

Methicillin-Resistant *Staphylococcus aureus* (MRSA) in Food of Animal Origin: A New Challenge in Food Safety?

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Abstract

Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) causes a wide range of infections, sometimes fatal, and represents a major problem in both human and veterinary medicine. The global spread of intensive farming and the high and indiscriminate use of antimicrobials has favoured the selection and circulation of MRSA in livestock and, consequently, in food of animal origin. The presence of MRSA is well documented in foodstuff, such as, beef, pork, poultry and rabbit meat as well as fish, raw milk and table eggs. The strains mostly isolated from food are animal associated, i.e. CC398; however, human strains have also been isolated from foodstuff. Some of these MRSA strains are capable of synthesizing staphylococcal enterotoxins.

Objective of the Study: In this review, the origin and the significance of MRSA in food of animal origin are discussed from a food safety point of view.

Keywords: MRSA; Antimicrobial-Resistance; Food Safety

Introduction

Antimicrobial resistance (AMR) in bacteria is a great challenge for the XXI century [1]. The WHO stated that “the *post*-antibiotic era, in which common infections and minor injuries can kill, far from being an apocalyptic fantasy, is instead a very real possibility for the 21st Century” [2]. Antimicrobial pressure in a bacterial population promotes the selection, survival and spread of resistant bacteria. In fact, AMR occurs due to a mutation in the bacterial genome which enables the microorganism to survive in the presence of antimicrobial molecules, thus rendering them ineffective; it could also arise due to the acquisition of an antimicrobial-resistance pattern through DNA fragments from other microorganisms *via* conjugation, transformation or transduction.

The emergence of intensive farming, where a lot of animals are confined in restricted spaces, has led to increased stress levels in these animals forced to live in conditions which are far from ideal. This condition facilitates the transmission of microbial pathogens between animals, leading to the arise of infectious diseases with a significant economic loss for farmers. To curb this problem, the extended use of antimicrobials for prophylaxis and metaphylaxis (other than for therapeutic purposes), largely used in the intensive farming, should be significantly reduced. In addition, in many countries the use of antimicrobials as growth promoters is still permitted [3]. In fact, every year 131.109 tons (73%) of all antimicrobials sold worldwide are used in animals [4]. Under this extraordinary selective pressure, some

populations of pathogenic or harmless bacteria have emerged and reached human beings and are having several effects on them: first of all, infections which are difficult to treat and are sometimes fatal [5]. The secondary side effect of AMR is that farmed animals represent a great reservoir of antimicrobial resistant genes which may increase the chance of other bacteria acquiring them by gene exchange with the animal microbiota or through the environment. Therefore, the presence of AMR bacteria in livestock, food-producing animals and food derived thereof represents an important source of AMR bacteria for humans [6]; in fact, consumers might acquire infections caused by these microorganisms, *via* handling or consuming contaminated foods [7]. In this framework, among others, an important theme is debated by food-safety experts: the role of methicillin-resistant *Staphylococcus aureus* (MRSA) as a foodborne pathogen.

Molecular epidemiology of MRSA

MRSA is a well-known human and animal pathogen which can cause severe infections [8] so much so that the WHO has included it on the list of antibiotic-resistant “high priority pathogens” [9]. Methicillin resistance is due to the synthesis of the penicillin binding protein 2a (PBP2a), a protein encoded by the *mecA* gene, with a low affinity for methicillin and oxacillin and practically for all the β -lactams antibiotics [10,11]. The epidemiology of MRSA can be divided into three major phases: during the ‘80s, MRSA infections were mostly considered a nosocomial problem affecting hospitalized patients presenting several risk factors such as catheterization and prolonged hospitalization [12]. The main clonal complexes (CCs) isolated from these patients were CC5, CC8, CC22, CC30 and CC45 [13]; these multidrug-resistant strains were called Hospital-Acquired (HA)-MRSA [14]. Subsequently, in the late ‘90s, a spread of MRSA infections in the community was observed (Community-Acquired (CA)-MRSA); the people affected were non-hospitalized patients living in a community, such as prisoners, military personnel or athletes (sharing the same space), with unknown risk factors [15,16]. The main strains involved belonged to the Sequence Type (ST) 1, 8 and 80; although these strains were not multi-drug resistant, they were more virulent due to the synthesis of the Panton-Valentine leukocidin (PVL) [17]. Finally, in the early 2000s, a high prevalence of MRSA was observed in Dutch pig breeders, in which it was 760 times higher than in the rest of the population. Further investigations showed that pigs were highly colonized by MRSA and that the isolates mainly belonged to the CC398; these strains were called Livestock-Associated (LA)-MRSA [18].

