A General Outlook on Methicillin Resistance \textit{Staphylococcus aureus}

ABSTRACT

Methicillin resistant \textit{Staphylococcus aureus} (MRSA) is a kind of bacteria which is resistant against methicillin and other kind of many antibiotics. \textit{S.aureus} and MRSA can lead to seriously problem in human as well as animals. The problem can be from skin infections and sepsis to pneumonia and bloodstream infections. Firstly, MRSA was largely related to hospital-acquired (HA) infection. However, it is well understood that there is other source of MRSA. Nowadays, MRSA has been divided three group; (1) Hospital-Associated MRSA (HA-MRSA), (2) Community-Acquired MRSA (CA-MRSA) and (3) Livestock-Associated MRSA (LA-MRSA). In addition to the three groups, according to study results have shown that it has been animal origin foods (beef, poultry and pig meats and milk like that) and their products contaminated with MRSA. Therefore, food of animal origin can be involve in MRSA bacteria, and it can spread to human and animal through food chains. MR (methicillin resistant) in \textit{S. aureus} is primarily mediated by overproduction of the penicillin-binding protein (PBP) 2a, and altered PBP with extremely low affinities for ß-lactam antibiotics. The \textit{mecA} gene encodes a PBP2a form that is absent in susceptible isolates. The importance of MRSA; (i) it could become antibiotics resistant more easily than could other microorganisms, (ii) it acquires resistance to one antibiotics and to go into antibiotic groups, (iii) the Panton-Valentine leucocidin (PVL) toxin is one of the very important virulence factor in CA-MRSA strains, and these strains are commonly considered far more likely to carry the gene coding for the toxin than are other MRSA strains, and (iv) MRSA infections require long-term inpatient cure and have a high rate of mortality. For these reasons, today, MRSA is among the most important causes of antimicrobial-resistant health care-related to infections across the world.

Keywords: MRSA, animal origin food, public health

1. INTRODUCTION
Antimicrobial resistance is a crucial public health fear across the world based on the persistent circulation of resistant bacterial strains in the environment and thereafter contamination of foods as well as water. Foods, especially animal origin, are important vehicles for introducing pathogenic microorganisms to the common population. Generally, in animals, for 1 kg meat production, roughly 100 mg antimicrobial drugs are used in Europe [1]. For this reason, animal origin foods are also significant in the consumer’s gastro-intestinal system of antibiotic resistance (AR) bacteria. The major factor contributing to the raising of AR in animal origin foods may be due to administration of antibiotics to food-producing animals for therapeutic aims or as growth supports [2]. For instance, the use of avoparcin as a food additive in farm animals, especially in pigs and poultry, develops resistant enterococci against vancomycin in the intestinal system of animals. As a result of which, the resistant bacteria go into the human intestinal system after the food consumption [3]. An increase in AR bacteria isolated from animals of various origin has also been observed. Mainly, *S. aureus* and other *Staphylococcus* species have been commonly reported to show multi- antimicrobial resistance patterns [4].

*S. aureus* is a highly important pathogen causing considerable human mortality and morbidity around the world. The bacteria are also a major causative agent for infective endocarditis, bacteremia and besides skin and soft tissue, osteoarticular, device-related infective diseases and pleuropulmonary [5]. At the beginning, most *staphylococcal* infections were susceptible against penicillin. Generally, *staphylococcal* infections can be treated with penicillin or penicillin-related antibiotics. That time, it is called methicillin-sensitive *S. aureus* (MSSA). Nevertheless, many diseases became resistant to penicillin and methicillin in the 1950s and MRSA identified in 1962 are nowadays a widespread global problem [6]. MRSA has been admitted as a significant causative agent of HA-MRSA in humans for many years. After that, until the 1990s, MRSA was identified but was occasionally outside the health care environment. However, infections of MRSA were admitted in human living out side of the hospital or in no touch with people in nursing centers in the 1990s. After that time, more often MRSA patient has highly increased in human living in population. During 2006s, more than 50% of patient with skin infections because of MRSA happened in or else well people living in the population. Therefore, MRSA strains have come to existed, which are involved in CA infections in humans in plenty of countries [7]. Methicillin resistance *S. aureus* and CA-MRSA are thought on a large scale affect humans and, generally, are not taken in infection of farm animals. Nevertheless, people may be contaminated with LA-MRSA by direct touching...
to animals with MRSA in the farms or at the abattoir during slaughtering[8]. Then, the LA-
MRSA isolation from livestock and accompany animals have been informed, too[9,10,11].
Numerous MRSA isolates showed multiple resistances against the prevalent used
antimicrobial drugs such as oxacillin, penicillin, tetracycline, erythromycin and amikacin [12].
Hence, MRSA is one of the highly important hospital-acquired pathogenic bacteria due to
resistant to much kind of antibiotics. The multiple resistance properties against many
antibiotics of MRSA create difficulties in treatment of MRSA’s patients[13].

