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Review article

STAPHYLOCOCCUS AUREUS - DO WE REALLY HAVE TO LIVE WITH IT?

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Summary: Staphylococcus aureus (S. aureus) is still one of the most prevalent mastitis pathogens in dairy herds all over the world. Effective and economic S. aureus control programs rely on prevention rather than treatment. Since the introduction of the standard mastitis prevention program, much progress has been achieved in decreasing the prevalence of intramammary infections (IMI). However, at the farm level, staphylococcal mastitis remains the disease causing the highest financial losses. Among S. aureus strains isolated from the bovine mammary gland resistance to penicillin increased rapidly from approximately 20 % in 1965 to 45 % in the mid 70s and decreased again in the 1990s to approximately 30 %. Although the therapeutic value of penicillin is limited in many countries, there are still sufficient antimicrobials available for treatment of S. aureus IMI. Currently there are no founded indications that methicillin-resistant S. aureus (MRSA) strains are involved in bovine mastitis. To control S. aureus mastitis at the farm level complex measurements, which involves strategies for treatment of existing infections and also prevention of new mastitis cases should be implemented.

Key words: cattle diseases – preventive and control; mastitis, bovine – drug therapy; *Staphylococcus aureus*; cattle – female

Introduction

Staphylococci are Gram-positive spherical bacteria that occur in microscopic clusters resembling grapes. In 1884, Rosenbach described two pigmented colony types and proposed the appropriate nomenclature: *Staphylococcus aureus (S. aureus)* (yellow) and *S. albus* (white). The latter species is nowadays named *S. epidermidis* (1). Until now more than 40 different species and many subspecies in the genus *Staphylococcus* have been described. Staphylococci are found worldwide in warm-blooded animals.

Among bacterial species *S. aureus* is one of the most frequently isolated major bovine mastitis pathogen (2).

Mastitis is the most common and costly production disease affecting dairy cows. Many interpretations of the word “mastitis” exist in research and in farming practice. Literally, “mastitis” means “inflammation of mammary gland tissue”. Inflammation of the bovine udder is usually caused by infection, mostly by bacteria, yeasts or fungi, but it can also be the result of sterile inflammation due to chemical, physical or mechanical trauma (3).

In spite of many proofs for contagious character of *S. aureus,* the bacterium is ubiquitous on dairy farms. *S. aureus* strains can be isolated from healthy bovine teat skin, human skin, milking equipment and bovine milk (4).

Although *S. aureus* can, usually, be effectively combated with the 5-point program, later extended to the 10-point program, including segregation, it still causes problems on dairy farms, making clear that it is difficult to control *S. aureus* mastitis and that it may be impossible to eradicate the disease (5). Most herds do not have facilities or labour to handle additional groups or individual mastitic animals and are not willing to cull infected animals. Therefore, in recent years more emphasis has been placed on the treatment rather than prevention. However, little progress had been made during the previous ten years towards solving some of the basic problems associated with antimicrobial treatment of staphylococcal mastitis, i.e. the low cure rate for clinical and subclinical *S. aureus* infections. Staphylo-

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cocci spread by direct or indirect contact, but interspecies spread (e.g. humans - cows, dogs - humans) appears to be limited (6). Many animal infections are probably endogenous, that is, caused by a resident strain. The objectives of the article were to review current knowledge about *S. aureus* epidemiology, pathogenesis, diagnosis, treatment and control.

Epidemiology and importance of S. aureus mastitis

The most common transmission pathway occur through transfer from an infected mammary gland to an uninfected gland via devices, such as milking equipment, common udder cloths, or the milker's hands. In herds that do not practice backflushing, residual milk remains in the teat cups. If the last cow milked with that unit had a *S. aureus* udder infection, then the next cow, milked with the same unit, will be directly exposed to the pathogen. If employed, common clothes or sponges can be a major means of spreading *S. aureus* as nearly every cow in the herd would be exposed on a daily basis. The importance of the milker's hands in spreading *S. aureus* could be equally as important as a common udder cloth, especially in herds that practice forestripping. The milking parlor and the lactating period represent the place and time period where most new IMI occur, but *S. aureus* can result in new IMI during the dry period and also in heifers. Although the infected mammary gland could still be the source of these infections, it is obviously not the only reservoir of *S. aureus* on dairy farms (7).

In many countries the number of mastitis cases, particularly subclinical, caused by *S. aureus* is still very high. In Slovenia, for example, the proportion of *S. aureus* udder infections was 48,2 % in 1997, 45 % in 1998, 48 % in 1999 and 53,7 % in 2000 (8). Comparable results were found in the Netherlands 17,2 % in 1950, 42,8 % in 1975 and 40,5 % in 2000 (9). In Italy the prevalence of subclinical *S. aureus* udder infections was 21 % in 2001 (10). In an Austrian study from 2003, *S. aureus* was found in 43 % of subclinical mastitis cases (11).

