Livestock-Associated Methicillin-Resistant Staphylococcus Aureus (LA-MRSA) CC398: An Emerging Infectious Disease

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Abstract. Livestock-associated methicillin-resistant Staphylococcus aureus (LA-MRSA) is a pathogenic bacterial strain that can infect livestock, pets and humans. LA-MRSA was identified for the first time in 2005 where the new MRSA clone of sequence type 398 (ST398) was grouped and identified in the clone complex 398 (CC398). Cases of LA-MRSA CC398 infection began to be reported frequently in the next few years. From 2000 onwards, case reports of LA-MRSA CC398 infection are becoming more frequent. LA-MRSA CC398 transmission to the host is generally mediated by physical contact with livestock, but also through contaminated dust. LA-MRSA CC398 has the same virulence potential as Staphylococcus aureus found in humans and is generally associated with the same clinical features. Rapid detection of LA-MRSA examination can be done with a nasal swab, it is very important to adequately identify individuals who have been infected with LA-MRSA and molecular detection of LA-MRSA CC398 using polymerase chain reaction (PCR). Several other antibiotics such as linezolid, telavancin, daptomycin, tedizoid, dalbavancin, oritavancin, ceftobiprole, and ceftaroline have been developed and approved for the treatment of the LA-MRSA CC398 infection. Interventions that need to be done to prevent transmission and infection of LA-MRSA CC398 include screening, isolation of contacts, hand hygiene, cohorts, and decolonization as additional standard precautions.

Keywords: LA-MRSA; CC398; Emerging Infectious Disease

1 Introduction

Livestock-associated methicillin-resistant Staphylococcus aureus (LA-MRSA) was first identified in 2005 [1] in which the new MRSA clone of sequence type 398 (ST398) was grouped and identified in the clone complex 398 (CC398). The term LA-MRSA CC398, which originally appeared in pigs in Europe in 2005, has also been found in other livestock species in various European countries and in North America [1-5]. The spread of LA-MRSA is very common in livestock environments and can cause fatal cases of infection in animals and even humans, so that LA-MRSA is a pathogenic bacterial strain that is dangerous to the health of livestock and humans [6, 7]. However, the cases of human disease caused by LA-MRSA infection are lower

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than that of other MRSA strains (such as CA-MRSA and HA-MRSA) possibly because LA-MRSA infected patients show different demographic conditions because they live in a farm environment and only a short stay in the hospital, the clinical symptoms of patients infected with LA-MRSA CC398 are usually mild and not severe [8], so that cases of LA-MRSA CC398 infection still receive less serious attention from the public than other strains of Staphylococcus aureus [9]. In fact, LA-MRSA is a strain of Staphylococcus aureus which has become an emerging infectious disease worldwide [10].

Several previous studies have been conducted, showing the result that there has been a rapid increase in the number of people infected with LA-MRSA CC398 in recent years. Not everyone infected with LA-MRSA CC398 has had direct contact with livestock [11, 12]. The incidence of LA-MRSA CC398 invasive infection has also increased sharply and peaked in 2014 in the European region [13, 14].

LA-MRSA CC398 associated with soft tissue and skin infections can affect healthy and young farmers, but LA-MRSA transmission can also occur in the human population, which includes elderly people and people with immune disorders at risk of exposure to LA disease. LA-MRSA is invasive [11]. In the last ten years the strain of LA-MRSA CC398 can cause zoonotic disease cases in humans and has now become a major problem in public health in the world [15]. The purpose of writing this review is to explain the general definition, description, emergence, epidemiology, transmission, infection, diagnostic detection, the public health consequences, treatment, and prevention of LA-MRSA.

2 Methodology

2.1 General definition of LA-MRSA

Livestock-associated methicillin resistant *Staphylococcus aureus* (LA-MRSA) is a pathogenic bacterial strain that can contaminate livestock, pets and humans. MRSA cases in livestock were first informed in 1972 in cases of dairy cattle with mastitis in Belgium, where at that time MRSA cases were usually found in humans [16]. Since then, cases of MRSA in livestock have been reported in many European countries [17]. In 2005 [1] a new lineage of MRSA with sequence type 398 (ST398) was identified in the clone complex 398 (CC398) which began to be called LA-MRSA CC398 and capable of infecting human. In addition, LA-MRSA CC398 has also been informed globally in horses, pigs, poultry, and cattle [18].

