Perspectives of Methicillin-Resistant *Staphylococcus Aureus* (MRSA)

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Abstract: *Staphylococcus aureus* is a gram positive, non-motile bacterium which normally colonizes in skin and mucosa of human and animal, transmitted by direct contact or via contaminated surfaces, which causes infections like skin infections , respiratory infections and food poisoning. Methicillin is a narrow spectrum beta-lactam antibiotic of the penicillin class which was previously used for the treatment of infections caused by Staphylococcus aureus. In 1948 it was observed that 50% of staphylococcal isolates from patients in a United Kingdom hospital were resistant to penicillin. Since then 90 to 95% strains of *S. aureus* were resistant to penicillin. In 1959 methicillin, a penicillinase-resistant penicillin was introduced to overcome the penicillin-resistant *Staphylococcus aureus*, but after few years, *S. aureus* strain became resistant to methicillin also and so the birth of MRSA occurred. MRSA has been detected in wide range of species including companion animal and wildlife animal. Pigs are considered to be true reservoir hosts for MRSA, causing mastitis in cattle, dogs are more infected with MRSA in comparison to cats, in horses most of the cases of MRSA infections were reported in large studs. MRSA has been isolated from wild animals like cottontail rabbit, lesser yellow migratory shore bird, Wild rat, wood mice red deer, Iberian ibex, vulture, wild boar etc. Certain facts showed that these organisms can be transferred from human to animals and from animals to humans. Most of MRSA infections are skin infections producing symptoms like cellulitis, boils, abscesses, sty, carbuncles, impetigo and rash. For the diagnosis of MRSA antimicrobial susceptibility tests (AST) such as agar disc diffusion technique is used. Cefoxitin disc diffusion is the most sensitive methods for detecting MRSA isolates showing negative and positive predictive values of 100% and 98%, respectively. For the treatment of clinical cases of MRSA, antibiotics such as trimethoprim-sulphamethoxazole, clindamycin and doxycycline, topical treatments and other measures have been used successfully.

I. INTRODUCTION

Staphylococcus aureus is a bacterium which normally colonises in skin and mucosa of human and animal causes disease particularly if there is an opportunity for the bacteria to enter the body through broken skin or during medical procedure.[1]. *S. aureus* is not always pathogenic but commonly cause skin infections such as abscesses, respiratory infections such and food poisoning, inflammation of the mammary gland in bovine and the lower part of the foot in poultry [2]. A pathogenic strain causes infections by producing potent protein toxins and expressing cell-surface proteins that It is transmitted by direct contact or via contaminated surfaces. It causes disease in immune compromised patient like HIV or in those undergoing chemotherapy. The related species *Staphylococcus epidermidis* (used to be known as *S. albus*) also exists on skin and may play a protective role against *S. aureus* in normal conditions.

The basic characteristics of *S. aureus* are as mentioned below

1. Gram positive.
2. Non-motile.
3. Spherical.
4. Grows in bunches (resembling clusters of grapes).
5. Golden color colonies (especially in old culture)
6. Hemolytic on blood agar
7. Produces coagulase, catalase enzymes, hyaluronidase (breaks down hyaluronic acid and helps in spreading it), deoxyribonuclease (which breaks down the

DNA), lipase (digest lipids), staphylokinase (dissolve fibrin and aid in spread), and beta-lactamase (for drug resistance).

Initially penicillin and its derivative i.e. methicillin was used for treatment most *Staph* infections. In the 1950s staph organism became resistant to penicillin and methicillin. Thus, the term methicillin-resistant *Staphylococcus aureus* (MRSA) was derived. *Staph* that can be treated with penicillin-related drugs are called methicillin-susceptible *Staphylococcus aureus*, or MSSA. Strains of *Staph* that have become resistant to methicillin are known as MRSA.

