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Review Article

Staphylococcus aureus Resistance against Methicillin in Pets: a Review

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Abstract

Present review was carried out in order to explore the geographical distribution, prevalence and resistance mechanism of Staphylococcus aureus against methicillin worldwide. Study indicated that Staphylococcus aureus infections in pets are a common problem worldwide. Countries where antibiotics like methicillin is frequently misused, resistance has developed in the host. Resultantly antimicrobial therapy fails. Further, Staphylococcus aureus resistant to methicillin (SARM) possess a gene mec-A which play key role in the resistance mechanism. These genes have code sequencing GAT GAA ATG ACT GAA CGTCCG ATTA and CAA ATT CCA CATTGT TTC GGT CTAA. However, using PCR this organism can easily detected. The mecA gene is responsible for resistance to methicillin and encoding the low-affinity penicillin-binding protein (PBP 2). Researchers also reported that dogs are more infected with Methicillin Resistant Staphylococcus aureus (MRSA) compared to cats. Human can significantly be infected when by contact with MRSA infected pet. In conclusion, MRSA is a common threat to the pets including cats and dogs throughout the globe and antibiotics misuse is the major reason for that.

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INTRODUCTION

Antibiotics are a group of medicines that are used to treat the infections caused by microbes. Antibiotics have always been considered one of the wonder discoveries of the 20th century but the real wonder is the rise of antibiotics resistance in the pets at the hospitals and environmental concomitant [1]. Methicillin is a narrow-spectrum β-lactam antibiotic of the penicillin group. It acts by inhibiting the synthesis of bacterial cell wall and inhibiting cross-linkage between the linear peptidoglycan polymer chains by binding to and competitively inhibiting the transpeptidase enzyme. This enzyme is also known as Penicillin Binding Proteinase (PBPs) [2]. Methicillin is actually pencillinase-resistant β-lactam antibiotic. Penicillinase is a bacterial enzyme produced by bacteria resistant to β-lactam antibiotics. This enzyme hydrolyzes the antibiotic and render it nonfunctional [3].

Antimicrobial resistance has been a significant problem in veterinary medicine. Resistance has developed due to several factors, however one of the most important cause is the misuse of antibiotics due to the risk of zoonotic transmission [4]. Methicillin resistant *S aureus* (MRSA) is an emerging nosocomial pathogen all over the world. Many recent reports showed that MRSA is becoming an emerging issue in the veterinary medicine mostly in in the pets [5]. In 1972 first case of MRSA was detected in the cow's milk with mastitis [6]. Staphylococcal infections are frequently treated with antibiotics and thus antibiotics acquired resistance has developed [6]. Pets like cats and dogs are in direct contact with large proportion of human population thus there is the potential for transfer of bacteria or resistance genes between pets and humans. Pets can acquire MRSA from humans and can act as potential reservoir for human MRSA infection [7]. Uses of veterinary drugs and intravenous catheters have been identified as main risk factors for MRSA infections in dogs [8]. Dogs having post-operative or wound related MRSA infection, can cause infection in the whole animal as well as human, such as inflammation of bones, rashes, and septicemia and mange etc [9]. Keeping in view these all facts present review was planned, whereby the main objective of study was to explore the worldwide geographical distribution, prevalence and resistance mechanism of *Staphylococcus aureus* against methicillin in pets. Results so obtained will be anticipated for providing useful information to the veterinary field as well as human clinicians about the prevalence of methicillin resistant strains of *S aureus* and recommend the preventive strategies.

