Annals of Clinical Case Studies

ISSN: 2688-1241

Review Article

Characterization of Methicillin-Resistant *Staphylococcus Aureus* (MRSA): Biochemical and Molecular Aspects

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Abstract

Methicillin-Resistant *Staphylococcus Aureus* (MRSA) has emerged as a significant concern in ruminant health, with far-reaching implications for animal welfare, food safety, and human health. The misuse and overuse of antimicrobials in veterinary medicine have accelerated the evolution of MRSA, rendering traditional treatment options ineffective. MRSA colonization and infection in ruminants can lead to various clinical manifestations, resulting in significant economic losses and posing a risk to human health. Effective control and prevention strategies require a multifaceted approach, including improved hygiene and biosecurity, reduced antimicrobial use, and vaccination. Understanding the epidemiology, transmission, and risk factors associated with MRSA in ruminants is essential for developing targeted interventions. Further research is needed to develop effective vaccines, diagnostics, and control measures to combat MRSA infections in ruminants.

Keywords: Methicillin-resistant *Staphylococcus Aureus* (MRSA); Ruminants; Antimicrobial; Resistance; Zoonotic

Introduction

Methicillin-Resistant *S. Aureus* (MRSA) has emerged as a significant concern in ruminant health, with far-reaching implications for animal welfare, food safety, and human health [1]. MRSA is a zoonotic pathogen, meaning it can be transmitted between animals and humans, and has been detected in various animal species, including ruminants such as cattle, sheep, and goats. The emergence of MRSA in ruminants is attributed to the misuse and overuse of antimicrobials in veterinary medicine, leading to the selection and dissemination of resistant bacterial populations. The widespread use of antimicrobials in agriculture has accelerated the evolution of MRSA, rendering traditional treatment options ineffective. MRSA colonization and infection in ruminants can lead to various clinical manifestations, including mastitis, skin infections, respiratory tract infections, and surgical site infections. These infections can result in significant economic losses for farmers and animal producers due to reduced productivity, increased morbidity, and mortality. Furthermore, MRSA in ruminants poses a risk to human health, as it can be transmitted through direct contact with infected animals or contaminated animal products. Human exposure to MRSA can lead to severe infections, particularly in immunocompromised individuals. The transmission of MRSA between ruminants and humans is a significant concern, as it can occur through various routes, including direct contact, contaminated feed and water, and veterinary equipment [2]. Furthermore, the sharing of antimicrobial resistance genes between bacteria can accelerate the spread of MRSA.

The prevalence of MRSA in ruminants varies globally, with reports ranging from 0.5% to 20.6% in cattle and 1.4% to 15.6% in sheep. The disparity in prevalence rates highlights the need for enhanced surveillance and monitoring programs to detect MRSA in ruminant populations. Early detection and diagnosis of MRSA in ruminants are crucial for effective management and prevention of infections. Traditional diagnostic methods, such as bacterial culture and susceptibility testing, are time-consuming and may not detect all MRSA strains. Molecular diagnostic techniques, such as PCR and whole-genome sequencing, offer improved sensitivity and specificity for MRSA detection. Effective control and prevention strategies for MRSA in ruminants require a multifaceted approach, including improved hygiene and biosecurity, reduced antimicrobial use, and vaccination [1]. Understanding the epidemiology, transmission, and risk factors associated with MRSA in ruminants is essential for developing targeted interventions. The development of effective vaccines against MRSA is a promising approach for preventing infections in ruminants [3]. Several vaccine candidates are in various stages of development, including those targeting surface proteins, toxins, and capsular polysaccharides.

In addition to vaccination, other control measures such as improved hygiene and biosecurity, reduced antimicrobial use, and enhanced surveillance and monitoring programs are essential for mitigating the spread of MRSA in ruminants. Understanding the molecular mechanisms of MRSA pathogenesis and transmission is crucial for developing effective control strategies. Recent studies have identified several virulence factors, including adhesins, toxins, and immune evasion molecules, that contribute to MRSA's ability to

Citation: Verma RK, Jaiswal S, Saurabh. Characterization of Methicillin-Resistant *Staphylococcus Aureus* (MRSA): Biochemical and Molecular Aspects. Ann Clin Case Stud. 2024; 6(2): 1098.