Pathogenesis

S. aureus expresses many potential virulence factors:

- surface proteins that promote colonization of host tissue
- invasins that promote bacterial spread in tissues (leukocidin, kinases, hyaluronidase)
- surface factors that inhibit phagocytic engulfment (capsule, protein A)
- biochemical properties that enhance their survival in phagocytes (carotenoids, catalase production)
- immunological disguises (Protein A, coagulase)
- membrane-damaging toxins that lyses eukaryotic cell membranes (hemolysins, leukotoxin, leukocidin)
- exotoxins that damage host tissues or otherwise provoke symptoms of disease
- inherent and acquired resistance to antimicrobial agents (12)

For the majority of diseases caused by *S. aureus*, pathogenesis is multifactorial, so it is difficult to determine precisely the role of any given factor. However, there are correlations between strains isolated from particular diseases and expression of particular virulence determinants, which suggests their role in a particular disease. In the last decade the application of molecular biology has led to advances in unraveling the pathogenesis of staphylococcal diseases. Genes encoding potential virulence factors have been cloned and sequenced, and many protein toxins have been purified (13).

Infection of the mammary gland can start when *S. aureus* cells penetrate the teat canal. Most bacteria penetrate the teat during milking, when the sphincter muscle is relaxed. Shortly after penetration, the bacteria rapidly multiply in milk and adhere to epithelial cells. Bacteria that have not adhered to epithelial cells will be removed during next milking. In case of successful colonization, large quantities of bacteria can be found in milk after twenty-four hours. Four days after infection, *S. aureus* is already present in interstitial tissue and also intracellularly in epithelial cells. In the beginning of staphylococcal udder infection, only small areas of the gland may be involved. Cells of the alveoli and ducts gradually degenerate and slough from the cistern lining and, together with somatic cells, occlude milk ducts that drain milk-producing areas. This obstruction leads to involution of the remaining functional alveoli and formation of scar tissue. Occluded ducts may reopen, releasing pathogens to other areas of the gland. This process is then repeated, initiating a continuous cycle of infection of different areas of the quarter. During the early stages of infection, tissue damage is minimal and reversible. If effectively treated, the quarter will return to near normal milk production in subsequent lactations. If microorganism remains within the occluded area, abscesses may become quite large and can be palpated in the udder tissue (14).

Symptoms

In many countries *S. aureus* is the most common cause of subclinical udder infection but not necessarily of clinical mastitis. It does not often cause peracute mastitis, usually producing a chronic disease with occasional occurrences of clinical mastitis. Partly due to the poor response to antibiotic therapy it is the most persistent of infections, frequently lasting for several months and even years (15). In cows strains of *S. aureus* rarely produce toxins that cause blood vessel constriction and massive clotting, which leads to interruptions in the blood supply of the affected area. The consequence is a gangrenous course of mastitis, which is uncommon in the bovine mammary gland, but very frequent in small ruminants (16).

Diagnosis

S. aureus is a Gram-positive, facultative anaerobic, non-sporeforming coccus, belonging to the family of *Micrococcaceae*. The bacterium is coagulase and catalase positive and oxidase negative. In the laboratory beside the Gram stain, the catalase and the slide coagulase test are performed to differentiate *S. aureus* from other species.

S. aureus forms on blood agar large colonies with characteristic pigmentation and hemolytic patterns (17). To identify staphylococcal isolates at the species level, commercial biochemical tests are available (18).

Treatment and antimicrobial susceptibility

Susceptibility testing is by far the most important laboratory test used in selection of the therapeutically relevant antimicrobial drug. The clinicians rely increasingly on this test, as it is the only relevant information applied for therapy design. However, these tests have numerous shortcomings concerning their technical performance as well as the interpretation of the results. Even if the susceptibility testing was correctly performed and interpreted, very little is understood about the implications concerning selection of specific drug formulations, adequate dosage and sufficient dosing interval. The test result that the clinician receives from the laboratory, relate to the established break point values. These values are largely unknown to the clinician. Therefore, the clinician is unaware of what the target plasma concentrations should be and how they can be reached. However, this particular information is critical for selecting the correct therapeutic agent. Moreover, it is crucial to select the right pharmaceutical formulation of the appropriate drug. For instance, equal doses of benzylpenicillin G, procain penicillin and benzathine penicillin will produce completely different penicillin plasma concentrations (19). Consequently, the results of in vitro susceptibility testing can provide only restricted therapy guidelines.