2.2 LA-MRSA colonal complex 398 (CC398)

LA-MRSA CC398 is a major clonal complex that is widely identified in North America and Europe. It has occasionally been identified in Asia [19] and has also been identified in Africa [20, 21]. This clonal complex is associated primarily with the incidence of LA-MRSA infection in pigs and calves [17, 22-27]. LA-MRSA isolate CC398 has rarely been identified in poultry [28] and horses [29, 30]. All genome sequencing has shown that the CC398 clonal complex is of human origin [15], indeed in humans the case of LA-MRSA CC398 infection still occurs primarily as methicillin-susceptible *Staphylococcus aureus* (MSSA) [31-34], although it has a low prevalence. MSSA CC398 has also been detected in animals such as pigs [35], dogs [36], cattle [32], and poultry [32, 37].

Currently LA-MRSA CC398 has 43 types of genome sequences [38], but in pigs the main genome sequence is ST398. Other types of sequences (ST) found in pigs are ST1968, ST1967,

ST1966, ST1965, and ST541 [39-41]. However, previous studies have indicated that there is a certain subgroup of the ST398 strain in humans, but different from LA-MRSA ST398 [42], which can be easily distinguished by detection of Single Nucleotide Polymorphism (SNP), and the appearance of scn and tet (M). [43]. The results of a study conducted in the Netherlands reported that all CC398 strains found there were LA-MRSA [12]. However, the prevalence rate of LA-MRSA CC398 infection continues to increase in various countries, even though each country has different geographical conditions [44-46].

LA-MRSA CC398 is not considered to be highly pathogenic in humans. Whereas in animals, LA-MRSA CC398 was involved in cases of bovine mastitis [25, 47-50] and arthritis of the legs in turkeys [37]. There is still little information about LA-MRSA CC398 in pigs because the main type of pathogen frequently found in pigs is *Staphylococcus hyicus* [51], although *Staphylococcus aureus* can still be found from lesions in pigs [51]. However, recent reports suggest that LA-MRSA CC398 infection is more prevalent in pigs and humans than previously thought [52-54], but this study requires further research.

2.3 Emergence of LA-MRSA

From 1970 to 2000, MRSA strains were rarely dissociated from animals, especially livestock, because MRSA strains are usually found only in humans, as indicated by bio-typing. So that until the end of the 20th century, it was estimated that the reservoir in livestock was not associated with MRSA which causes disease in humans. It is believed that cases of MRSA infection are a problem that occurs due to the misuse of antibiotics in human medicine [55]. In 1972 it was reported for the first time a case of MRSA infection was isolated from a dairy cow with mastitis [56]. Then cases of this infection began to be reported several times in the next 28 years. From 2000 onwards, case reports of LA-MRSA infection have become more frequent, in 2007 there were reports of MRSA (ST1; spa-type) transmission between cow and humans [57]. The first case of LA-MRSA infection in humans was reported in 2005 in a girl who was hospitalized for six months in the Netherlands.

The girl was still detected positive for LA-MRSA despite various treatment attempts. Both of the girl's parents apparently lived in a pig farm area and both of the girl's parents were also infected with LA-MRSA [1]. LA-MRSA cannot be categorized by standard pulsed-field gel electrophoresis (PFGE), then it is further accessed to regional LA-MRSA reservoirs and pig farmers [58]. A study of LA-MRSA in pigs in Slaughterhouses (RPH) showed that LA-MRSA was widely distributed among pigs in the Netherlands [59].

The genotype examination showed that the LA-MRSA strain isolated from pigs and hog breeders could not be categorized as standard PFGE because this strain was resistant to digestion of the SmaI enzyme that is used routinely, therefore it is called asnon-typeable. MRSA (NT-MRSA). Subsequent studies have shown that the LA-MRSA strain can be typed if other enzymes are used [60]. The LA-MRSA strain has clonal complex 398 (CC398), with most LA-MRSA having sequence type 398 (ST398). The risk factor for humans being exposed to LA-MRSA is if they are on cattle and pig farms [61]. From 2005 onwards, more cases of LA-MRSA infection were reported in different livestock such as cattle [25], pigs [58, 62], and poultry [63, 64], occurring in European countries [65], as well as in America [3] and Asia [66, 67].