Publisher Name: Medtext Publications LLC

Published date: Oct 08th, 2024

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colonize and infect ruminants [4]. The role of the environment in the transmission and persistence of MRSA in ruminant populations is also an important area of research. Studies have shown that MRSA can survive on surfaces, in water, and in soil, highlighting the need for effective cleaning and disinfection protocols. In conclusion, MRSA in ruminants is a complex and multifaceted issue that requires a comprehensive approach to control and prevention. Further research is needed to understand the epidemiology, transmission, and pathogenesis of MRSA in ruminants, as well as to develop effective vaccines, diagnostics, and control measures. The economic impact of MRSA in ruminants is significant, with estimated losses in the billions of dollars annually. The costs associated with MRSA infections in ruminants include reduced productivity and milk yield, increased morbidity and mortality, veterinary care and treatment costs, losses due to carcass condemnation, and costs associated with implementing control measures. Understanding the economic impact of MRSA in ruminants is essential for developing effective control strategies and allocating resources. In addition to the economic impact, MRSA in ruminants also has significant animal welfare implications.

Historical Overview

Alexander Fleming's discovery of penicillin in 1928 marked a breakthrough in modern medicine, ushering in the antibiotic era and significantly reducing the mortality and morbidity caused by bacterial infections. However, the widespread use of penicillin soon led to the emergence of resistant strains of bacteria. By the early 1940s, penicillin resistance in *S. Aureus* had already been reported. To counter this growing issue, methicillin, a semi-synthetic beta-lactam antibiotic, was developed in 1959 to target penicillin-resistant S. aureus strains by binding to and inhibiting the bacterial enzyme Penicillin-Binding Protein (PBP).

Despite its initial success, Methicillin-Resistant *S. Aureus* (MRSA) emerged just two years later in the UK [5]. This early detection of resistance marked the beginning of an ongoing battle against MRSA, which rapidly became a significant pathogen in healthcare settings, causing hospital-acquired infections (HA-MRSA). HA-MRSA is typically associated with severe infections such as bloodstream infections, pneumonia, and surgical site infections in patients with prolonged hospital stays or those with weakened immune systems [6]. The adaptive ability of MRSA, particularly through the acquisition of the mecA gene, which encodes for an altered penicillin-binding protein (PBP2a) that methicillin cannot effectively inhibit, enabled it to become resistant not only to methicillin but to other beta-lactam antibiotics as well.

By the late 1990s and early 2000s, MRSA had spread beyond hospitals, leading to the identification of community-associated MRSA (CA-MRSA) strains. Unlike HA-MRSA, CA-MRSA infections occur in otherwise healthy individuals without recent healthcare exposure and are commonly associated with skin and soft tissue infections [7]. CA-MRSA strains tend to carry different genetic markers, such as the smaller staphylococcal cassette chromosome mec (SCCmec) type IV, and are often more virulent, producing toxins like Panton-Valentine Leukocidin (PVL), which is linked to necrotizing pneumonia and severe skin infections [3].

In the early 2000s, another lineage of MRSA, known as livestock-associated MRSA (LA-MRSA), was identified, highlighting the zoonotic potential of the bacterium [2]. Were among the first to report the transmission of LA-MRSA between livestock, particularly pigs, and humans. This strain, typically associated with *S. Aureus* Sequence Type (ST) 398, has since been found in various livestock species, including cattle and poultry [8]. LA-MRSA poses a dual threat: it can spread from animals to humans through direct contact or consumption of contaminated food products, and it may act as a reservoir for resistance genes that can be transferred to other bacterial populations.

The emergence of LA-MRSA has raised concerns regarding antimicrobial use in livestock, particularly the routine use of antibiotics for growth promotion and disease prevention, which is thought to contribute to the selection of resistant bacteria. Additionally, LA-MRSA underscores the importance of a One Health approach, as the interconnection between human, animal, and environmental health has become increasingly evident. Effective control measures must address antimicrobial stewardship in both human medicine and veterinary practices to curb the spread of resistant strains.