In most of MRSA case infection occurred through hospitals. But in the 1990s MRSA infections were found in non hospitalized animals. Since then, the frequency of MRSA cases has greatly increased; in 2006, more than one-half of all cases of skin infections were due to MRSA [3]. Today MRSA infection is classified in three specific groups:

1. Hospital-associated MRSA
2. Community-associated MRSA
3. Livestock-associated MRSA

The emergence of antibiotic-resistant strains of *S. aureus* such as MRSA is a worldwide problem in clinical medicine. and veterinary species [4]. Reports of MRSA isolation in domestic animals seems to be rising in number [5]. The epidemiology of MRSA isolates from human and animal sources showed that for certain strains, a cross-infection might have happened [6]. Animals can be a potential source of MRSA infection to humans [7,8].

II. METHICILLIN

Meticillin or methicillin is a narrow spectrum beta-lactam antibiotic of the penicillin class which was developed in 1959 and was previously used to treat infections caused by *Staphylococcus aureus*. The manufacturing of methicillin is no longer done as more stable and similar penicillins such as oxacillin, fluclocillin and dicloxacillin are used for treatment of staph organisms. Methicillin has recently been renamed meticillin according to European law.

III. HISTORY

Staphylococcus was discovered in 1880 in Aberdeen, Scotland, by the surgeon Sir Alexander Ogston in pus from a surgical abscess in a knee joint. This name was later appended to *Staphylococcus aureus* by Friedrich Julius Rosenbach. In the 1940s, treatment of *S. aureus* infections became routine and successful through penicillin. In 1944 penicillinase production was discovered in *S. aureus* that was capable of hydrolyzing the penicillin [9]. In 1948, it was observed that over 50% of staphylococcal isolates recovered from patients in a United Kingdom hospital were resistant to penicillin [10]. Since then to date, 90 to 95% strains of *S. aureus* are resistant to penicillin. In 1959 methicillin apenicillinase-resistant penicillin was introduced to combat with penicillin-resistant S. aureus, but in few years, S. aureus strain became resistant to methicillin also and so-called birth of MRSA [11].

IV. SPECIES AFFECTED

MRSA has been detected in wide range of species including domesticated ruminants, pigs, horses, dogs, cats, rabbits, rodents, captive marine mammals, a captive elephant, a bat, birds (including poultry, pigeons and psittacine birds) and turtles. Pigs seem to be true reservoir hosts for MRSA CC398, which is also called "non-typeable MRSA" (NT-MRSA) or livestock-associated MRSA (LA-MRSA). CC398 has been also detected in other species like horses, cattle, poultry, dogs and in rats living in pig farms. Mastitis in cattles is caused by many MRSA strains of human origin. Poultry is infected with either CC398 or ST9 MRSA strains. In horses MRSA strains are varied and their origin is unknown. Many of the common strains in this species (e.g., CMRSA5 [USA500; MRSA ST8 SCCmecIV]) belong to older human lineages that were common in the past, but have been superceded by other strains, or to less common groups. Most infections by these species are acquired from people and carriage is often transient. There is very little knowledge about MRSA in exotic animals.

V. MRSA IN COMPANION ANIMALS

Dogs, cats and horses have now become part of the most families, therefore, there are high chances of human colonization or infection with MRSA from these animals and dogs are more infected with MRSA in comparison to cats [12]. MRSA strains commonly isolated from hospitals are EMRSA-15 (ST22) and EMRSA-16 (ST36) [13]. Reports of MRSA infection in horses with a percentage rate of 0 to 11% has been published [14]. Most cases of MRSA infections were reported in large stables and post-operative complications [12] (Morgan, 2008). MRSA lineages isolated from horses were distinct from the strains present in humans [15].

VI. MRSA IN WILDLIFE

The role of wildlife for MRSA infection has not yet been properly understood, there are several reports of presence of MRSA in many captive wildlife animals [16]. MRSA has been isolated from cottontail rabbit, lesser yellow migratory shore bird, Wild rat, wood mice red deer, Iberian ibex, vulture, wild boar. The most common animal lineage that causes infection in wild life is CC130 and ST425 [17] . Wild animals can also serve as source of infection in human, particularly through park rangers and zoo keepers.