Characteristics and epidemiology of LA-MRSA

The overuse of antibiotics in pig farming has contributed to the selection and emergence of LA-MRSA. The origin of LA-MRSA CC398 is in question. It is likely that a human methicillin susceptible *S. aureus* (MSSA) strain ST398 has acquired the *mecA* gene from other staphylococci, probably coagulase negative staphylococci (CNS), and has adapted to pigs by losing human-specific immunomodulators (bacteriophage ϕ Sa3) and *pvl* genes [19].

CC398 was also isolated in other animals, including cattle, poultry, rabbits, horses and dogs, as well as humans, worldwide [20]. These strains showed the presence of SCC-*mec* type IV or V and the possible presence of genes coding for Staphylococcal enterotoxin(s) [21].

LA-MRSA strains harboring SCC-*mec* types IV and V are resistant to several classes of antibiotics, because of the selective pressure linked to the large use of antimicrobials in animal farming. However, although LA-MRSA CC398 can cause human and animal infections, it shows low virulence for humans because they have not the ability to synthesize the PVL. In fact, despite the high exposition level in countries with high pig density, few human infections caused by LA-MRSA are reported [22].

On the other hand, the substantial spread of LA-CC398 in farmed animals might represent a risk for humans, in whom it could reacquire the virulence genes that would enable the inter-human spread of MRSA infections [23].

Recently, a LA-MRSA CC9/CC398 *spa* type t899 has been described; this represents a unique genotype with a CC398 chromosomal back bone and a smaller CC9 region, which contains the staphylococcal protein A [19]. This genotype has been isolated from colonized or infected poultry and humans, which means that a subpopulation of CC9/CC398 carrying the ϕ Sa3 phage has adapted to humans and poultry [24]. This raises the possibility that ϕ Sa3-positive CC9/CC398 isolates more than the ϕ Sa3-negative ones might be disseminated, *via* the foodborne route and *via* human-to-human transmission.

MRSA in food of animal origin and its significance for food safety

Many authors have reported the presence of MRSA in food of animal origin worldwide: it has been found with different prevalence in meats such as pork (0.004 - 50%), poultry (0.7 - 43.8%), beef (1 - 15.2%), lamb (6.2%), rabbit (12.5%) and wild boar (25%), as well as in raw milk (1.7 - 17.6%), table eggs (11%) and fish (13.5%) [8,25-34]. On the other hand, it is important to stress that human MRSA strains, too, have been isolated from food, because of contamination during food handling [35]; in fact, depending on the epidemiology of the geographical area considered, about 0.7 - 1.5% of human beings are colonized by MRSA [36-38]. Therefore, nowadays, it is well known that there exists an interchange between human and animals' MRSA clones [39] but it is still unclear whether there is a foodborne risk linked to food contaminated by MRSA. However, in 1994 the 1st foodborne outbreak at the University Hospital Rotterdam, where 5 out of 27 patients died, occurred; the outbreak was caused by a human strain isolated from a worker who contaminated the food during meal preparation [40]. Also, in 2001 there was the 1st food poisoning outbreak caused by a staphylococcal enterotoxin C (SEC) producing MRSA isolated from roasted pork contaminated by food handlers [41].

Conclusion

The spread of MRSA in the food chain represents a risk for consumers who might be colonized or acquire infections by handling and/or by consuming contaminated foods [7]. In particular, CC398 *S. aureus* strains have been found in pork, chicken products, and raw turkey meat. It may be transmitted to humans from meat products by handling contaminated foods or by the cross contamination of household surfaces due to poor kitchen hygiene [42]. The therapeutic options for treating the infections caused by MRSA could be dramatically reduced because this organism is frequently multi-drug resistant. Moreover, MRSA should also be considered to be a new professional bio-hazard in the production chain of food of animal origin; thus, slaughterhouse workers, veterinarians and transport workers are at greater risk of colonization by LA-MRSA [43-46]. Several actions should be taken to reduce the public health impact of MRSA along the food chain; for example, it would be useful to implement the good hygienic practices (GHP) in farms and in food production plants as well as in domestic kitchens using appropriate training programs for breeders, food business operators and consumers. Health authorities should introduce continuous surveillance of the proper use of antimicrobials in food-producing animals and the adoption of GHP by food producers along the meat and milk production chain. Finally, to better assess the significance of MRSA as a foodborne pathogen and the related public health risks, it would be useful to investigate: i) the MRSA prevalence in less investigated food-producing species, such as buffaloes and camels, which produce a large amount of milk worldwide; ii) the ability of MRSA to survive in the human stomach and intestine; iii) the ability of MRSA to survive and multiply in food of animal origin, especially in ready-to-eat foods, such as cheeses and fermented meats.