The epidemiology of MRSA continues to evolve, with new strains and resistance mechanisms being identified. The global spread of MRSA and its ability to adapt to different environments, including healthcare, community, and livestock settings, underscores the complexity of controlling this pathogen. Continued surveillance, research, and the development of novel antimicrobial agents or vaccines are essential to combat MRSA infections effectively [1].

Biochemical Characterization of MRSA

Beta-Lactam resistance

MRSA, or methicillin-resistant *S. Aureus*, is able to resist a group of antibiotics called beta-lactams, which includes methicillin and penicillin. The key to this resistance is a special protein called PBP2a (penicillin-binding protein 2a). Normally, antibiotics work by targeting proteins that help bacteria build their cell walls. However, PBP2a has a very low attraction for beta-lactam antibiotics, meaning these drugs can't easily bind to it. This protein allows MRSA to keep building its cell wall even in the presence of antibiotics, making the bacteria difficult to kill. The gene that produces PBP2a is called mecA, and it is located on a mobile piece of DNA known as the staphylococcal cassette chromosome mec (SCCmec) [9].

The mecA gene, and the PBP2a protein it encodes, allow MRSA to survive in the presence of methicillin and other similar antibiotics by bypassing the usual pathways that these drugs block. This ability to keep building the bacterial cell wall even when beta-lactam antibiotics are present is what makes MRSA infections so challenging to treat [10].

In addition to the mecA gene, MRSA has another mechanism that boosts its resistance: the production of beta-lactamase. Beta-lactamase is an enzyme that breaks down the beta-lactam ring, a critical structure in beta-lactam antibiotics, which makes the drugs ineffective. The production of this enzyme is controlled by the blaZ gene, which is part of a system regulated by the blaR1 sensor and the blaI repressor [11]. When beta-lactam antibiotics are present, the blaR1 sensor detects them, which in turn triggers the production of beta-lactamase by turning off the blaI repressor. This enzyme then breaks apart the antibiotics, allowing the bacteria to survive even more effectively.

Over the years, these mechanisms have allowed MRSA to become one of the most resistant bacteria to beta-lactam antibiotics, making infections difficult to treat, especially in healthcare settings. The combination of the mecA gene for PBP2a and the blaZ gene for beta-

lactamase production makes MRSA highly resistant to a wide range of commonly used antibiotics.

Biofilm formation

Another important feature of MRSA is its ability to form biofilms, which makes it even harder to treat. A biofilm is a community of bacteria that stick together and produce a protective coating, called an extracellular polymeric matrix. This coating shields the bacteria from antibiotics and the body's immune system. The sticky substance that helps form this shield is mostly made up of a material called Polysaccharide Intercellular Adhesin (PIA), and the production of PIA is controlled by a set of genes known as the icaADBC operon [12].

In addition to the icaADBC operon, MRSA biofilm formation is regulated by another system called the Accessory Gene Regulator (agr), which controls the production of surface proteins and toxins. These surface proteins help the bacteria attach to surfaces like medical devices (catheters or prosthetic joints), while the toxins can damage tissues [13].

Biofilms are especially problematic because they can form on medical devices used in hospitals, such as catheters, heart valves, and artificial joints. Once MRSA forms a biofilm on these surfaces, it becomes much harder to eliminate, leading to chronic and persistent infections. Antibiotics often can't penetrate the biofilm properly, and the bacteria inside the biofilm can become dormant, further reducing the effectiveness of treatment [14].

This biofilm-based resistance means that infections involving biofilms can last much longer and require more aggressive treatment or even the removal of infected medical devices.

