A Focus on Aquatic Animals

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Contributor: Gilberto Igrejas, Patrícia Poeta, Vanessa Silva, José Pereira

Staphylococcus aureus (S. aureus) are one of the best-known opportunistic pathogens capable of causing different types of infections in animals. Furthermore, it has the ability to acquire resistance to various antibiotics very easily. Methicillin-resistant S. aureus (MRSA) are currently of great concern as they are the leading cause of infections in humans and animals, with a major impact on health and the economy.

Keywords: MRSA ; wildlife ; aquatic animals

1. Introduction

The rapid emergence of multiresistant bacteria is one of the greatest threats to public health worldwide. According to the European Center for Disease Prevention and Control, in Europe alone, antibiotic resistance has an economic impact of around EUR 1.5 billion and is estimated to be responsible for approximately 33,000 deaths each year [1]. This problematic situation is, in large part, related to the incorrect prescription of these drugs, their overuse, and the lack of development of new drugs due to the low economic investment in the pharmaceutical industries [2]. Epidemiological studies have already shown that there is a direct relationship between the overuse of antibiotics and the emergence of resistant bacterial strains. However, despite warnings about the consequences of their overuse, these drugs continue to be highly prescribed worldwide [3], especially penicillins, which currently account for 85% of beta-lactams used [4]. The penicillinase enzyme was first detected in Staphylococcus aureus (S. aureus) shortly after penicillin began to be used, which shows that the consumption of an antibiotic will eventually favor the selection of resistant strains [5]. Furthermore, in some countries, antibiotics can be easily purchased without the need for a medical prescription and at a low cost, which can cause their consumption to be uncontrolled [6]. The incorrect prescription of antibiotics in the hospital sector also contributes to the emergence of resistance. According to some studies, the choice of antibiotic, as well as the duration of treatment, is incorrect in 30–50% of cases [7]. The incorrect prescription of these drugs has questionable therapeutic benefits and can bring potential complications for the patient [8]. The use of these drugs in the agricultural sector has also been identified as a risk factor for the emergence of resistance and has received special attention in recent years. Although the administration of antibiotics in farm animals has already been banned in Europe, in many countries, antibiotics continue to be used indiscriminately to promote the growth of these animals [9]. The indiscriminate use of antibiotics, whether in human or veterinary medicine, creates a natural selective pressure in which resistant bacteria survive and reproduce, even in the presence of the antibiotic [10]. When used in sub-inhibitory concentrations, an antibiotic is able to promote genetic alterations, such as alterations in gene expression, horizontal gene transfer and mutagenesis [11]. Antibiotic-induced changes in gene expression can increase the virulence of the bacterial strain in question, while mutagenesis and horizontal gene transfer processes promote antibiotic resistance and its spread, respectively [11]. Although this issue has emerged in clinical practice, antimicrobial resistance is found in several other sectors such as animal production facilities, agriculture, effluents and water systems, making it a problem that involves not only humans and animals, but also the entire environment [12][13][14][15][16]. In addition, the microorganisms found in the environment converge with human and animal pathogens, and there may be exchanges and transfers of resistance genes between different bacterial strains, which further aggravates this problem [5]. Due to this situation, it has already been estimated that most antibiotics currently used to fight bacterial infections will become completely useless within five to ten years, taking us back to the pre-antibiotic era [10].

2. Staphylococcus spp.

The Staphylococcus genus belongs to the Staphylococcaceae family and features cocci-shaped microorganisms that are capable of causing various infections. This family includes more than 45 species and 24 subspecies, presenting typically respiratory and fermentative metabolisms, most of them aerobic or facultative anaerobic [17]. These bacteria were first described by surgeon Sir Alexander Ogston in the 1980s and their name comes from the Greek staphylos (grape) and

kokkos (berry). They are typically characterized as being Gram-positive and catalase-positive, although some strains have been identified as catalase-negative. Furthermore, these bacteria are capable of producing a huge variety of virulence factors responsible for their level of pathogenicity [18].