The baseline EU-study relates to the prevalence of LA-MRSA in the pig industry in most European countries, indicating that LA-MRSA infections are common in pig farms. It is different from studies in Europe and America, LA-MRSA ST398 does not seem to be the dominant strain of MRSA in pig farms in Asia. Several previous studies have shown that the dominant LA-MRSA strain in pig farms in Asia is sequence type 9 (ST9) [66-68]. Meanwhile ST72 is the dominant LA-MRSA strain found in meat products in Korea [69, 70].

The LA-MRSA strain has also been detected in domestic animals, but this type of LA-MRSA is generally different from that of livestock. The underlying reason is that there is a transmission route thought to be from humans to pets, therefore the LA-MRSA strain in humans may also be found in domesticated animals [71].

2.4 Epidemiology of LA-MRSA

In the early 21st century, to be precise in 2005, the LA-MRSA strain isolated from pigs was identified with sequence type 398 (ST398) and then the strains were associated and grouped collectively into clone complex 398 (CC398) [72]. LA-MRSA CC398 was first detected in pigs and breeders, then since then LA-MRSA has been detected in other livestock (cattle, poultry), pets (dogs), and humans in several European states, Australia, North America, Asia, and South America. This finding of the LA-MRSA CC398 strain led to an increased incidence of livestock-related MRSA, when there had previously been the incidence of hospital-acquired MRSA infection (HA-MRSA) and community-acquired MRSA infection (CA-MRSA) [72].

CC398 is the type of LA-MRSA most identified in most European countries [72-75], so that most people assume that the terms CC398 and LA-MRSA are practically interchangeable. However, while the LA-MRSA CC398 strain has been detected in worldwide, livestock-related epidemiology of *Staphylococcus aureus* has been identified as distinct in other geographic areas. Several studies that have been carried out in Asia have shown that the LA-MRSA ST9 strain is the LA-MRSA type that is most often found in several Asian countries [67, 76-79]. In poultry there was also the LA-MRSA CC398 strain [28, 37, 80] but other types of LA-MRSA were also found that were not related to LA-MRSA CC398, one of which was LA-MRSA CC5 [37, 81] or other types [28]. In North America, a greater diversity of livestock-related *Staphylococcus aureus* has been found than is found in Asia or Europe, with reports of LA-MRSA CC398 infection as well as various other strains of *Staphylococcus aureus* in live animals.

The epidemiology of LA-MRSA CC398 and other types of LA-MRSA that have been detected in humans and animals [67] has led to the idea that further investigations of LA-MRSA CC398 in the host appear to be related to animals and humans and can lead to active cases of sympathetic infection in both species [62, 82]. Further studies, LA-MRSA CC398 and LA-MRSA CC5 isolated from poultry have been photogenically analyzed and have shown that transmission originates from humans, transmitting the LA-MRSA strain to animals, then these strains spread and evolve so that they can carry out various adaptations to animal's host [15, 83]. Therefore, the LA-MRSA CC398 strain associated with both livestock and humans is a complex study or association in the host based solely on the type of sequence.

2.5 Transmission of LA-MRSA

Staphylococcus aureus transmission to the host is generally mediated by physical contact. The condition of dusty cattle sheds is also prone to LA-MRSA transmission [84]. So there is a possibility that the case of LA-MRSA infection in farmers occurs through inhalation of dust that has been contaminated by LA-MRSA [85]. On nasal swab examinations, as many as 77-86% of farmers working in the stable test positive for LA-MRSA [86, 87]. The degree of LA-MRSA colonization appears to depend on the intensity of direct contact with the animal and the duration of exposure [88]. When the farmer is on vacation or is not active in the cage, LA-MRSA colonization continues even though there is no farmer exposure [89, 90]. Meanwhile, people who live near farms are less likely to be exposed to LA-MRSA, with a prevalence of 4-5% [86].

In comparative longitudinal studies conducted in Denmark, Belgium, and the Netherlands, it was stated that the intensity of contact with livestock was a major contributing factor for LA-MRSA transmission among members of the farmer family (Denmark 0%, Belgium 29%, and

the Netherlands 6%). The increased rate of LA-MRSA transmission observed among family members from Belgium appears to be related to country-specific differences in exposure to livestock [91]. Another study conducted in the Netherlands revealed that direct contact with livestock and breeders who have been infected with LA-MRSA is a major factor in the transmission of LA-MRSA transmission between members of the breeder family [92].