Epidemiology of Methicillin Resistant *Staphylococcus aureus* (MRSA)

Recent reports suggested that livestock veterinarians compared to small animal veterinarians have significantly greater prevalence of MRSA colonization [10,11]. In North America MRSA was investigated in horses, dogs, and cats [12,13] MRSA is frequently colonized in companion animals such as cats, dogs and horses and cause variety of infections [14,15]. In a study, few scientists reported prevalence of MRSA among dogs in United Kingdome. They reported 2.3 to 9% infection in overall population of dogs [16]. Some other researchers reported the prevalence of MRSA among dogs in Canada. They indicated overall 20% outbreak of MRSA among dogs in Canada [17]. Further, in the

Canada MRSA infection was also isolated from bedbugs [18]. In the Netherlands it was reported that pig farmers were 760 times more affected with MRSA compared to other human population [19]. In the mid-1990s, the first reported cases of communities associated to methicillin resistant Saureus began to appear in Australia, New Zealand, United Kingdom, United States, France, Finland, Samoa and Canada. The cases were famous because MRSA infection was concerned with such peoples who had not been exposed to any healthcare setting before [20].

In another research, few scientists reported dairy cattle herd and bovine milk containing MRSA is frequently increasingly worldwide. The majority of strains are belonging to (ST) 398 with low prevalence [21] MRSA lineages isolated from companion animals generally matched the dominant lineages found in the same geographical area in the human populations in North America. In North America CA-MRSA has been found to be most prevalent. It is interesting to note that CA-MRSA was first reported among dogs in the Canada and later it became prevalent in the North America. This strain has been identified as particular cause of soft tissue and skin infections in dogs [22].

Staphylococcus areus Resistance against Methicillin

Methicillin is a β-lactam antibiotic. It is earliest semisynthetic penicillase resistant antibiotic that acts by inhibiting penicillin-binding proteins (PBPs). Methicillin is involved in the synthesis of peptidoglycan that surrounds the cell as a necessary mesh like polymer. Methicillin and other β-lactam antibiotic are resisted by *S aureus* through the expression of a foreign PBP and PBP2a [23]. Resistance against methicillin was first observed in 1960. During that time pets though were under intensive care in the hospitals were used to suffer from methicillin resistance. Afterward methicillin resistance was started to appear in the local pet population. However, currently methicillin resistance has been a common problem worldwide in the local pet population [24]. The mecA gene is the part of a mobile genetic element responsible for methicillin resistance. It is found in all MRSA strains [25]. Further, penicillin is another related class of antimicrobial drugs used in both human and animal medicine for diversity of dissimilar diseased condition [26]. Penicillin has been reported to exhibit resistance to all Staphylococci strains. Zoonotic infections have been caused by Methicillin-Resistant *S aureus* and *S intermedius* strains in humans [27]. It is because penicillin and its derivatives with methicillin have are frequently used to treat the infections caused by *S aureus* [28]. A gene namely mecA encodes for penicillin binding protein (PBP2A) and is responsible for the development of resistance against methicillin (Figure 1) [29].

Methicillin-Resistant *S aureus* (MRSA) possess mec-A gene and that is transferred horizontally from unknown bacterial species. Some other familiar resistant *S aureus* strains include Oxacillin-Resistant S aureus (ORSA) and Multiple-Resistant *S aureus* [30]. In a study resistance potential of *S aureus* against methicillin was assessed in contrast to some other antibiotics such as gentamycin, tetracycline, sulphamethoxazol, optochin, erythromycin, neomycin, streptomycin. It was found that the growth of *S aureus* was significantly less sensitive to the methicillin group of antibiotics compared to other antibiotics (Figure 2). Due this resistance ability, MRSA is the most repeatedly encountered bacteria among the pet animals. Severity of MRSA infections range from mild to fatal [31]. *S aureus* (including MRSA strains) are facultative aerobic, cluster forming, gram positive cocci with essential ability to ferment carbohydrates, producing deep yellow to white pigmentation on solid culture media (Figures 1-3) [32]. Methicillin-resistant *S aureus* (MRSA) is a significant pathogen causing community-onset and nosocomial infections, play major role in endemic and epidemic [33].