The development of bacterial resistance has nearly always followed the therapeutic use of antimicrobial agents. When penicillin was introduced for clinical use in 1941, virtually all strains of *S. aureus* were susceptible. In 1944, first reports on penicillin resistant *S. aureus* strains appeared, and within less than a decade, serious resistance problems have been observed in many countries (20). 1960 new β-lactamase-resistant antibiotics (methicillin) were developed to fight staphylococcal infections, but 15 years later the first methicillin-resistant *S. aureus* (MRSA) strains emerged. Afterwards vancomycin was the drug of choice to treat these infections. Finally, in 1996 vancomycin-resistant (VRSA) strains were reported from Japan. Nowadays, *S. aureus* is consistently one of the top four causes of nosocomial infections in humans, along with *Escherichia coli*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa* (21).

In cattle the rate of narrow-spectrum penicillin resistance *S. aureus* strains varies per country and also over time within countries. For example, in the U.K., penicillin-resistance in *S. aureus* isolated from bovine mastitis has increased from 2 % in 1949 to approximately 70 % in the 1980s (22). However, most recent results indicate a decrease in penicillin resistance; except in Germany, where levels of penicillin resistant *S. aureus* has remained at 30-40 % from the 1960s through to the 1990s. In general comparisons between and even within countries are difficult due to the various methods of resistance determination. Sensitivity of *S. aureus* to antimicrobials other than penicillin has remained good over a long period of time (23). Occasionally a dual resistance against lincomycin and erythromycin is detected, but the rate of resistant strains is generally under 10 %. Sometimes in strains of *S. aureus* isolated from bovine mastitis minimal inhibitory concentrations high enough to qualify them as oxacillin-resistant are observed. However, the general opinion is that the mechanism of resistance is probably due to hyperproduction of β-lactamase rather than to the altered penicillin-binding protein found in human strains of MRSA (methicillin-resistant *S. aureus*). *S. aureus* isolates are some-

what site specific, and not all strains are equally capable to cause IMI. MRSA strains of human origin are obviously unable to adapt to the circumstances in the bovine udder and there are no indications that MRSA strains are momentarily involved in bovine mastitis (24).

We can conclude that there seems to be no urgent need for new antibiotics for treatment of *S. aureus* mastitis. With exception of penicillin in β-lactamase-positive strains, all products currently available on the market have sufficient potential.

Therapy of infectious disease should either assist host defenses in eliminating invading pathogens or reduce pathophysiologic consequences of infection without degrading host defenses. Logically, emphasis in mastitis therapeutics has focused on the elimination of pathogens by use of antimicrobial agents. Also in the control of *staphylococcal* mastitis antibiotic therapy still play an important role (25). Despite of a variety of effective antibiotics, success of treatment of *S. aureus* mastitis particularly during lactation is disappointing (26). Among veterinarians and dairy farmers, therapeutic success is often measured by evaluating reduction of clinical symptoms (clinical cure). However, for long-term effects, total elimination of the pathogen from the gland (bacteriological cure) should be achieved.

In the last decades several antibiotic preparations have been introduced for the treatment of this disease, but a "problem solving drug" has not been invented. So in the majority of mastitis cases where treatment with antibiotics is indicated, benzylpenicillin may still be the drug of choice.

Penicillin has several advantages in the treatment of mastitis:

The minimum inhibitory concentration (MIC) of benzylpenicillin for sensitive mastitis pathogens is ten times lower than in other antibiotics.

Resistance seems not to increase in line with the use of penicillin. The percentage of penicillin resistant staphylococci is lower in Scandinavia than in many other countries despite the fact that the majority of antibiotic-treated mastitis cases in Scandinavia are treated with penicillin.

The pharmacokinetic and –dynamic properties of penicillin are suitable for the treatment of mastitis. Benzylpenicillin is chemically a week base and it distributes well to the mammary tissue and becomes trapped in the milk phase. The half live of penicillin is long enough to allow once a day treatment.

Penicillin has low tissue irritation, which is an advantage especially in the intramammary application.

Penicillin is an environmentally safe substance. As a narrow spectrum antibiotic, which is inactivated by enzymes, penicillin is potentially less harmful for the environment than for instance fluoroquinolones and tetracyclines (27).

Early detection and treatment of *S. aureus* IMI has a considerable impact on the success rate. Treating cows within the first 30 days of infection may offer a 70-80 % cure rate. Every month treatment is delayed; the chance of a cure drops by 20 %. Even dry cow therapy is therefore often ineffective at curing existing *S. aureus* infections (28). The method of administration of antibiotics (intramuscular and/or intramammary) is also of influence for the outcome of the therapy. In many studies it has been described that a combination of an intramuscular and intramammary treatment of clinical and subclinical *S. aureus* mastitis was superior to intramammary treatment alone. It was also shown that the success rate increases as the length of treatment increases. Results of research (9) support the concept that extended antimicrobial therapy is significantly more effective at eliminating natural and experimental IMI than standard treatment regimes.

