatment of subclinical mastitis in lactating cows. The results of the study indicated that nisin had bacteriological cure rates of 90.1% for Streptococcus agalactiae, 50% for Staphylococcus aureus, 58.8% for coagulase-negative staphylococci that summarize to 65.2% in average. Meanwhile, spontaneously recovery rate among untreated cows was 15.9%. The given data allowed the authors to conclude that nisin may need further study to clarify its effects on mastitis caused by different pathogens.

Herry V. et al. [15] studied the efficacy of the vaccine to control mastitis in dairy cows. They immunized cows with mastitis, either intramuscularly or intramammaly with the E. coli P4 preparation. It was found out that accelerated bacteriological cure was not linked to an increase in the initial efficiency of phagocytosis in milk. Authors concluded that antibodies did not play a major role in the clinical improvement and that cell-mediated immunity may play more important role in E. coli vaccine-induced protection of the mammary gland.

So, the former research data indicate that reliable, alternative to antibiotics, treatments of mastitis in dairy cows are not still developed and further research is needed to improve their efficacy.

Meanwhile the antibiotics therapy remains dominant and its responsible use demands to take into account the latest research data on the matter. Special consideration has to be addressed to the use of antibiotics in lactating cows due to the danger of milk contamination.

The study of J.W. Barlow et al. [16] demonstrated positive direct effects of lactation antimicrobial of subclinical S. aureus mastitis and indirect effects consisting of the preventing new mastitis cases and reducing incidence of clinical mastitis within dairy herds. And the earlier treatment of Staph. aureus mastitis is more effective than later one [17].

Linder M. et al. [18] were analyzing the effects of an antibiotic treatment at chronic subclinical S.aureus mastitis during lactation. They found that animals treated with antibiotics showed a pathogen elimination rate of 35.9% and a cure rate of 21.9% while the rates for the control group were 21.4% and 8.6%, respectively. It showed that efficacy of intramammary cephalexin and subcutaneous marbofloxacine lactation treatment is low but still significantly better than without any antibiotic use. The later conclusion was supported by B.H. Borne et al. [19]. They showed that lactational treatment did not limit the spread of Staph. aureus at high transmission rates. On authors opinion to improve udder health in a dairy herd, lactational treatment of contagious subclinical mastitis has to be paralleled by management measures that lower the transmission rate − one of the options studied was culling an uncured cows after two month of subclinical intramammary infection.

The use of antibacterial lactational treatment of streptococcal mastitis in dairy cows prevented clinical mastitis [20]. The authors also concluded that the treatment may contribute to reduction of bulk milk SCC and to prevention of pathogen spread in dairy herds. The data obtained by W. Steeneveld et al. [21] showed that for the average cow, treatment of chronic subclinical mastitis (caused by Str. uberis) was not efficient economically. But, the risk of high costs was much higher in cases when cows were not treated. In general, profitability of treatment of chronic subclinical Str. uberis mastitis depended on farm-specific factors (price of milk) and cow-specific factors (time of diagnosis, duration of infection, transmission and cure rates).

Deluyker H.A. et al. [22] studied the associations of bacteriological and quarter SCC cure after intramammary antibiotic treatment with treatment duration, cow parity and pretreatment bacteriology and SCC. They found out that: bacteriological cure rate was significantly higher for lower parity, lower number of colonies in the pretreatment culture, longer treatment duration, and for Streptococci compared with Staph. Aureus; posttreatment SCC was significantly higher with increasing parity, in rear quarters, and with shorter duration of treatment; in the group of second and third parity animals post-treatment SCC was more reduced in front quarters than in rear quarters; the difference in posttreatment SCC between younger and older cows increased with higher pretreatment SCC.