The range of MRSA infection is not limited to human medicine, but also in Veterinary Medicine. There is evidence of MRSA transmission between animals-to-humans and human-to-animals [34] Thus, there are high chances of human infections from MRSA infected animals. Dogs are more infected with MRSA compared to cats [34]. Large stables and post-operative complications were reported in most cases and outbreak of MRSA infections [35]. MRSA that is acquired in a hospital or health care setting is called Healthcare-Associated Methicillin-Resistant *S aureus* (HA-

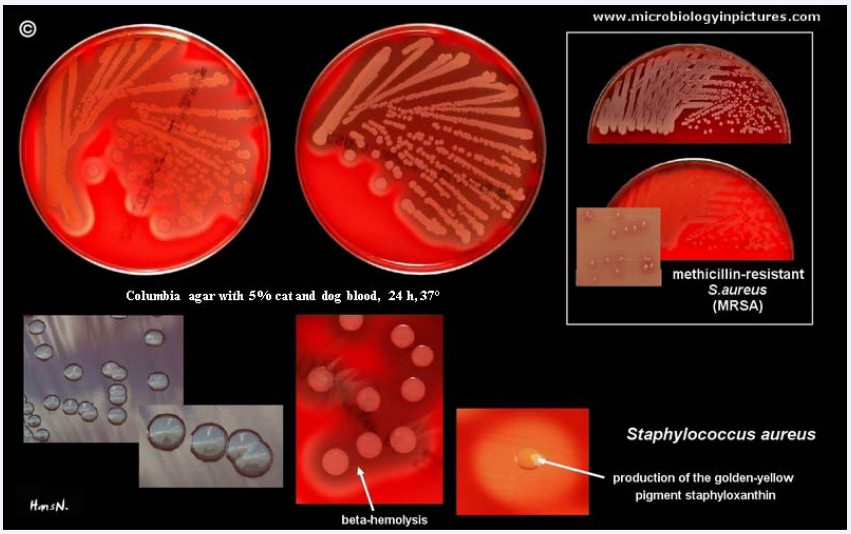

Figure 1 Resistance of *Staphylococcus aureus* against methicillin.

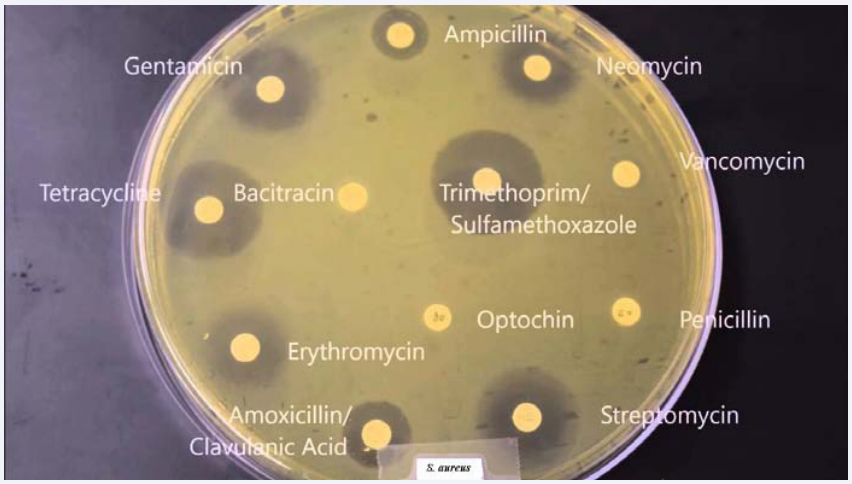

Figure 2 Sensitivity of *Staphylococcus aureus* against methicillin compared to other antibiotics.