In the Netherlands, a national program to reduce the use of antibiotics in livestock began in 2010. In Germany a longitudinal study revealed that LA-MRSA colonization in farm animals, humans who are active in livestock pens occurred due to a 44% reduction in antibiotic use in livestock. Livestock is associated with decreased LA-MRSA prevalence in livestock and humans, regardless of farm animal contact [93]. In Taiwan, the results of isolation from pig nose swabs showed a higher prevalence of LA-MRSA ST9 on large-scale farms (34%) compared to those on small-scale farms (7%), this is reflected by the level of intensity of direct human contact with pigs, which in large-scale farms has a higher intensity (36.8%) than on small-scale farms (9.1%) [79].

LA-MRSA colonization was also observed from nasal swabs of slaughterhouse workers [64, 94], also in veterinarians in Germany [87, 95], and in veterinarians in Belgium [96], where the presence of a veterinarian is also a factor one of the main risk factors. Veterinarians' family members may also contract LA-MRSA [86, 97]. Sequencing of the whole genome map for LA-MRSA colonization among veterinary families suggests the possibility that LA-MRSA transmission may occur between humans [98]. In studies in conventional agriculture, LA-MRSA CC398 was not found in livestock and humans in German organic farms [99], and less frequently found in livestock in organic farming compared to conventional farms in the Netherlands [100]. It is extremely rare for LA-MRSA to spread among humans outside of farms, as was the case in a study in Germany which had a high density of pig farms in northwestern Germany [86].

But in addition, based on the results of screening for hospitalized patients, the prevalence of LA-MRSA in northwest Germany is much higher than in the rest of Germany [101]. This is consistent with a study conducted in the Netherlands, where livestock density was identified as a major risk factor for the transmission of LA-MRSA transmission [102].

Recent studies have shown LA-MRSA emissions in the air free of livestock pens and have been found in the air up to 350 meters above pens and as far as 500 meters above ground level of pens [103]. LA-MRSA has also been identified in livestock manure from chicken farms and has also been identified in soils treated with manure from livestock manure [104]. In this study, the appearance of LA-MRSA in stool samples in Austria is an interesting matter to be investigated [105]. It needs further explanation that humans who live in close proximity to conventional farms will be at risk of being infected with LA-MRSA. A study in Lower Saxony in Germany revealed that LA-MRSA colonization was found in about 1% of the humans living adjacent to the farm site [106].

In the results of an epidemiological study in Pennsylvania, United States, where cases of skin and soft tissue infections by LA-MRSA were more common in humans who lived near fields that were given manure. However, research in this sector is still limited due to the lack of data on the amount of LA-MRSA in livestock manure and human waste [107]. Whereas LA-MRSA which is identified in pets such as dogs and cats will have the potential for transmission to humans, therefore it is necessary to remember the importance of maintaining the cleanliness of the house and cage [108].

It can be assumed that human-to-human transmission of LA-MRSA CC398 transmission is rare. However, there are recent studies from Spain [109] and from Germany [110] regarding LA-MRSA infection in humans despite no history of contact with livestock. It was observed in

the Netherlands in 15% of all cases of LA-MRSA CC398 infection in some humans is all of these humans had no direct contact with cows and pigs [12].
Apart from animal-to-human, human-to-human, LA-MRSA environmental and transmission exposure, LA-MRSA strains can also be found in contaminated livestock meat products. This can be very risk in humans who are accustomed to eating livestock, a study in the Netherlands revealed that people who regularly consume poultry are at increased risk of being infected with LA-MRSA [111].

2.6 Infection of LA-MRSA

LA-MRSA CC398 has the same virulence potential as *Staphylococcus aureus* found in humans and is generally associated with the same clinical features. In hospital patients infected with LA-MRSA CC398 have symptoms of skin and soft tissue infections requiring surgical intervention. LA-MRSA infected patients are usually people who have direct contact with farm animals and frequently visit livestock pens. LA-MRSA CC398 represents about 13% of cases of severe skin and soft tissue infections resulting from being infected with LA-MRSA CC398 [112]. The incidence of LA-MRSA infection is rare in Germany so it is not known.