A number of authors compared systemic and local antimicrobial treatment regimens in cows with mastitis. An efficacy of single intramammary infusion containing sodium nafcillin, procaine benzylpenicillin and dihydrostreptomycin and systemic cefquinome administered intramuscularly, twice at a 24-h interval in dry cows with subclinical S. aureus intramammary infection was studied by N.Y. Shpigel et al. [23]. The intramammary treatment resulted in a higher cure rate compared with systemic one. The cure rate after systemic cefquinome treatment was comparable to the spontaneous cure rate. The unfavourable results of the cefquinome systemic regimen the authors attribute to inadequate pharmacokinetic properties of the drug regarding poor penetration in udder with subclinical mastitis and shorter antimicrobial effect compared with the intramammary application.

A randomized controlled field trial was performed to evaluate the efficacy of a 3-day treatment regimen with intramascular penethamate hydriodide compared with no treatment in lactating cows with subclinical mastitis [24]. It was found that systemic treatment with penethamate resulted in bacteriological cure in 59.5% of quarters and 52.2% of cows, compared with 16.7 and 10.9% in the

untreated, SCC decreased significantly in the penethamate-treated cows especially in the cases of bacteriological cure.

The analysis of latter articles allowed us to conclude that treatment of subclinical mastitis during lactation depends on a group of factors. These factors include treatment regimen (duration, method of drug input, drug choice) and risk factors on cow (parity, rare or front quarters, infection recurrences) and on farm (hygiene algorithm) level.

One should agree with C. Pinzón-Sánchez and P.L. Ruegg [25] that information about the etiology, history of clinical and subclinical mastitis and parity are useful to review when developing tactical and strategic treatment regimens.

The open question remains as to duration of the antimicrobial treatment of cows with mastitis. Some research shows lower efficacy of short term treatment [26] and higher of long duration [27] while the others are not so unambiguous.

Oliver S.P. et al. [28] established that efficacy of ceftiofur therapy against all subclinical mastitis was 38.8, 53.7, and 65.8% for the 2-, 5-, and 8-d treatment regimens, respectively. At the same time only 10.5% sick cows in control group were cured without any treatment and the 8-d long ceftiofur treatment was significantly better than the standard 2-d long treatment. The authors also noticed that different pathogens react differently on the same regime treatment. For example, the cure rate for the 8-d treatment regimen was 70% for Corynebacterium bovis, 86% for coagulase-negative Staphylococcus species, 36% for Staph. aureus, 80% for Streptococcus dysgalactiae ssp. dysgalactiae, and 67% for Strep. uberis.

The results of the other study [29] indicate that both the 5- and 8-d ceftiofur treatment regimens had significantly higher bacterial cure rates than the standard 2-d ceftiofur treatment regimen.

Date obtained by B.E. Gillespie et al. [30] indicate that extended pirlimycin therapy was effective in eliminating intramammary infections caused by environmental streptococci and S. aureus. Their date proved that efficacy of pirlimycin therapy of mastitis caused by environmental Streptococcus spp and S. aureus was 44.4%, 61.1%, and 95.0% for the 2-, 5-, and 8-day long regimens, respectively while none of the infections in the untreated control quarters was cured. The authors found significant differences in efficacy between the 8- and 2-day treatment regimens, and between the 8-day and 5-day treatment regimens ($P < \text{or} = 0.05$).

The use of 2-day pirlimycin regimen for experimental S. uberis mastitis eliminated the infection in 58.1%, 5-day regimen − in 68.8 and 8-day regimen − in 80.0% of involved quarters [31]. At the same time, following therapy, in quarters where treatment was successful in eliminating S. uberis the number of somatic cells in milk decreased significantly. However, the authors did not find any evidence to conclude that extended therapy with pirlimycin resulted in a greater reduction in somatic cell counts in milk than the 2-day treatment.