VII. ZOONOTIC POTENTIAL

There are a number of strains of MRSA which predominantly colonize and circulate in the population. They include the common hospital-associated clones CC5, CC8, CC22, CC30 and CC45, and additional community-associated strains. There are facts that these organisms can be transferred from human to animals and from animals to humans. Peoples get infected or colonized with MRSA clonal complexes maintained in animals, such as CC398. The duration of the colonization persists, is still uncertain.

VIII. GEOGRAPHIC DISTRIBUTION

MRSA is now present in all around the world but its prevalence varies between regions. CC398 is predominant MRSA in pigs of Europe, but it is also been found in North America and Singapore. ST9 appears to be the prevalent MRSA strain among pigs in China, Hong Kong and Malaysia, and CC398 is uncommon or absent in these regions. The most common strains in dogs and cats are those found in humans, which differ between geographic regions. MRSA isolates in equine also appear to vary with the location.

IX. TRANSMISSION OF MRSA

MRSA can be transmitted through skin without any signs or symptoms of the illness. As *S. aureus* is an opportunistic pathogen it can be found as normal commensals on the skin (especially the axillae and perineum), the nasopharynx and anterior nares. In humans MRSA are usually transmitted by direct contact often via the hands with colonized or infected people. Humans remain infectious as long as the carrier state persists or the clinical lesions remain active. MRSA can also be disseminated on fomites and in aerosols. MRSA is released into the hospital environment either through skin cells, stools of infected patient, medical instrument, beddings, clothing, furnitures, toiletries and the atmosphere [18]. Presence of MRSA in samples collected from veterinary hospitals. Carrier animals serve as reservoirs for disease and transmit MRSA to other animals or people. Some MRSA strains like CC398, are transmitted to host species to which they are adapted. The transmission of human-adapted MRSA lineages between animals is poorly understood [19].

X. MECHANISM OF RESISTANCE

mecA gene is responsible for development of methicillin resistance. *mecA* gene is chromosomally located on a mobile genetic element called the staphylococcal cassette chromosome (SCC) which encodes for penicillin-binding protein 2a (PBP-2a) and responsible for synthesis of penicillin-binding protein 2a (PBP2a; also called PBP2) a 78-kDa protein. Expression of PBP-2a is controlled by *mecR1* and *mecI* regulator genes located upstream of *mecA* gene. A mutation in the *mec* regulators leads to expression of *mecA* gene (PBP-2a). A PBP2a substitutes for the other PBPs and because of its low affinity for all β-lactam antibiotics, this enables staphylococci to survive exposure to high concentrations of these agents [20].

XI. SYMPTOMS OF A MRSA INFECTION

MRSA signs and symptoms depend on what area of the body is infected. Although MRSA bacteria are present in mucosa they may never display any symptoms of active infection. Most MRSA infections are skin infections that produce the following signs and symptoms like cellulitis, boils, abscesses, sty, carbuncles, impetigo and rashes.

Staph skin infections, including MRSA, appear as a bump or sore area of the skin that could be mistaken for an insect bite. The infected area of skin becomes red, inflamed, painful, hot to touch, full of pus or other liquid, accompanied by a fever. MRSA infection in the blood or deep tissues causes fever of 100.4 degrees F or higher, Chills, Malaise, Dizziness, Confusion, Aches and pains of the muscles, Swelling and tenderness in the affected body part, Cough, Breathlessness and Wounds that do not heal. MRSA has also been found in other conditions like pneumonia, rhinitis, sinusitis, otitis, bacteremia, septic arthritis, osteomyelitis, omphalophlebitis, metritis, mastitis (including gangrenous mastitis) and urinary tract infections.