LA-MRSA CC398 infection can spread to the hospital through patients suffering from LA-MRSA CC398 infection who are in need of intensive care and patients who have LA-MRSA colonization of the nose. This spread of LA-MRSA can lead to nosocomial infections such as infection after joint arthroplasty, infection at the surgical site, septicemia, and ventilator-related pneumonia [14, 113]. A study of LA-MRSA CC398 colonization in the Brandenburg hospital, southern Germany, a region with a low livestock density, reported an LA-MRSA CC398 colonization of 0.08% of the 13,855 individuals studied [114]. In the Ems-Dollart region of the state of North Rhine Westphalia which has a high livestock density, the proportion of LA-MRSA CC398 among all MRSA strains identified in hospitalized patients (LA-MRSA CC398 detected 1.6% of all infected individuals studied) increased from 14% in 2008 to 23% in 2011.

Meanwhile, in line with the proportion of LA-MRSA CC398 among all identified MRSA types, there were cases of wound infection which increased from 7% in 2008 to 10% in 2011 [102]. The proportion of LA-MRSA CC398 among all MRSA strains that have been identified as having septicemia in this region is about 10%, while it is still substantially lower (1.8%) in all regions of North Rhine Westphalia [115], which corresponds to that proportion has been reported throughout Germany [112]. The proportion of LA-MRSA CC398 among all MRSA strains of infection and colonization in humans should be investigated in relation to overall MRSA prevalence. This is due to the possibility that there is a high prevalence of cases of LA-MRSA CC398 infection in countries that have a low prevalence of HA-MRSA, such as in the Netherlands of all the patients screened at admission to the hospital there were 9.7% positive MRSA of all individuals, of these positive MRSA numbers, it was found that 78% were LA-MRSA CC398 infection and 22% were non-LA-MRSA [116].

Human-to-human infection of LA-MRSA CC398 in the hospital is still rarely observed [117], because LA-MRSA CC398 infection is very rare in hospital compared to HA-MRSA infection [118]. LA-MRSA CC398 infection may occur in the hospital, as demonstrated in all genome sequencing-based phylogenetic analyzes for subclade obtained from environmental isolates and newborns in Scottish hospitals [119]. In cases of LA-MRSA CC398 infection requiring antibiotic therapy, the antibiotic resistance profile of LA-MRSA CC398 has varied resistance and sensitivity. Usually LA-MRSA CC398 is resistant to β-lactam antibiotics, glycosamides, macrolides, tetracyclines, streptogramin, and some fluoroquinolones and cotrimoxazole.

The LA-MRSA CC398 strain is still sensitive to glycopeptide antibiotics, tigecycline, daptomycin, fosfomycin and fusidic acid, and some exceptions to linezolid. Therapy using linezolid requires high awareness of the patient's health. In addition to ribosomal protein mutations and 23S rRNA, linezolid resistance can be transferred with plasmid activity storing the transferable cfr gene that mediates multi-resistance to linezolid, fenicol, lincosamides, and pleuromutilin by methylated by 23S rRNA in human medicine [120]. Thus, selective pressure that supports spread can be provided in treatment using linezolid in humans, as well as thiamulin and florfenicol in veterinary medicine [121].

The cfr gene was isolated for the first time in coagulase-negative Staphylococcus from livestock in Europe [122] and has recently been reported in China [123]. In general, linezolid resistance is still rare in staphylococcus coagulase (CNS) that infects humans [124], but a group of nosocomial infections in *Staphylococcus epidermidis* containing the cfr gene [125] has been reported. Only a single LA-MRSA CC398 isolate containing the cfr gene has been found in livestock in Europe [126], but cases of this infection are more frequently reported in China [123]. Linezolid resistance is still rare in MRSA isolated from humans [127]. There has only been one report of a human isolate resistant to linezolid, apart from the emergence of a HA-MRSA epidemic containing the cfr gene in a Madrid hospital [128].