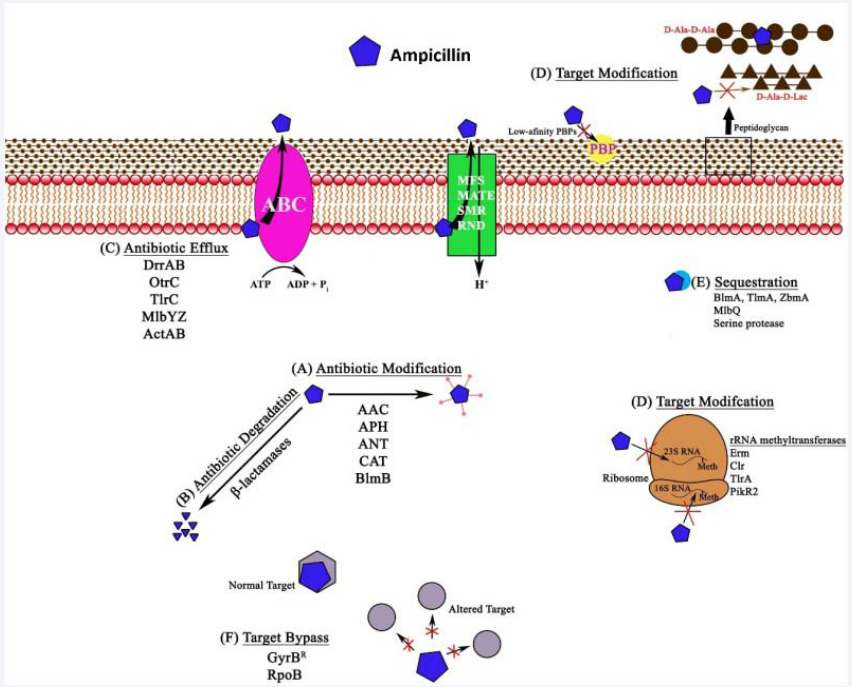

Figure 3 Resistance mechanism of *Staphylococcus aureus* against ampicillin.

MRSA). MRSA causes an infection, when methicillin and other antibiotics do not kill the bacteria, as a result it becomes hardest to treat the infection [36]. Further, MRSA has emerged as one of the most frequently isolated bacteria in wound cultures [37]. Wound healing times increased by this highly resistant microbe, and causes greater risk of mortality and adverse postoperative complications [38].

Polymerase Chain Reaction PCR and Methicillin Resistance *Staphylococcus aureus* Detection

This method of creating copies of specific DNA fragments has ability to produce million copies of a particular DNA segment of *S aureus*. It has already been reported that mecA gene can be detected in *S aureus*, *S intermedius*, *S epidermidis* by using PCR [39]. A PCR method for identifying *S aureus* and mecA genes have been successfully used for detection of MRSA [40]. PCR-assay from clinical swabs was developed for direct detection of MRSA. PCR method was developed to detect MRSA by using a forward primer targeting the SCCmec element region [41]. Recently, differentiation of MRSA was developed by a multiplex PCR for Methicillin-Resistant Coagulase Negative Staphylococcus (MR-CNS). However, real-time PCR was used to detect MRSA in isolates and clinical samples. This method of detection is much accurate for identification of MRSA in pets as well as humans [42]. MRSA is mediated by the penicillin binding protein (PBP2a) and encoded by mec-A gene. This mec-A gene is spread on the

SCCmec genetic element and reduces the affinity for β-lactams in *Staphylococcus* species. The carriage of toxin gene is different among studies. MRSA carried by the Panton-Valentine Leukocidin (pvl) gene was recovered from pets and humans. MRSA strain isolated from domestic pets having molecular typing and whole genomic sequencing suggest that pet obtain MRSA through colonized owner. Nosocomial pathogen in human hospitals was first reported as MRSA. MRSA cause the same type of infection as other *S aureus* do. Hospital associated strains have become resistant to most common antibiotics and its treatment can be challenging. Resistance to aminoglycosides and fluoroquinolone as well as other antimicrobial classes is being increasing by MRSA and thus making this problematic pathogen of humans and pets concern. In another study it was observed that bacterial resistance to antibiotic isolates is depending on the location, age, sex and species.

CONCLUSION AND RECOMMENDATIONS

S aureus resistance against methicillin is a common threat to the pets throughout the world. All the countries where antibiotics including methicillin are misused, resistance has developed in the hosts and that results failure of antimicrobial therapy and higher mortality. It is recommend to avoid misuse of all antibiotics in animals as well humans otherwise all the therapies against microbes would fail in near future.

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