Bibliography

1. Nolte O. "Antimicrobial resistance in the 21st century: a multifaceted challenge". *Protein and Peptide Letters* 21.4 (2014): 330-335.
2. World Health Organization (WHO). "Antimicrobial resistance global report on surveillance" (2014).
3. World Organization for Animal Health (OIE). Third Annual report on antimicrobial agents intended for use in animals (2019).
4. Van Boeckel TP. "A global plan to cut antimicrobial use in animals". The Center For Disease Dynamics, Economics and Policy. Antibiotic Resistance Blog (2017).
5. Li B., et al. "Bacteria antibiotic resistance: new challenges and opportunities for implant-associated orthopedic infections". *Journal of Orthopaedic Research* 36.1 (2018): 22-32.
6. Landers TF, et al. "A review of antibiotic use in food animals: perspective, policy, and potential". *Public Health Reports* 127.1 (2012): 4-22.
7. European Food Safety Authority (EFSA). "Scientific opinion of the panel on biological hazards on a request from the European commission on Assessment of the public health significance of methicillin-resistant *Staphylococcus aureus* (MRSA) in animal and foods". *The EFSA Journal* 993 (2009): 1-73.

8. Doulgeraki AI, *et al.* "Methicillin-resistant food-related *Staphylococcus aureus*: a review of current knowledge and biofilm formation for future studies and applications". *Research in Microbiology* 168.1 (2017): 1-15.
9. World Health Organization (WHO). Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics (2017).
10. Matsuhashi M, *et al.* "Molecular cloning of the gene of a penicillin-binding protein supposed to cause high resistance to beta-lactam antibiotics in *Staphylococcus aureus*". *Journal of Bacteriology* 167.3 (1986): 975-980.
11. Ubukata K, *et al.* "Occurrence of a 3-lactam-inducible penicillin binding protein in methicillin-resistant staphylococci". *Antimicrobial Agents and Chemotherapy* 27.5 (1985): 851-857.
12. Doyle ME, *et al.* "Methicillin-resistant staphylococci: implications for our supply?" *Animal Health Research Reviews* 13.2 (2012): 157-180.
13. Enright MC, *et al.* "The evolutionary history of methicillin-resistant *Staphylococcus aureus* (MRSA)". *Proceedings of the National Academy of Sciences of the United States of America* 99.11 (2002): 7687-7692.
14. Vanderhaghen W, *et al.* "Methicillin-resistant *Staphylococcus aureus* (MRSA) in food producing animals". *Epidemiology and Infection* 138.5 (2010): 606-625.
15. Herold BC, *et al.* "Community-Acquired Methicillin-Resistant *Staphylococcus aureus* in children with no identified predisposing risk". *Journal of the American Medical Association* 279.8 (1998): 593-598.
16. Chambers HF. "The changing epidemiology of *Staphylococcus aureus*?" *Emerging Infectious Disease* 7.2 (2001): 178-182.
17. DeLeo FR, *et al.* "Community-associated methicillin-resistant *Staphylococcus aureus*". *The Lancet* 375.9725 (2010): 1557-1568.
18. Voss A, *et al.* "Methicillin-resistant *Staphylococcus aureus* in pig farming". *Emerging Infectious Diseases* 11.12 (2005): 965-966.
19. Price LB, *et al.* "*Staphylococcus aureus* CC398: host adaptation and emergence of methicillin resistance in livestock". *American Society for Microbiology* 3.1 (2012): e00305.
20. Fitzgerald JR. "Livestock-associated *Staphylococcus aureus*: origin, evolution and public health threat". *Trends in Microbiology* 20.4 (2012): 192-198.
21. Riva A, *et al.* "Methicillin-Resistant *Staphylococcus aureus* in raw milk: prevalence, SCCmec typing, enterotoxin characterization, and antimicrobial resistance patterns". *Journal of Food Protection* 78.6 (2015): 1142-1146.
22. Monaco M, *et al.* "Livestock-associated methicillin-resistant *Staphylococcus aureus* responsible for human colonization and infection in an area of Italy with high density of pig farming". *BMC Infectious Diseases* 13 (2013): 258.
23. van der Mee-Marquet N, *et al.* "Analysis of prophages harbored by the human-adapted subpopulation of *Staphylococcus aureus* CC398". *Infection, Genetics and Evolution* 18 (2013) 299-308.
24. Larsen J, *et al.* "Evidence for human adaptation and foodborne transmission of livestock-associated Methicillin-resistant *Staphylococcus aureus*". *Clinical Infectious Diseases* 63.10 (2016): 1349-1352.
25. de Boer E, *et al.* "Prevalence of methicillin-resistant *Staphylococcus aureus* in meat". *International Journal of Food Microbiology* 134.1-2 (2009): 52-56.