Human’s MRSA is generally separated into two groups: HA-MRSA and CA-MRSA [4]. In
addition to these, there has been a third MRSA group, known as LA-MRSA. Today, LA-
MRSA has come to existed and infected to farm animals, wild animals and pets [15]. In
addition, related to animal with MRSA, animal origin foods has seen last group of MRSA
sources.

1.1.CA-MRSA

Over the past 25 years arising in the MRSA prevalence was recorded around the world. Based
on epidemiological data, in nosocomial settings, in terms of risk factors related to cure or care.
HA-MRSA is distinguished from CA-MRSA in terms of independent the risk factors [16].
Although infection of CA-MRSA has been a public health challenge in many countries
throughout the world like South America and the US, and in the most European countries, they
are comparatively rare [17]. CA-MRSA like HA-MRSA have been generally distinguished by
their functional and structural genomic properties [18]. The hospital-onset infections
monitoring caused by CA-MRSA genotypic [19] and the HA-MRSA establishment in the
community [20] can not clear the epidemiological distinction.

1.1.1.CA-MRSA and PVL

Besides MR properties, another important concern in Staphylococci is a PVL toxin. The toxin
of PVL is a bicomponent cytotoxin. The toxin is encoded by luk-S-PV and luk-F-PV genes. The
luk-S-PV and luk-F-PV genes, two contiguous and co-transcribed genes, produce 32 and 38
kDa protein, respectively. The PVL toxin causes the occurrence of pores in the mitochondrial
membrane, which subsequently results in leukocyte destruction. Staphylococci containing
PVL genes are responsible for CA infections such as soft-tissue and skin abscesses, invasive osteomyelitis and necrotizing pneumonia [21].

After the mid-1990s, in the United States, in many epidemiological studies results have shown that PVL carriage genes has been mainly related to infections brought about by CA-MRSA. The genes of PVL have been found in CA-MRSA isolates (by various definitions) at some 60-100% ratios. For instance, it was reported from Minnesota reported by the CDC definition case that PVL gene determined in 77% MRSA’s patients given rise to by CA-MRSA strains, in 2000, whereas PVL genes detected just only 4% ratio in HA-MRSA isolates [22]. In 2003, in Texas, among 812 military with recruit’s nasal infection, 45 MRSA isolates were obtained, and PVL genes detected in 66% out of 45 MRSA isolates [23].

1.2. LA-MRSA

Transmission of MRSA from animals to humans is of big worry because of the inference of the health care system and human health. Both MRSA and MSSA have been related to companion and animals growing for food. In 1972, first LA-MRSA was seen in Belgium. It was detected in bovine mastitis milk. After that, MRSA cases in different food and accompanying animals, like pigs, cats, chickens, dogs, cattle and horses, have arisen[10]. LA-MRSA is initially related to livestock [24]. It is distinguished from genotypic of HA and CA-MRSA in its genomic properties. In 2005, in the France and Netherlands, it was seen a new kind of MRSA type which described firstly. The new kind of MRSA variant related to CC398 (clonal complex 398) [25,26]. Later, MRSA CC398 is also found in other farm animals-veal calves and poultry like that[27,28]. For this reason, it was done a new definition called LA-MRSA. LA-MRSA CC398 is distinguished from other two group of MRSA mentioned above. Since, mostly, it is not contain *scn, sea, sak and chpd* genes as well as PVL. These genes found in the human CC398 MRSA lineage, and the genes refer to the human-associated immune evasive gene cluster. LA-MRSA has also seen in Germany, Italy and Denmark, [10], Northern America [29], Asia [8], Northern Africa and Australia [30]. According to many studies results, among people who works in the livestock industry, there have been growing risk for infected or colonized with LA-MRSA[31,32,33], but LA-MRSA infection rates are growing among the population, too (34,35). In Germany, Cunny et al. [36] found that at least 10% of these sporadic infections are because of LA-MRSA, which is originally related to livestock. The most MRSA cases are associated with CC398 clonal complex (CC).
50% traditional farms of pig, LA-MRSA CC398 colonizes the animals asymptotically. It was reported that for about 77%-86% of humans with contact to pigs because of the job, it was detected in their nasal carriage. When they cut or interrupted touch to farm animals, it can be lost. At the same farms, only 4–5% is colonized among family members living.