XII. DIAGNOSIS

Depending upon the type of infection present, an appropriate specimen is obtained accordingly and sent to the laboratory for definitive identification by using biochemical or enzyme-based tests. Sites for collection of MRSA organism include nose, skin, perineum and rectal or cloacal swabs [21. For environmental samples, swabs are taken from dust samples, tables, containers, feed material or faeces and bedding material [22]. Other samples like milk and meat from animals and cloacal swab from poultry are cultured for MRSA detection. First a Gram stain is performed to show typical gram-positive bacteria, cocci, in clusters. Than the isolate is cultured on mannitol salt agar, which is a selective medium with 7–9% NaCl that allows *S. aureus* to grow producing yellow-colored colonies. Then for differentiation on the species level catalase and coagulase test, pigment production and anaerobic growth test is performed [23].

Additional methods include Minimum Inhibitory Concentrations to detect presence of mecA gene or PBP20 protein. Enrichment media like Oxacillin Resistant Screening Agar Base (ORSAB) and CHROM agar can be used for identification of MRSA [24]. Antimicrobial susceptibility tests (AST) such as agar disc diffusion technique is used in diagnostic laboratories to diagnose MRSA. Cefoxitin disc diffusion is the most sensitive methods for detecting MRSA isolates showing negative and positive predictive values of 100% and 98%, respectively [25]. Molecular methods such as

PCR, Pulsed-field Gel Electrophoresis (PGFE), Multilocus Sequence Typing (MLST), Staphylococcal Protein A Gene (spa) locus typing and Staphylococcal Cassette Chromosme (SCCmec) typing are used now for diagnosis of MRSA gene sequence.

XIII. TREATMENT

Antibiotics, topical treatments and other measures have been used successfully to treat clinical cases of MRSA. Antibiotic therapy should be based on susceptibility testing. MRSA strains are resistant to penicillins, cephalosporins, cephems and other ß-lactam antibiotics. Antibiotics like trimethoprim-sulphamethoxazole, clindamycin and doxycycline are effective in the treatment of CA-MRSA infection. Newer drugs such as oritavancin, ztelavancin omadacycline, tedizolid and dalbavancin have a promising impact on the treatment of MRSA.

Local treatment with antiseptic compounds such as chlorhexidine or povidone iodine may be helpful in some types of infections. Animals treated with topical therapy alone must be monitored closely for signs of localized progression or systemic spread. Certain antimicrobials, such as vancomycin and tigecycline, are critically important for treating human illnesses caused by MRSA. In some cases, they may the drugs of last resort. The use of these drugs in animals may place selection pressure on isolates that can infect humans. Thus, they are controversial for treating MRSA-infected animals, and should be avoided if at all possible

XIV. PREVENTION

Veterinary hospitals should establish guidelines to minimize cross-contamination by MRSA and other methicillin-resistant staphylococci. In addition to hand hygiene, infection control measures [26] (with particular attention to invasive devices such as intravenous catheters and urinary catheters), and environmental disinfection, barrier precautions should be used when there is a risk of contact with body fluids or when an animal has a recognized MRSA infection. MRSA-infected wounds should be covered whenever possible. Researchers have recommended that veterinary hospitals initiate surveillance programs for MRSA, particularly in horses. Screening at admission allows isolation of carriers, the establishment of barrier precautions to prevent transmission to other animals, and prompt recognition of opportunistic infections caused by these organisms. On farms, MRSA may sometimes be introduced when buying new stock, and spread during livestock movements. Biosecurity measures, including dedicated clothing and showering in, may decrease the risk of MRSA introduction to a farm by human visitors or reduce transmission between units. CC398 strain of MRSA has been detected in rats living on pig farms, rats should be considered in control programs. Avoiding routine antimicrobial use in food animals might reduce selection pressures, and lower the prevalence of these organisms in livestock. . The best method to eliminate MRSA carriage in animals in poorly understood and may vary with the species.

XV. CONCLUSION

MRSA is now a growing worldwide problem, the occurrence of MRSA infection is increasing specially in the cases of domestic animals particularly in dogs and cats. Initial reports has shown less occurrence of these MRSA infection but recent reports are indicating high frequency of occurrence in domestic and companion animals. MRSA infections in animals are mainly associated with exposure to hospitals, human contact, extensive wound, prolonged hospitalization and immune suppression.

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