2.7 Rapid clinical detection of LA-MRSA

Rapid detection of LA-MRSA tests can be performed with a nasal swab, it is very important to adequately identify individuals who have been infected with LA-MRSA and can be given appropriate infection control immediately. In addition, the rapid detection of LA-MRSA examination from clinical samples of patients can also help optimize the care of patients who have been infected with LA-MRSA. The clinical problem that often occurs is that patients experience sepsis and are found to have clustered Gram-positive cocci in the blood (GPCCL). It is likely the highly pathogenic organism *Staphylococcus aureus* or Staphylococcus coagulase (CNS). CNS contributes 60% -80% [129, 130] of GPCCL isolates in blood and prosthetic materials, contamination that occurs in blood is usually initiated by LA-MRSA colonization through the surface of the injured skin. With this, it is necessary to have high accuracy in rapid detection to differentiate CNS and *Staphylococcus aureus* [130].

After it was confirmed that *Staphylococcus aureus* was found, there were still further clinical problems whether this was MSSA or MRSA. These patients are usually given broad-spectrum antibiotic therapy until the susceptibility of new organisms is fully established 24 hours later after antibiotic administration. If the doctor gives empiric antibiotics for MSSA to a patient infected with LA-MRSA, there will be an increased risk of death in the patient, and vice versa. A number of studies have revealed that antimicrobials that target LA-MRSA infection, such as vancomycin, produce sustained bacteremia and a higher risk of death than β-lactams used to treat MSSA therapy, such as cloxacillin [131].

In one retrospective study looking at MSSA bacteremia in drug users, the risk of death was 39.4% in vancomycin-treated patients, but only 11.4% in flucloxacillin-treated patients. In the subgroup of patients treated with vancomycin for 48 hours to wait for outcome susceptibility occurred a mortality of 40%, of which incidence suggests that empiric antibiotic treatment had a major impact on clinical outcome [132]. Because it is necessary to do a quick detection to distinguish MSSA and MRSA with a high degree of accuracy.

Several prospective studies have been conducted to analyze the usefulness of rapid diagnostic tests for the detection of LA-MRSA and its impact on antibiotic prescribing. Implementation of rapid diagnostic testing will result in timely, effective therapy, significantly reducing hospital costs and length of stay [133, 134]. In comparison, the adjustment time

referred to as a turnaround time (TAT) on the BD GeneOhm™ StaphSR Assay was 13.2-21.6 hours shorter than chromogenic media, namely 46.2-79.2 hours in detecting LA-MRSA [135]. Rapid detection of LA-MRSA resulted in a 21% reduction in overall patients treated with anti-MRSA antibiotics.

On the other hand, among patients with negative blood culture (BC) for *Staphylococcus aureus*, the mean duration of antibiotic therapy was reduced from 19.7 hours to 12.2 hours and there was a reduction in the mean 6.2 days of hospital stay in patient's hospital. In the implementation of rapid molecular detection, the optimal treatment time would decrease to 44.6-38.4 hours among patients with the MSSA bacteremia [136, 137]. With this, the rapid detection of LA-MRSA will have a direct impact on infection control and patient care.

2.8 Molecular detection of LA-MRSA

LA-MRSA CC398 is encoded by the *mec*A and *mec*C coding genes located on the mobile genetic element of the *mec* cassette chromosome chromosome (SCC*mec*). To date, there are at least 11 types of SCC*mec* (I-IX) and are accompanied by many subtypes (IVa, IVb, IVc, IVd, IVg, and IVh) in the LA-MRSA CC398 strain [138, 139]. Molecular detection of LA-MRSA requires target-specific detection of *Staphylococcus aureus* with the *nuc*, *gyr*B, or Staphylococcus A protein gene, coupled with the identification of LA-MRSA with the genes encoding *fem*A, *mec*A, *mec*C, or SSC*mec*-orfX [140-143]. So those different kits are needed in molecular detection of LA-MRSA CC398 using polymerase chain reaction (PCR). However, the emergence of the *mec* variant on LA-MRSA CC398 suggests that the specific target for the detection of LA-MRSA CC398 needs to be continuously re-evaluated.

2.9 Public Health Consequences of LA-MRSA

Humans who have had direct contact with LA-MRSA positive animals will have a higher risk of contracting LA-MRSA. It has also been reported in humans who work in horse stables, veterinary clinics, and livestock environments [71]. It has been reported that LA-MRSA CC398 has limited host specificity, however this strain can colonize and cause cases of infection in multiple hosts. To date, the mechanism of host adaptation to LA-MRSA CC398 infection is poorly known [144]. It is of concern that LA-MRSA CC398 infection can cause infection and serious (invasive) outbreaks [145].