1.3. MRSA in Foods

In different countries, staphylococcal food poisoning (SFP) is a foodborne disease, and its prevalence is highly common [37]. A different kind of foods can support the growth of Staphylococcus species. Some Staphylococci isolated from food poisoning cases are also multi drug resistance and vancomycin resistance, and because of lack of alternative antibiotics, infection caused by these resistant strains may be fatal. The first outbreak of foodborne MRSA was reported in 1995 by Kluytmans et al. [38]. This outbreak resulted in five deaths out of 21 reported cases. Since 1994, consumption of animal origin foods containing MRSA has been recognized as a health hazard and a lost studies have highlighted the public health threat associated with the MRSA presence in foods [39,40,41,42, 43]. In several studies, a high MRSA prevalence has been detected in various retail foods across the world, including milk, beef and fish [39,42,43].

Many researches on MRSA in beef have been conducted in different countries. In these studies, the contamination rate has been reported as high as 10.6% [3, 33,39, 43, 44,45, 46]. S. aureus is present high prevalence in different kind of retail meat products. For instance, DFSA (A Dutch Food Safety Agency) analyzed 2217 different kinds of meats samples in retail stores according to the bacteria, and MRSA had been found 1.9% of them. The MRSA distribution within different meat types was reported as 10.7% of pork, 10.6% of beef, and 15.2% of veal; 6.2% of mutton and lamb, 3.4% of fowl, 16.0% of chicken, 3.3% of turkey, and 2.2% of game. Whole of the MRSA isolates, 85% out of the isolates belonged to ST398; possibly the other STs were belong to human origin [44]. According to another research reported from Nederland that S. aureus was detected in 46% of retail meat samples. In the study, MRSA was determined in two (2%) of which: while one of them was CC39, the other one was USA300 [33]. From Japan and Switzerland, there have been studies in these countries, and according to the study results, the prevalence of S. aureus in meat products was to be 65% and 23%, respectively [47]. MRSA has been detected in beef samples; for this reason, the threat to humans from this kind of food is a concern. Beef can become contaminated with MRSA in
different ways. Mainly, the use of antibiotics to promote animal growth can select for resistant bacteria and can result in antibiotic residues in animal tissue and meat products. Another contamination source is the slaughterhouse. Hence, cross contamination can occur in various parts of the slaughter and abattoir environments that have become contaminated with MRSA. The contamination sources could be either the animals moving into the abattoir for slaughter or the workers involved in processing the end products[48].

In the early 1970s, in Belgium, the first MRSA report in farm animals (dairy cows’ milk of with mastitis) was published, and the clustered CC398 group was identified [15]. In Korea, MRSA has been found in cows or cows’ milk samples [49]. From Brazil, the USA, Pakistan, Nigeria, Turkey and Italy, there have been many MRSA reports from cows or their milk [50].

In commonly, according to detection of prevalence in bovine mastitis, it was found that the quite low MRSA prevalence in the bovine mastitis isolates [51]. Following the initial MRSA isolation from mastitic cow’s reports [52], MRSA were isolated from the cow’s milk at 0.18% ratio. According to one report from Belgium, a high (15%) MRSA prevalence was determined in the animals of dairy farms in which there had been lactating cows which had a previous MRSA history[51]. Take into account of the years since the first MRSA cattle determination between the humans closely touch and udders of the dairy cattle, the prevalence of low MRSA mastitis in long-term has been fairly surprising. In Germany, at slaughter, the nasal swaps obtained from veal calves was found the highest MRSA prevalence (4.1% out of 45%), whereas bulk tank milk had the lowest MRSA rate.

The most isolates, not depended on sources, were the clonal complex CC398 (from spa type’s t011 and t034). In Germany, the LA-MRSA CC398 finding in tank’ milk claimed that the reason was related to udder colonization and quite likely cases of subclinical mastitis in dairy cattle [53]. Near contact between dairy cattle and humans could give rise to a strains move from human to dairy cattle or versus. From Hungary, there has been one report, and in this reports, MRSA isolates obtained from a worker and mastitic cows were determined as a same by genotypic and phenotypic analysis results. The findings indicated that there was a transfer between cows and human [54]. Numerous studies have also addressed MRSA in milk. Some of them have revealed a relationship of MRSA with mastitistic cows’ milk[40,41]. In other studies, MRSA has been found in bulk tank milk samples [42]. There have been several contamination ways of milk with milk with MRSA. Contaminated milk from mastitic cows contaminates milk of bulk and in turn contaminates raw milk products. Dairy workers’s hand...
swabs and food handlers’ unveiling a high percentage of CPS (coagulase positive staphylococci) on their skin, and these workers and handlers may compose of another source CPS contamination source in dairy products [42].