Prevention and control

Mastitis is an extremely difficult disease to control because several different microorganisms can invade the udder, multiply there and produce harmful substances that result in inflammation. Microbes that most frequently cause mastitis can be divided into two categories: contagious pathogens that are spread from cow to cow, primarily during the milking process; and environmental pathogens that are found throughout the environment of dairy cows. Current mastitis control programs, which were devised in the 1960s, are based on hygiene including teat disinfection; antimicrobial therapy and culling of chronically infected cows. Acceptance and application of these measures throughout the world has led to considerable progress in controlling mastitis caused by *Streptococcus agalactiae* and to a much lesser extent *S. aureus* (29). This failure can be partly explain by ecological observations of *S. aureus* infections, which indicates that the udder of the adult cow is not the only reservoir of the organism and that transmission is not necessarily limited to the milking process. Therefore sources other than infected udder of lactating cows are likely involved in the epidemiology of *S. aureus* IMI in the dairy herd (30). Recent studies (3) have provided some evidence that substantial variation in epidemiology exists within one bacte-

rial species. Also in case of *S. aureus* there is a large variation in the genome of individual strains and it seems, that also very different clinical patterns emerge from these strains. A better understanding of strain-specific epidemiology within bacterial species will consequently have a major impact on the specific control strategies that are successful to prevent or at least reduce IMI in herds. Experiences from countries where *S. aureus* udder infections were significantly reduced in the last decade indicate that culling of chronically infected cows is the most powerful tool to achieve this goal. However, especially in smaller herds, where culling for mastitis is limited to two or three animals per year, elimination of infected cows alone will not solve the problem. In such cases, beside general accepted preventive measures, which are directed to reduce the spread of *S. aureus* during milking, herd-specific factors should be recognized. In herds where culling of all infected cows is not possible segregation of infected cows or using separate milking clusters on infected cows is a viable option. Smaller herds can designate one or two milking clusters as "Staph" units. These claws should be clearly marked and only used on infected cows. Another option is to milk the uninfected cows first and the "Staph" cows last. This method relies on the post-milking sanitation procedures to effectively remove potential udder skin contamination. Larger herds can create a "Staph" milking group. Even though these cows are housed in the same free stall barn, they can be separated at milking time and milked last. Heifers and new herd additions can be potential sources for introduction of *S. aureus* into uninfected herds. Therefore all new herd additions including heifers should be cultured within 30 days of entering the lactating herd (29).

Conclusions

Understanding the epidemiology of a disease, including disease distribution and transmission, is important for the development of prevention and control programs. Procedures that may be very successful in control or eradication of contagious mastitis, may not be effective in the control of environmental mastitis, and vice versa .

The best way to control *S. aureus* mastitis in a dairy herd is to identify infected cows and prevent the exposure of healthy mammary glands to the pathogen. Elimination of existing infections is best achieved with an appropriate therapy regime during the lactation period; complete dry cow therapy and culling chronically infected cows. New infections can be prevented by proper milking time procedures, post-milking teat dipping, maintaining excellent teat skin condition, and segregating infected cows.

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STAPHYLOCOCCUS AUREUS - ALI RES MORAMO ŽIVETI Z NJIM?

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Povzetek: *Staphylococcus aureus* (*S. aureus*) še vedno sodi med najpogostejše povzročitelje vnetja mlečne žleze po svetu. Programi za zmanjševanje števila mastitisov, ki jih povzroča *S. aureus*, temeljijo predvsem na preprečevanju novih okužb in ne na zdravljenju obstoječih vnetij mlečne žleze. Navkljub znatnemu napredku na tem področju, pa predstavljajo mastitisi, ki jih povzroča *S. aureus* za posamezne rejce veliko finančno breme. Odpornost na penicilin se je med sevi *S. aureus* izoliranimi iz mlečne žleze od leta 1965 ko je znašala približno 20 % hitro povečevala in v sedemdesetih letih dosegla 45 %. V zadnjem obdobju pa smo priča ponovnemu padcu odpornosti *S. aureus* na penicilinske preparate, ki je danes približno 30 %. Čeprav je terapevtska vrednost penicilina v mnogih državah omejena, pa je na tržišču dovolj učinkovitih preparatov za zdravljenje stafilokoknih mastitisov. Sevi *S. aureus* odporni na meticilin (MRSA), ki jih v zadnjih letih vse pogosteje povezujemo z okužbami pri ljudeh, vsaj zaenkrat ne povzročajo mastitisa pri govedu. Pri sanaciji problematičnih čred je potrebno upoštevati tako dejavnike povezane z zdravljenjem obstoječih okužb, kot tudi mere za preprečevanje novih primerov stafilokoknega mastitisa.

Ključne besede: govedo, bolezni – preprečevanje in nadzor; mastitis, bovini – zdravljenje z zdravili; *Staphylococcus aureus*; krave