There is a potential risk of introducing LA-MRSA CC398 from livestock as a reservoir to the hospital via humans as a vector. Therefore, in the Netherlands, cattle and hog farmers are classified as a risk group as defined by the "Search and Destroy" policy. As a result, the number of patients admitted to hospital with suspected LA-MRSA CC398 colonization and requiring MRSA screening has increased in the Netherlands. This is a major problem for the health care system in hospitals [146].

Identification of factors and knowledge of LA-MRSA CC398 infecting humans is very important in the success of the "Search and Destroy" policy. A proper understanding of the mechanisms underlying the transmission and exposure of LA-MRSA CC398 in livestock and humans can have a significant impact on antibiotic therapy policy and infection control in the hospital. It also provides information for evidence-based guidance regarding the development of new measures and strategies for the control and prevention of LA-MRSA CC398 infection [147].

2.10 Treatment of LA-MRSA

The emergence of methicillin resistance was accompanied by the development of resistance of *Staphylococcus aureus* to most of the non-β-lactam antibiotics and led to reduced options for treating cases of infection caused by LA-MRSA CC398. In the 1980s, several LA-MRSA strains were resistant to all available antibiotics except vancomycin [148, 149]. This situation was exacerbated by the emergence of strains of *Staphylococcus aureus* which became insensitive to vancomycin in the late 1990s [150], along with vancomycin-resistant strains of *Staphylococcus aureus* (MIC: ≥32 mg / L) in the United States and other countries [149].

Vancomycin-resistant *Staphylococcus aureus* may acquire the *van*A gene complex from vancomycin-resistant enterococci, whereas vancomycin-resistant *Staphylococcus aureus* intermediate is due to the thickening of the bacterial cell wall and is able to bind vancomycin thereby reducing diffusion into cells [151]. This development led to the selection of new antibiotic alternatives that have activity against LA-MRSA CC398. Furthermore, several other antibiotics such as linezolid, telavancin, daptomycin, tedizoid, dalbavancin, oritavancin, ceftobiprole, and ceftaroline have been developed and approved for clinical treatment.

2.11 Prevention of LA-MRSA infection

The number of pathogenic bacteria that are resistant to several antibiotics such as LA-MRSA CC398 continues to increase globally in health care facilities and in the community [152]. The emergence of multi-antibiotic resistant strains of LA-MRSA has reduced options for treatment caused by LA-MRSA infection. From this incident, research and discovery of antibacterial agents were carried out to overcome these problems.

However, the multi-antibiotic resistant LA-MRSA strains have wide variations in their temporal and geographic distribution. LA-MRSA strains resistant to multiple antibiotics also vary in their virulence and epidemic capacity. The factors that mediate the transmission of transmission in health care facilities are not well known. On the other hand, there is a serious threat if there is resistance to newly developed antimicrobial agents, therefore it is necessary to implement other methods to limit the spread of pathogens that are resistant to various antibiotics. Some of the strategic steps taken are active surveillance of resistant LA-MRSA pathogens, supervision of antibiotic therapy, and better infection control methods [152].

Infection prevention measures will reduce the risk of transmission of multi-antibiotic resistant LA-MRSA in health care settings [153] and reduce the medical costs incurred by LA-MRSA infection [154]. Interventions that need to be taken to prevent LA-MRSA transmission and infection include screening, contact isolation, hand hygiene, cohorts, and decolonization as additional standard precautions. This procedure should be continued until the patient is tested negative for LA-MRSA which is resistant to various antibiotics.

3 Conclusion

LA-MRSA has been identified in livestock, mostly in cattle and pigs. However, other animals such as poultry and domestic animals are infected with LA-MRSA, because this strain can be transmitted to other animal species and humans. Like other pathogenic bacteria, LA-MRSA can adapt to new hosts and produce toxins. It has been identified that the most common LA-MRSA clone complex is CC398. It has been reported that humans who have had direct contact with LA-MRSA positive livestock are at risk of being infected with LA-MRSA. Monitoring of frequent cases of LA-MRSA infection in livestock and humans is necessary to

observe changes in the epidemiology and to determine strategies for effective LA-MRSA infection control measures.

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