The objectives of the study of R. Kasravi et al. [32] were to evaluate the efficacy of intramammary-administered cefquinome for the treatment of sub-clinical mastitis in lactating dairy cows and to determine if extended therapy would enhance treatment efficacy. Seventy-three Holstein dairy cows from a single farm with 150 infected quarters were enrolled in the study. The three regimens were tested. First, standard regimen (75 mg of cefquinome administered three times at 16-h intervals. Second, extended regimen (75 mg of cefquinome administered six times at 16-h intervals and third, untreated control regimen). Most of the causative pathogens were coagulase-negative staphylococci, streptococci and coliforms. The overall bacteriological cure rates for sub-clinical mastitis were 84.61%, 91.37 and 20% for the conventional, extended and the control groups, respectively. Also there were found significant differences in SCC between the both treated versus the control group ($P < 0.001$). The authors notice no differences, as to bacteriological cure rate or SCC, between the extended and the conventional groups and concluded that extended therapy did not enhance treatment efficacy at the conditions studied.

While some of the discrepancies of antibiotic efficacy may be explained by differences in study design or others subjective causes one may argue that in most of the cases the pathogen properties may be responsible. Here the issues of antibiotic resistance and susceptibility tests arrive. Apparao D. et al. [33] was determining the association between results of in vitro antimicrobial susceptibility tests and outcomes in cows with subclinical mastitis that received intramammary treatment with pirlimycin hydrochloride. Test group cows with mastitis receiving 50 mg of pirlimycin intramammary every 24 hours twice. Control

group cows had no treatment. Overall treatment success rate was 66% (128/194) for both groups. The resistance to pirlimycin ranged from 0% (S. aureus) to 50% (gram-positive cocci). The authors did not find any treatment efficacy differences between the treated and control groups and concluded that in a case described the susceptibility test is not an efficient procedure to do.

On the other hand Ö. Aslantaş and C. Demir [34] while investigating the antibiotic resistance and biofilm-forming ability of Staph. aureus from subclinical bovine mastitis cases found out that the cocci were mainly resistant to β-lactams and, to a lesser extent, to tetracycline and erythromycin. Also, the studied pathogen was possessing at a high rate the biofilm- and adhesion-related genes, which are increasingly considered as an important virulence factor in the pathogenesis of Staph. aureus infections.

The aim of this study done by M. Bochniarz et al. [35] was to recognize selected factors of virulence that determin the adhesion of Staphylococcus chromogenes to cows' udder tissues in subclinical mastitis and to evaluate the susceptibility of this pathogen to antibiotics. There was confirmed the ability of the pathogen to produce slime in 24 isolates (63.2%), and protease in 29 isolates (76.3%). In every slime-producing isolate, there were no found bap, fnbA and eno genes.

Owens W.E. et al. [36] found out that bacteriologic cure rates for newly acquired Staphylococcus aureus intramammary infection (< 2 wk in duration) at 28 d posttreatment were 70% and cure rates for chronic infection (> 4 wk duration) − 35%. The authors also found out that in vitro testing was a high predictor of therapy outcome for mastitis caused by Staphylococcus spp., newly acquired Staph. aureus, Strep. uberis, Strep. dysgalactiae, and Strep. agalactiae, but was not an accurate predictor of efficacy for chronic mastitis caused by Staph. aureus.

The need and efficacy of antimicrobial susceptibility testing was reviewed by J. Barlow [37]. He found that in spite of seemed necessity of susceptibility testing for treatment decisions its usefulness has been challenged in a number of publications.

The analysis of the reviewed articles allowed elaborating following conclusions:

1. The research on antibiotic use in mastitis cases in dairy cows is numerous.

2. The dominant isolated mastitis pathogens are Staphylococcus and Streptococcus spp., Escherichia coli and some other enteric bacteria.

3. Antibiotics are the most common medicines used in mastitis cases in dairy cows.

4. Resistance and survival properties of mastitis causative pathogens are changing and the fact has to be taken into account.

5. The treatment of mastitis depends on a group of factors. These factors include treatment regimen (duration, method of drug input, drug choice) and risk factors on cow (parity, rare or front quarters involvement, infection recurrences) and on farm (hygiene algorithm) level.

The further study needed to evaluate the distant influence of treatment regimen (short or prolonged duration, dosage, frequency of use) on pathogen resistant properties and mastitis reoccurrence rate.