S. aureus are one of the species of the Staphylococcaceae family, classified as coagulase-positive (SCoP), oxidase-negative and salt-tolerant (they are able to grow in a medium containing 10% NaCl) [17]. These bacteria are generally commensal residents of the human flora, residing in the skin and mucosa of about 30% of individuals. However, commensal staphylococci are recognized as opportunistic pathogens capable of causing a wide variety of infections [19]. In the case of S. aureus these infections can range from skin and soft tissue infections to more severe infections such as necrotic pneumonia, endocarditis and osteomyelitis [20]. This bacterium has the ability to infect almost every organ system in the human body, often with fatal consequences. This remarkable adaptability is largely due to the wide range of virulence factors they produce, many of which are encoded in plasmids, transposons, prophages, and pathogenicity islands [5]. The acquisition of resistance genes to a variety of antibiotics has made S. aureus one of the most important pathogens today. Methicillin-resistant S. aureus (MRSA) are currently a serious problem in hospitals around the world. These bacteria are estimated to be responsible for around 171,200 infections in Europe each year [21]. These bacteria were first described in 1961 in England, shortly after methicillin was introduced into clinical practice [22]. However, the genome sequencing of some isolates suggests that these bacteria may have emerged in the 1940s, due to the excessive use of penicillin [22]. In fact, just 2 years after the introduction of penicillin, around 80% of S. aureus isolates were resistant to this antibiotic [23]. Methicillin resistance occurred through two distinct mechanisms: firstly, by producing enzymes that hydrolyze and destroy beta lactams, called beta lactamases, which were encoded by the bla Z gene [24]; then, by producing a modified penicillin binding protein (PBP2a) that participated in the synthesis of peptidoglycan, a natural component of the bacterial cell wall. However, this modified protein had an inaccessible active site, preventing antibiotic binding and thus, cell wall synthesis was not affected, allowing the bacteria to survive [23]. The PBP2a protein was encoded by the mec genes (mec A/ mec C). These genes were embedded within the staphylococcal mec cassette (SCC mec), a highly transmissible mobile genetic element between bacteria, which could be classified into at least 14 different types (I-XIV) [25].

Initially, MRSA was restricted only to the hospital environment, causing different types of nosocomial infections and, for this reason, they were called HA-MRSA (Hospital-acquired MRSA) [26]. Years later, MRSA began to be identified in individuals with no prior contact with the hospital environment and thus came to be called CA-MRSA (Community-acquired MRSA) [27]. More recently, a third type of MRSA strain associated with farm animals (LA-MRSA) has been reported. Genotypically CA-MRSA strains were newer and more virulent and usually contained SCC mec type IV or V [26]. Despite being susceptible to non-beta lactam antibiotics, these strains generally carried the gene for Panton-Valentine leukocidin, a protein associated with greater virulence [28]. On the contrary, HA-MRSA strains were associated with SCC mec types I, II, and III, and were resistant to non-beta lactam antibiotics, especially aminoglycosides, macrolides, lincosamides and fluoroquinolones [26].

CA-MRSA strains have been extensively studied in recent years and have been reported in several animals including domestic pets, cattle, pigs and horses, as well as in wild animals. Conversely, MRSA strains associated with farm animals (LA-MRSA) have emerged in the human population, which highlights the idea that there is a traffic of these microorganisms between different species.

3. MRSA in Animals

The first reported case of MRSA infection in animals was the case of a bovine mastitis that occurred in Belgium in the early 1970s. After this case many others followed in both companion and farm animals. Molecular typing studies demonstrated that some MRSA strains have host specificity, while others were capable of colonizing or infecting a wide variety of animals [29]. Typing studies were of high clinical and epidemiological importance as they allowed for the determination of causes of infection, modes of transmission and relationships with other bacteria, as well as accessing the specific characteristics of a particular genetic lineage [5]. Thus, MRSA were generally characterized by Multilocus Sequence Typing (MLST), spa -typing or SCC mec typing. **Table 1** describes the main MRSA genetic lines associated with companion and farm animals.

Table 1. Major MRSA strains associated with companion animals and farm animals.

	ST	***spa*-Types**
Companion animals	**ST5, ST22, ST398**	**t032, t432, t747, t4726**

	ST	*spa*-Types
Horses	**ST1, ST8, ST22, ST254, ST398**	**t11, t036, t127**
Pigs	**ST1, ST9, ST97. ST398**	**t011**
Cattle	**ST8, ST130, ST398**	**t011, t034**
Birds	**ST5, ST398**	**t011, t567**

ST: sequence type.

In farm animals, the first case of MRSA colonization was reported in 2005 in the Netherlands [30]. This new MRSA clone with ST398 was identified in pigs and clustered within the clonal complex (CC) 398 [9]. In another European study that analyzed the presence of MRSA associated with pigs, it was found that the most frequent strain was ST398, but other strains such as ST1, ST9 and ST97 were also reported [31]. In fact, it is scientifically well-known that the CC398 strain asymptomatically colonizes about half of these animals in swine farms. Although ST398 is mostly associated with swine, this lineage has also been reported in other farm animals [32][33]. This strain has a broad host spectrum and is commonly found in 77–86% of people with occupational activities who have direct contact with pigs, causing the same type of infections in humans as other strains of S. aureus or MRSA in general [34]. Additionally, the strain CC130 appears to have a low host specificity. In a very large study by Monecke et al. , 2016, this strain was identified in a huge variety of animals such as the rat, hedgehog, red fox, common hare and deer [35]. Some MRSA strains appear to be specific to bovines, namely CC130, ST425 and CC1943 [29]. In fact, S. aureus is currently the leading cause of infection in cows, with a huge economic impact on the dairy industry [29]. A study by Tenhagen et al. concluded that most MRSA isolates obtained from these animals, regardless of their origin, belonged to the types t011 and t034, both associated with the CC398 clonal complex [36].