Toxin production

MRSA produces various toxins that make it more dangerous and harmful to the body. One of the most well-known toxins is Panton-Valentine Leukocidin (PVL), which is produced by certain community-acquired MRSA (CA-MRSA) strains. PVL is linked to serious skin infections, like boils and abscesses, as well as a deadly lung infection called necrotizing pneumonia. PVL works by attacking and destroying white blood cells, which are important for fighting infections. This damage causes inflammation and the death of tissue in the infected area [15]. In addition to PVL, MRSA also produces other toxins that contribute to its harmful effects. One such toxin is toxic shock syndrome toxin-1 (TSST-1), which is responsible for causing toxic shock syndrome. TSST-1 acts as a superantigen, meaning it can overstimulate the immune system, leading to an extreme release of inflammatory molecules called cytokines. This massive cytokine release can cause widespread inflammation and damage to organs [16].

Another group of toxins produced by MRSA are the staphylococcal enterotoxins, which are linked to food poisoning. These toxins can cause nausea, vomiting, and diarrhea when contaminated food is consumed [17]. In simpler terms, MRSA's toxins not only destroy cells but also trigger excessive immune responses that can cause serious illnesses, making it a particularly dangerous pathogen.

Enzyme production

MRSA (Methicillin-resistant *S. Aureus*) produces enzymes that help it invade tissues and avoid being destroyed by the immune system. These enzymes play an important role in making the infection more severe and harder to treat. Proteases, like serine and cysteine proteases, are enzymes that break down proteins in the body. This allows MRSA to damage tissues and spread more easily. In addition, these enzymes destroy important proteins in the immune system, making it harder for the body to fight off the infection [18].

Lipases are another type of enzyme that breaks down fats and oils. These enzymes help MRSA grow in oily parts of the skin, such as near the sebaceous glands (oil-producing areas). By breaking down these fats, MRSA can stick to the skin and avoid being removed [18]. In simple terms, MRSA uses these enzymes to break down the body's natural defenses, allowing the infection to spread and making it more difficult for the immune system to fight back.

Molecular Characterization of MRSA

Molecular characterization of MRSA is essential to understand its epidemiology and the genetic basis of its antibiotic resistance and virulence. Key molecular techniques include SCCmec typing, multi-locus sequence typing (MLST), Pulsed-Field Gel Electrophoresis (PFGE), and Whole-Genome Sequencing (WGS).

SCCmec typing

The SCCmec element carries the mecA gene and other antibiotic resistance genes. It has been classified into 13 types (I to XIII), with types I, II, and III commonly associated with healthcare-associated MRSA (HA-MRSA), while types IV and V are more frequent in community-associated MRSA (CA-MRSA) (IWG-SCC, 2009). SCCmec typing provides valuable insights into the epidemiology and spread of MRSA strains.

Multi-Locus Sequence Typing (MLST)

MLST is used to analyze the sequences of seven housekeeping genes to classify MRSA into distinct Sequence Types (STs). This method has revealed that MRSA strains belong to a few major Clonal Complexes (CCs), such as CC5, CC8, CC22, CC30, and CC45 [19]. These clonal complexes are responsible for the majority of MRSA infections worldwide.

Pulsed-Field Gel Electrophoresis (PFGE)

PFGE is another molecular typing technique used to differentiate MRSA strains based on the pattern of DNA fragments produced by restriction enzyme digestion [20]. PFGE has been widely applied in outbreak investigations to track the spread of MRSA strains in healthcare settings.

Whole Genome Sequencing (WGS)

WGS has emerged as a powerful tool for studying MRSA at the genome level, allowing for the identification of novel resistance mechanisms, virulence factors, and the evolutionary history of MRSA strains [21]. WGS has also been instrumental in tracking the spread of MRSA between humans and livestock [8].

mecA and mecC Genes

While mecA is the primary determinant of methicillin resistance in MRSA, the mecC gene, a homologue of mecA, was discovered in 2011. MecC encodes a variant of PBP2a and has been found in both humans and animals, particularly in rural areas [22]. This discovery underscores the importance of ongoing surveillance to detect emerging resistance mechanisms.

Epidemiology of MRSA

MRSA infections are categorized into three major groups based on the setting in which they occur: healthcare-associated MRSA (HA-

MRSA), community-associated MRSA (CA-MRSA), and livestock-associated MRSA (LA-MRSA).

