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The clinical impact of livestock-associated methicillin-resistant *Staphylococcus aureus* of the clonal complex 398 for humans

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ABSTRACT

In the past decade, livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) strains in particular of the clonal complex (CC) 398 have emerged in many parts of the world especially in areas with a high density of pig farming. In those regions, farmworkers and other individuals with professional contact to livestock are very frequently colonized with LA-MRSA. These persons are the presumably source for LA-MRSA transmission to household members and other parts of the human population. Altogether, colonization and/or infection of these individuals lead to the introduction of LA-MRSA into hospitals and other healthcare facilities. Since LA-MRSA CC398 have been found to be specifically adapted to their animal hosts in terms of the equipment with virulence factors, their pathogenicity to human patients is a matter of debate with first reports about clinical cases. Meanwhile, case reports, case series and few studies have demonstrated the capability of LA-MRSA to cause all types of infections attributed to *S. aureus* in general including fatal courses. Human infections observed comprise e.g. bacteremia, pneumonia, osteomyelitis, endocarditis and many manifestations of skin and soft tissue infections. However, inpatients affected by MRSA CC398 generally show different demographic (e.g. younger, shorter length of hospital stay) and clinical characteristics (e.g. less severe complications) which may explain or at least contribute to a lower disease burden of LA-MRSA compared to other MRSA clonal lineages.

1. Introduction

Since the earliest times of the differentiation of pathogens, *Staphylococcus aureus* is one of the leading causes of bacterial infections within and outside of the hospital. Infections are associated with high morbidity, mortality and economic impact (Becker et al., 2015; Ogston, 1882). The burden of disease by this opportunistic pathogen is even more severe, if methicillin-resistant *S. aureus* (MRSA) strains are involved. Therefore, it was somewhat surprising that following the first descriptions of humans colonized or infected by livestock-associated MRSA (LA-MRSA) a debate started whether LA-MRSA isolates are characterized by the same pathogenicity and virulence as "normal" members of *S. aureus* species. These considerations were due to observations of the first years of the LA-MRSA CC398 epidemics (i) with no fatal cases reported and an imbalance between colonization and infection rates (Grundmann et al., 2010; van Cleef et al., 2011; Wulf and Voss, 2008), (ii) with published data about the specific adaptation of this clonal lineage on animal hosts (Price et al., 2012; Schijffelen et al., 2010) and (iii) with the suggestion of this lineage being a poor persistent colonizer in humans (Gravelland et al., 2011). Moreover, the vast majority of colonized pigs, cattle and poultry develop no clinical signs of infection. However, many case reports and case series as well as some studies have demonstrated in the meantime the capability of the CC398 clonal lineage to cause all types of human infections attributed to *S. aureus* in general including mild and severe manifestations and even fatal courses.

2. Colonization and transmission

Compared to infections due to hospital-associated MRSA (HA-MRSA) or non-livestock-associated community-acquired MRSA (CA-MRSA), the assessment of the general epidemiology and clinical impact of LA-MRSA is hampered by the fact that there hitherto is no uniform spread of MRSA CC398, but a regionally increased occurrence of this lineage in healthcare facilities located in areas with a high density of (pig) farming (Feingold et al., 2012; Schaumburg et al., 2012). In these regions, a high number of

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farmworkers and other individuals with professional contact to livestock or — in a lesser extent – processors of slaughter cattle and meat products is colonized with LA-MRSA (Bisdorff et al., 2012; Graveland et al., 2011; Köck et al., 2011; van den Broek et al., 2008; Vandendriessche et al., 2013; Wulf et al., 2008b). Besides occupational contact, private farm visits or contact with persons who are directly exposed to livestock may also increase the risk for LA-MRSA acquisition (Bisdorff et al., 2012; Cuny et al., 2009; Garcia-Graells et al., 2013). These persons are the presumably source for LA-MRSA transmission to other parts of the human population. Furthermore, transmissions to non-food-producing animals, in particular to horses, but also to other companion animals occur and these animals could act as contaminated vectors (Loeffler et al., 2011; van Duijkeren et al., 2010; Vincze et al., 2014). However, for a substantial number of MRSA CC398 colonized or infected persons (20% or even more), contact with livestock was not documented; thus, other potential indirect ways of MRSA CC398 acquisition may be relevant as well (Deiters et al., 2015; Lekkerkerk et al., 2012; Omland and Hoffmann, 2012; Wulf et al., 2012). Altogether, colonization and/or infection of respective individuals lead to the introduction LA-MRSA into human (and veterinary) hospitals and other healthcare facilities. Meanwhile, in some regions, e.g. in the Netherlands, Germany and Spain, the proportion of MRSA CC398 isolates among all MRSA isolates from human clinical specimens reached significant scales of up to 30% (Köck et al., 2013; Lozano et al., 2012; Schaumburg et al., 2012; van Cleef et al., 2011; Wulf et al., 2012). The fact that MRSA CC398 transmission between hospital personnel and patients can occur was highlighted by nosocomial outbreaks in the Netherlands (Verkade et al., 2012b; Wulf et al., 2008a). Exemplarily, a *spa* type t567 strain was able to affect five patients and to colonize five healthcare workers (Wulf et al., 2008a).