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Современные вызовы при антибиотикотерапии маститов у коров

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Инфекционные агенты являются основными этиологическими факторами мастита у молочных коров. Тем не менее, борьба с маститами на молочных фермах должна основываться на ряде мероприятий, включая выбор препарата и режим применения, совершенствование методов содержания и кормления, соблюдение правил гигиены на ферме, состояние здоровья коров, их возраст и тому подобное. Основная цель этого обзора состоит в освещении современных проблем антибиотикотерапии молочных коров с маститом.

Было установлено, что исследования по применению антибиотиков при маститах у молочных коров являются достаточно многочисленными. Доминирующими изолированными возбудителями мастита являются стафилококки и стрептококки, Escherichia coli и другие грамотрицательные энтеральные бактерии. Антибиотики являются наиболее распространенной группой препаратов, используемых при маститах в молочных коров. Резистентность и жизненная способность возбудителей мастита изменяются и этот факт следует учитывать. Эффективность лечения мастита зависит от группы факторов. Эти факторы включают наработку надлежащей схемы лечения (продолжительность, способ введения лекарственного средства, выбор лекарственного средства) и учета факторов риска для коров (возраст животного, задние или передние доли вымени, характер инфекции) и на ферме (алгоритм гигиены).

Дальнейшее исследование необходимо направлять на оценку отдаленного влияния лечения (короткое или длительное, дозировка, частота использования) на устойчивость патогенов и количество рецидивов.

Ключевые слова: корова, мастит, лечение, антибиотик, режим, резистентность.

Modern challnges in antibiotic treatment of mastitis in dairy cows

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The infection agents are the major ethiological factors of mastitis in dairy cows. Yet, the control of mastitis on dairy farms has to be grounded in a number of measures including drug choice and application regime, keeping and feeding systems, farm hygiene procedures, cows' health status and parity etc. The main purpose of this review was to evaluate the modern challenges of antibiotic treatment of dairy cows with mastitis.

It was found that the research on antibiotic use in mastitis cases in dairy cows is numerous. The dominant isolated mastitis pathogens are Staphylococcus and Streptococcus spp., Escherichia coli and some other gram negative enteric bacteria. Antibiotics are the most common medicines used in mastitis cases in dairy cows. Resistance and survival properties of mastitis causative pathogens are changing and the fact has to be taken into account. The treatment of mastitis depends on a group of factors. These factors include treatment regimen (duration, method of drug input, drug choice) and risk factors on cow (parity, rare or front quarters involvement, infection recurrences) and on farm (hygiene algorithm) level.

The further study needed to evaluate the distant influence of treatment regimen (short or prolonged duration, dosage, frequency of use) on pathogen resistant properties and mastitis reoccurrence rate.

Key words: cow, mastitis, treatment, antibiotic, regimen, resistance

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МОЛЕКУЛЯРНО-БІОЛОГІЧНІ МЕХАНІЗМИ РЕПАРАТИВНОГО ОСТЕОГЕНЕЗУ

Кісткова репарація є складним біологічним процесом відновлення пошкодженої тканини, яка супроводжується тривалими гіперкоагуляційними зрушеннями в системі гемостазу у вигляді різного ступеня розвитку коагулопатій, ендотеліальної дисфункції та зниженням синтезу оксиду азоту, що негативно впливає на ангіогенез і репаративні процеси. Це супроводжується надмірним проявом реакції гострої фази із значним підвищенням рівня білків гострої фази (гаптоглобіну, церулоплазміну, фібриногену, С-реактивного білка та маркерів сполучної тканини), що уповільнює консолідацію уламків кісток. При цьому регуляція репаративного остеогенезу відбувається на системному та локальному рівнях, що здійснюється із залученням ряду різних систем організму та численних біологічних речовин на рівні рецепторного апарату.

Ключові слова: репаративний остеогенез, кісткова регенерація, загоєння переломів, регуляція остеогенезу, тварини.