Healthcare-Associated MRSA (HA-MRSA)

HA-MRSA primarily affects patients in hospitals or long-term care facilities. These strains are often multidrug-resistant and are associated with serious infections such as pneumonia, bloodstream infections, and surgical site infections [23]. HA-MRSA strains carry large SCCmec elements and are more resistant to antibiotics than CA-MRSA strains.

Community-Associated MRSA (CA-MRSA)

CA-MRSA infections occur in otherwise healthy individuals with no recent healthcare exposure. These strains are often associated with skin and soft tissue infections and are typically more virulent but less resistant to antibiotics than HA-MRSA. CA-MRSA strains frequently carry smaller SCCmec elements (types IV and V) and often produce PVL [24]. Outbreaks of CA-MRSA have been reported in schools, military barracks, and sports teams [6].

Livestock-Associated MRSA (LA-MRSA)

LA-MRSA has emerged as a significant public health concern, particularly in Europe, where it was first identified in pigs [2]. LA-MRSA strains, such as ST398, have been found in various livestock species and have the potential to be transmitted to humans through direct contact [8]. The zoonotic transmission of LA-MRSA raises concerns about the use of antibiotics in agriculture and the spread of antibiotic resistance [1].

Virulence Factors of MRSA

MRSA possesses numerous virulence factors, including surface adhesins, exotoxins, and immune evasion proteins, which allow it to colonize host tissues, evade the immune system, and cause disease.

Surface adhesins

Surface adhesins such as Fibronectin-Binding Proteins (FnBPs), Clumping Factors (ClfA and ClfB), and collagen-binding protein (Cna) mediate the attachment of MRSA to host tissues and medical devices [4]. Adhesins are critical for the establishment of infections such as endocarditis and osteomyelitis [25].

Exotoxins

Exotoxins such as PVL, TSST-1, and staphylococcal enterotoxins contribute to the pathogenicity of MRSA. PVL, in particular, is associated with necrotizing pneumonia and severe skin infections [15]. TSST-1, a superantigen, can cause toxic shock syndrome by inducing a massive immune response [16].

Immune evasion mechanisms

MRSA evades the host immune system through the production of protein A (SpA), which binds to the Fc region of immunoglobulin G (IgG), preventing opsonization and phagocytosis [26]. Additionally, MRSA produces staphylokinase, which activates plasminogen to degrade fibrin clots and complement proteins, facilitating immune evasion and tissue invasion [18].

Treatment and Control of MRSA

The treatment of MRSA infections is complicated by the pathogen's resistance to multiple antibiotics. Vancomycin has been the mainstay of treatment for severe MRSA infections, but the emergence of vancomycin-intermediate (VISA) and Vancomycin-Resistant (VRSA) strains has necessitated the use of alternative therapies [27].

Antibiotic treatment

While vancomycin remains effective against many MRSA strains, newer antibiotics such as linezolid, daptomycin, and ceftaroline have been developed to treat MRSA infections. Linezolid inhibits bacterial protein synthesis, daptomycin disrupts the bacterial cell membrane, and ceftaroline binds to PBP2a to inhibit cell wall synthesis [27,28].

Infection control measures

Infection control measures such as hand hygiene, environmental cleaning, and the use of Personal Protective Equipment (PPE) are critical in preventing the spread of MRSA in healthcare settings [29,30]. In community settings, education on hygiene and wound care can help prevent the transmission of CA-MRSA [6].

Conclusion

Methicillin-Resistant *S. Aureus* (MRSA) remains a major public health threat due to its antibiotic resistance and ability to cause a wide range of infections. Understanding the biochemical and molecular characteristics of MRSA is essential for developing effective treatment and control strategies. Molecular tools such as SCCmec typing, MLST, PFGE, and WGS have provided valuable insights into the epidemiology and evolution of MRSA. The emergence of novel resistance mechanisms, such as mecC, underscores the importance of ongoing surveillance and research to combat the global spread of MRSA.

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