In the case of companion animals such as dogs and cats, a correlation between the clonal types found in these animals and the clonal types that infect humans in the same geographic region has already been verified [29]. Apparently, contact between pets and their owners favors the transmission of these bacteria. Therefore, the clonal types most frequently found in companion animals correspond to the clonal types dominant at that location. For example, in the UK, MRSA isolates from dogs correspond to the dominant HA-MRSA strain at that site, ST22 [37]. The same results are obtained in Portugal, where four different spa types were identified (t032, t432, t747 and t4726), with t032 being the most frequent [38].

In horses, the most frequently found MRSA strains are, as with companion animals, strains associated with humans. The strain, CC8 (ST8 and ST254), is associated with the most cases of colonization and infection in horses in Canada, while in Europe the most frequently reported strains are ST1, ST22, ST254 [39]. In the same study, the spa types reported were t036, t011 and t127, with t036 being the most frequent.

4. MRSA in Aquatic Animals

In general, it is possible to verify that there is a huge genetic variety of S. aureus associated with different animal species in several continents. Wildlife can serve as a reservoir for S. aureus , and later on there may be a transmission to domestic animals, farm animals and, directly or indirectly, to humans. These natural S. aureus reservoirs contribute to the exchange of resistance and virulence genes between bacteria, enhancing the appearance of new strains [40]. **Table 2** shows the genetic diversity of MRSA and methicillin-susceptible S. aureus strains (MSSA) strains isolated from aquatic animals.

Another study carried out in Italy linked the death of two dolphins to an infection caused by a strain of MRSA. In this study, the two animals of different origins were submitted to a detailed necropsy through microbiological examinations, among others. Confirmation of MRSA was done through genetic analyses such as spa-typing, PFGE and MLST. In both animals, the MRSA strain found belonged to ST8 and spa-type t008. Through the PFGE analysis it was possible to conclude that the analyzed strains were 100% identical. It was also possible to identify the presence of the nuc gene, as well as other genes responsible for antibiotic resistance such as the mec A gene and other penicillinase genes (bla Z, bla I, bla R). This is the first work to identify the ST8 t008 strain in dolphins, although this strain has already been randomly isolated from human patients, as well as from other animals [41]. Previous studies already expressed a concern for the potential pathogenicity of S. aureus in those animals [42][43][44][45]. However, the authors of this study consider that the predisposing factors impairing the immune system of these dolphins played a central role in their death. Consequently, the isolated bacteria should not be considered as the primary cause of their decease. However, these findings support the need for a continuous monitoring plan to be implemented in both wild animals and domestic animals under human care, both in open and closed water systems.

Colonization by S. aureus has also been reported in other aquatic animals such as white swan and common porpoise. One S. aureus isolate belonging to the clonal complex CC133 associated with a white swan and an isolate CC112 in a common porpoise has been identified [35].

Although only a few studies have been conducted regarding the presence of MRSA and MSSA in aquatic animals, the most common clonal lineage among these animals was ST8-t008. This particular clone is also known as the USA300 and is one of most widespread S. aureus clones [46]. Initially, this clone was associated with CA-MRSA, but it has been isolated from patients in healthcare facilities, animals and the environment [46][47][48][49]. USA300 gained much attention recently due to its pathogenic properties and virulence which were linked to severe infections [50]. MRSA USA300 strains had a few specific features such as belonging to SCC mec IV and being PVL-positive [47]. However, most of the studies mentioned above did not investigate the SCC mec type, nor the presence of PVL. MRSA ST72 was detected in two animals, namely, whales and sea bass, from the USA and Korea, respectively. ST72 was the most significant and prevalent CA-MRSA clone in South Korea [51]. Nevertheless, this clone has been identified in the meat and milk production chain in Korea [52][53]. CC133 and CC97 were also detected in aquatic animals. Both clonal lineages were associated with ruminants and were reported in [54][55]. Other MRSA and MSSA clonal complexes found among aquatic animals, such as, CC1, CC12 and CC15, were common in human strains, either causing infections or colonizing the organism [56].

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