26. Feßler A., *et al.* "Characterization of methicillin-resistant *Staphylococcus aureus* isolates from food and food products of poultry origin in Germany". *Applied and Environmental Microbiology* 77.20 (2011): 7151-7157.
27. Tenhagen BA., *et al.* "Methicillin-resistant *Staphylococcus aureus* in cattle food chains- prevalence, diversity, and resistance in Germany". *Journal of Animal Science* 92.6 (2014): 2741-2751.
28. Parisi A., *et al.* "High occurrence of methicillin-resistant *Staphylococcus aureus* in horses at slaughterhouses compared with those for recreational activities: a professional and food safety concern?". *Foodborne Pathogens and Disease* 14.12 (2017): 735-741.
29. Normanno G., *et al.* "Methicillin-resistant *Staphylococcus aureus* (MRSA) in foods of animal origin product in Italy". *International Journal of Food Microbiology* 117.2 (2007): 219-222.
30. Normanno G., *et al.* "Methicillin-resistant *Staphylococcus aureus* (MRSA) in slaughtered pigs and abattoir workers in Italy". *Food Microbiology* 51 (2015): 51-56.
31. Parisi A., *et al.* "Prevalence, antimicrobial susceptibility and molecular typing of Methicillin- Resistant *Staphylococcus aureus* (MRSA) in bulk tank milk from southern Italy". *Food Microbiology* 58 (2016): 36-42.
32. Syed MA., *et al.* "Detection and molecular characterization of methicillin-resistant *Staphylococcus aureus* from table eggs in Haripur, Pakistan". *Foodborne Pathogens and Diseases* 15.2 (2018): 86-93.
33. Mohammad MO., *et al.* "Prevalence of *Staphylococcus aureus* in imported fish and correlations between antibiotic resistance and enterotoxigenicity". *Journal of Food Protection* 78.11 (2015): 1999-2005.
34. Wendlandt S., *et al.* "Methicillin-Resistant *Staphylococcus aureus*: A Food-Borne Pathogen?" *Annual Review of Food Science and Technology* 4 (2013): 117-139.
35. Weese JS., *et al.* "Detection and quantification of methicillin-resistant *Staphylococcus aureus* (MRSA) clones in retail meat products". *Applied Microbiology* 51.3 (2010): 338-342.
36. Gorwitz RJ., *et al.* "Changes in the prevalence of nasal colonization with *Staphylococcus aureus* in United States, 2001-2004". *Journal of Infectious Diseases* 197.9 (2008): 1226-1234.
37. Wertheim HF. "Low prevalence of methicillin resistant *Staphylococcus aureus* (MRSA) at hospital admission in The Netherlands: the value of search and destroy and restrictive antibiotic use". *Journal of Hospital Infectious* 56.4 (2004): 321-325.
38. Munckhof WJ., *et al.* "Nasal carriage of *Staphylococcus aureus*, including community-associated methicillin-resistant strains, in Queensland adults". *Clinic Microbiology Infectious* 15.2 (2009): 149-155.
39. Zarazaga M. "Molecular epidemiology of *Staphylococcus aureus* lineages in the animal-human interface". Editor: Alexandra Fetsch, *Staphylococcus aureus*, Academic Press (2018): 189-214.
40. Kluytmans J., *et al.* "Food initiated outbreak of methicillin-resistant *Staphylococcus aureus* analyzed by pheno- and genotyping". *Journal of Clinical Microbiology* 33.5 (1995): 1121-1128.
41. Jones TF., *et al.* "An outbreak of community-acquired foodborne illness caused by methicillin-resistant *Staphylococcus aureus*". *Emergent Infectious Diseases* 8.1 (2002): 82-84.
42. Smith TC. "Livestock-associated *Staphylococcus aureus*: the united states experience". *PLoS Pathogens* 11.2 (2015): e1004564.
43. Van Cleef BA., *et al.* "High prevalence of nasal MRSA carriage in slaughterhouse workers in contact with live pigs in The Netherlands". *Epidemiology and Infection* 138.5 (2010): 756-763.

44. Hanselman BA, *et al.* "Methicillin-resistant *Staphylococcus aureus* colonization in veterinary personnel". *Emerging Infectious Diseases* 12.12 (2006): 1933-1938.
45. Oniciuc EA, *et al.* "Presence of methicillin-resistant *Staphylococcus aureus* in the food chain". *Trends in Food Science and Technology* 61 (2017): 49-59.
46. Li Z. "A Review of *Staphylococcus aureus* and the Emergence of Drug-Resistant Problem". *Advances in Microbiology* 8 (2018): 65-76.

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