There is limited knowledge about the rates of colonization of humans outside hospitals and other healthcare facilities (e.g. nursing homes). Within a prospective cohort study among 1878 non-hospitalized volunteers recruited from the general population of a "pig-dense" region in Germany only 0.8% individuals were colonized with MRSA. However, the proportion of MRSA on all *S. aureus* isolates was significantly higher in people with livestock contact with 40% of the MRSA strains belonging to *spa*-types indicative for the CC398 lineage (Kaspar et al., 2015).

3. Characteristics of hospital patients colonized with LA-MRSA

In general, hospitalized patients carrying MRSA CC398 differ in many characteristics from those patients being colonized or infected with classical HA-MRSA clonal lineages; characteristics of these patients are rather similar to those of patients affected by CA-MRSA. Comparing several clinical and demographic characteristics of inpatients of the University Hospital Münster, which is located in a German region with a high density of pig production (Köck et al., 2009), colonized with either MRSA CC398 or other clones, MRSA CC398 carriers were significantly younger (mean age: 53 vs. 59 years), usually male (70% vs. 57%), had a shorter length of hospital stay (LOS; 7.5 vs. 12.6 days) and were less frequently treated on intensive care units (ICUs) (12% vs. 17%) (Köck et al., 2011). Higher proportions of males and patients from >15 to <65 years of age for LA-MRSA were also noted in a recent Dutch study (van de Sande-Bruinsma et al., 2015). Due to the fact that age, LOS and ICU admission is associated with the risk of developing nosocomial infections, it seems reasonable that the risk of healthcare-associated infections is lower for MRSA CC398 colonized patients. In this study, this observation was supported by significant differences concerning the mean numbers of diagnoses per admission made for the MRSA patients (2.8 for CC398 MRSA vs. 4.1 for non-CC398 patients) and the mean number of medical procedures performed (6.8 for CC398 MRSA vs. 11.8 for non-CC398 patients). In particular, heart or respiratory diseases, metabolic disorders, anemia, diseases of the digestive system, and renal failure were significantly less frequent among patients colonized with MRSA CC398. Moreover, also a variety of invasive measures such as mechanical ventilation, endoscopies, blood cell transfusion and therapeutic catheterization were more often performed for non-CC398 MRSA patients (Köck et al., 2011).

Hence, MRSA CC398 patients do rather not represent a multi-morbid high-risk population as known for patients colonized or infected by HA-MRSA. These different inpatient characteristics may explain or at least contribute significantly (besides biological factors) to the more limited burden of infections due to LA-MRSA compared to HA-MRSA.

4. Infections due to CC398 LA-MRSA in the human host

Meanwhile, infections due to LA-MRSA CC398 have been reported from many European countries, predominantly from The Netherlands, the Northwestern part of Germany (mainly Westphalia and districts of Lower Saxony) and Spain; but also from Austria, Belgium, Denmark, Finland, France, Italy and Slovenia (Table 1). Many, but not all cases were reported from areas with a high density of livestock production or were found to be related with an occupation that is associated with livestock.

Outside Europe, *S. aureus* CC398-associated infections are rather rarely observed so far (Table 1). While the most predominant LA-MRSA lineage in Asia is ST9 (Chuang and Huang, 2015), fatal septicemia due to MRSA CC398 has been reported in Japan for a Chinese woman (Koyama et al., 2015). Several reports on CC398 detection in livestock or their recovery from human specimens of Chinese patients or from unrelated children in Denmark adopted from China suggest that China might be a hot spot for Asian MRSA CC398 (Stegger et al., 2009; Yu et al., 2008). In Canada, skin and soft tissue or wound infections caused by MRSA CC398 have been reported (Golding et al., 2010). While MRSA CC398 were found among industrial livestock operation workers in North Carolina (Rinsky et al., 2013), other North American studies in Pennsylvania and Iowa, states with a high livestock density, failed to detect MRSA CC398 isolates in patients (Casey et al., 2014; Eko et al., 2015), but demonstrated evidence that other MRSA strains, beyond CC398, may be involved in LA-MRSA infection in the United States (Casey et al., 2014). From Africa, CC398-associated infections have not been documented until now. However, a tetracycline-resistant MRSA isolate associated with *spa* type t899 (indicative for CC398) was recently recovered from a patient working as a farmer in Tunisia (Elhani et al., 2015).

While differences between subclones of the CC398 clonal complex in terms of the pathogenicity have been shown in vitro for *spa* type t108, which exhibited an increased adhesive and invasive potential paired with a better ability to evade phagocytosis (Ballhausen et al., 2014), there is hitherto little evidence for a subtype-specific association with specific diseases or courses of MRSA CC398 infection. In a Dutch retrospective analysis, an over-representation of *spa* t567 has been observed among clinical isolates (Wulf et al., 2012). CC398 subclones that were regularly found as causative agents for infections comprise t011, t034 and t108 as the most prevalent *spa* types, but infections with e.g. t588, t571, t899, t1451, t2346, t2576 and t2871 have also been described (Camoez et al., 2013; Köck et al., 2013, 2011; Monaco et al., 2013; Schaumburg et al., 2012; van Cleef et al., 2013).

The clinical spectrum of MRSA CC398 infections is as broad as known for *S. aureus* infections in general. Most of the described clinical presentations comprise several types of skin and soft tissue infections including superficial and wound infections, but also a case of necrotizing fasciitis has been published from Italy (Table 1).

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