There have been several studies around the world. For instance, Cho et al. [43] obtained from 74 S. aureus from 209 fish and raw meat samples. They found that 7 (35.4%) out of 74 isolates were evaluated as MRSA because of the resistance against oxacillin. For this, they searched present of mecA gene in the isolates. The gene was present in the 7 isolates with oxacillin resistance.

From Turkey, according to Can and Çelik[55]’s study results, a total 200 cheese samples were analysed for determination of S. aureus and MRSA, and S. aureus was detected in 122 (6%), and 2 out of 122 was MRSA. The other study from Turkey, Siriken et al. [46] found that, S. aureus was determined in 62 (35.4%) isolates (44 from beef, 9 from milk, and 9 from fish) among 175 coagulase positive Staphylococcus. 15 of 62 S. aureus isolates was found MRSA [(24.2%; 9 (60%) from fish), 4 (26.7%) from beef and 2 (13.3%) from milk]. A study again was published by Siriken et al. (45) from Turkey. In their study, 100 salted anchovy samples were analysed for determination prevalence of S. aureus as well as other kind of CPS species, and detection of methicillin resistance properties of the isolates. According to analyse findings, they were detected in 41 isolates. However, 16 (39.02%) isolates were resistance to methicillin. Igbinosa et al. (56) also reported that fifty isolates of MR-Staphylococcus species were detected in 14 (28%) beef, 26 (52%) pork and 10 (20%) chicken samples from 126 meat samples analysed. For MRSA determination, mecA gene was detected in whole beef and chicken origin isolates. In addition this, the researchers also detected in PVL gene in 100% of the MRSA isolates.

From Iranian, Arefi et al. (57) reported that 100 Iranian white and feta cheese samples were collected from different suppliers. Then, the samples were initially evaluated for the occurrence of S. aureus and MRSA. According to findings, S. aureus was detected in 25 (25%) isolates, and 8 (34.78%) of 25 S. aureus isolates were MRSA based on genotypic confirmation using PCR.

From Belgium, there has been a study reported by Bardiau et al. (41). The researchers evaluated the presence of MRSA in 430 S. aureus collected from cows milk with mastitis. They
obtained 19 MRSA isolates. Although seven CC mec types (IV and V) were determined, PVL not detected in the isolates. The isolates of MRSA were obtained from 4 (11%) cows with mastitis (n=36). In addition to these properties of the isolates, the researchers also studied for other characterization of the isolates. For this aim, they chose one MRSA per sample, and then they searched four MRSA isolates in term of typing by used two different pulsed field gel electrophoresis. Finally, they found that the four isolates belonged to t011-ST398- agr1 (accessory gene regulator)–SCC (Staphylococcal cassette chromosome) mecV and ApaI (restriction enzyme) patterns. There has been another study reported by Siva et al. [58] from Brazil. In the study, MRSA was detected in 4 (11%) out of 36 cows with mastitis.

From China, Wang et al. [59] carry out a study according to MRSA determination in retail food samples (n=1979). MRSA was detected in 0.6% (n=3), 1.4% (n=4), 0.6% (n=1), 2.3% (n=6), 2.5% (n=3) in ready-to-eat food, raw milk, pork sample, chicken meat and dumpling samples, respectively. However, MRSA isolates were not detected in infant foods. According to finding, from 17 MRSA detected samples, total 23 MRSA isolates were obtained. They also carried out antimicrobial susceptibility tests in the isolates. According to analysed findings, they found that these MRSA isolates were higher resistance ratio against clindamycin, erythromycin, and clarithromycin at ratio of 100%, 95.7% and 87.0%, respectively, than cefoxitin, penicillin, oxacillin and ampicillin. They reported also that the \( pvl, seg, seh, sed, \) followed by \( see, sec, \) and \( seo \) toxin genes were detected very frequently in the isolates. They also found that as \( SCCmec \) types, II, IV\( b \) and V were detected. In addition to these findings, t189, t377, t5762, t437, t10793, t899 and a new type were determined as a \( spa \) typing. As a result, the first range spa type was ST9 (52.2% of the isolates), and it was followed up by ST88, ST188, ST59, ST630 and ST72.

**CONCLUSION**

According to mentioned above results, besides HA-MRSA, there are other sources of MRSA-CA-MRSA, LA-MRSA and MRSA in animal origin foods. Among these groups, MRSA in foods could be other MRSA sources for human. There are MRSA transition in the environment between human and animal. In addition, in the MRSA spread, animal origin foods can also play an important role. Hence, MRSA goes into the human intestinal system after the food consumption. After that, the resistance gene (\( mecA \)) can transmitted other bacteria in the tract. At last, after defecation, it can spread into environment. Therefore,
controlling MRSA, one health concept may be remember. Food of animal origin can be check antibiotic resistance bacteria including MRSA especially risk group hospitalized people before prepare consumption.

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