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Community-acquired methicillin-resistant Staphylococcus aureus: what do we need to know?

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Abstract

Community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA) has become a matter of concern worldwide, in particular in the USA. For the analysis of emergence and spread, clear definitions based on epidemiological origin are needed for discrimination between CA-MRSA, healthcare-associated community MRSA, and healthcare-associated MRSA (HA-MRSA). Although its role in pathogenesis is currently under debate, the capability for Panton–Valentine leukocidin formation is associated with the majority of CA-MRSA isolates from North America and from Europe. Most CA-MRSA isolates are attributed to clonal lineages different from HA-MRSA; there are, however, clonal lineages from which both HA-MRSA and CA-MRSA have been reported (e.g. ST1, ST5, ST8, and ST22); CA-MRSA ST8 (USA300), which is most frequent in the USA, has meanwhile been reported from Europe. CA-MRSA ST80 is widely disseminated in Europe; because of its pronounced oxacillin heteroresistance phenotype, cefoxitin-based assays are advisable for reliable detection. So far, CA-MRSA infections seem to be much less frequent in Europe than in the USA, where patients with particular predispositions and low social status are at especial risk.

Introduction

Nosocomial infections caused by Staphylococcus aureus represent a considerable burden on healthcare; infected patients have prolonged hospital stays, entail high hospital costs, and suffer increased in-hospital mortality. With a few exceptions, methicillin-resistant S. aureus (MRSA) has been a problem in hospitalized patients for decades in many parts of the world [1]. Historically, patients who developed MRSA infections in the community had traditional risk factors associated with treatment in nosocomial settings [2,3]. With the recent emergence of MRSA infections in patients lacking contact with a hospital setting or with humans treated in hospitals, the term community-associated MRSA (CA-MRSA) has been introduced [3–5]. CA-MRSA was first reported from infections in remote populations in Australia, and in the USA, by the end of the 1990s, cases of fatal infections in children in Minnesota and North Dakota were the focus of attention [5–7]. Since then, MRSA infections have also been reported from Europe [8–13], from the near East, and from Asia and Oceania [14]. Particularly in the USA, CA-MRSA strains are pervasive among S. aureus isolates from skin and soft tissue infections (SSTIs) [15–18]. Although much less frequent than infections of the skin, CA-MRSA strains also can cause invasive, rapidly progressive, life-threatening infections, such as necrotizing pneumonia [18], severe sepsis [19], and necrotizing fasciitis [20]. Of particular concern are recent reports about the introduction of highly epidemic CA-MRSA strains into hospitals, followed by severe infections in hospitalized patients [19,21]. When dealing with CA-MRSA strains, the following questions need to be answered.

Are Clear Definitions Used for Discrimination of CA-MRSA?

Usually, patients affected by CA-MRSA infections lack the risk factors that are more commonly associated with the acquisition of healthcare-associated MRSA (HA-MRSA). These factors include prolonged hospital stay, care in intensive-care units, prolonged antibiotic treatment, surgical interventions, and close contact with MRSA-positive individuals. For patients with MRSA infection/colonization in the community but with previous hospitalization, residing in a nursing home, receiving home nursing or attending centres for dialysis and/or centres for diabetes who acquire MRSA of hospital origin [22], the term healthcare-associated community MRSA should be used.

Furthermore, the emergence and spread of MRSA among animals such as pets and horses has been observed [23–25]. Increasing reports on the wide spread of one particular clonal complex (CC398) among commercial livestock (livestockassociated
MRSA) are of particular interest [26–28].

The epidemiological definition of CA-MRSA suggested by Salgado et al. [3], and also advocated by the CDC [4], is shown in Fig. 1. This epidemiological definition seems to be sensible at first sight. However, several more recent studies in the USA have described a more complex epidemiology; both HAMRSA and CA-MRSA now circulate in the community, and strains exhibiting molecular traits of previously clearly community-associated MRSA (e.g. CA-MRSA 'USA300') are increasingly being reported from nosocomial infections [21,29–34].
In addition to epidemiological criteria, antibiotic susceptibility patterns and molecular typing have been thought to distinguish CA-MRSA from HA-MRSA. Although CA-MRSA isolates often remain more susceptible overall to erythromycin, clindamycin, and fluoroquinolones, we have to remember that there are HA-MRSA isolates that still have a narrow spectrum of resistance, such as ST45 in Europe [35], and CA-MRSA isolates with resistance to oxytetracycline and to fusidic acid, such as CA-MRSA ST80, and to macrolides and fluoroquinolones, such as CA-MRSA USA300 [36].

Regarding molecular typing characteristics, there are CA-MRSA isolates attributed to clonal lineages for which HA-MRSA isolates have not been reported so far, such as ST59 and ST152; there are, however, also clonal lineages from which both HA-MRSA and CA-MRSA isolates have evolved, such as ST1, ST5 [10,12], ST8 [36], and ST22 [37]. The use of staphylococcal cassette chromosome mec (SCCmec) IV as a marker for CA-MRSA has substantial limitations, as SCCmec IV elements are also present in a number of HA-MRSA lineages, such as ST5, ST254, ST22, and ST45 [38].

Epidemiological and clinical data provide strong evidence for a close association between epidemic CA-MRSA and the capacity for Panton–Valentine leukocidin (PVL) formation in isolates from North America and from Europe [39]. Interestingly, particular lineages of CA-MRSA that are widely disseminated in Japan and Hong Kong lack PVL [40,41]. Although the role of PVL in the pathogenesis of deep-seated SSTIs, sepsis, and necrotizing pneumonia is far from being understood, and other factors are probably also important, the PVL-encoding genes lukS-PV and lukF-PV can be used as markers for epidemic and CA-MRSA strains with comparably high virulence.

Is Diagnosis in Clinical Bacteriology Sufficiently Sensitive for Detection of MRSA with Low-Level Oxacillin Resistance?

Reliable detection of methicillin resistance is particularly problematic in MRSA isolates with pronounced heterogeneous expression of this resistance trait, such as isolates of HA-MRSA ST45 [42] and CA-MRSA ST80 [43], which represents the most widely disseminated CA-MRSA lineage in Europe.

When the disk diffusion assay is performed, the use of 5-µg disks and a semi-confluent inoculum is problematic [43], and the results need to be confirmed, as recommended by the CLSI [44]. This problem can be overcome by the use of cefoxitin as test substance [45]; here, attention needs to be given to the type of agar medium used (Mueller–Hinton Agar or IsoSensitest) when breakpoints and zone diameters are being interpreted [46].

How Frequent are Infections Caused by CA-MRSA in Europe?

In the USA, the emergence of CA-MRSA began with infections unrelated to hospitals in otherwise healthy individuals, at first in children [5,47], and later in professional players of American football and other sports [48], military teams [49,50], Alaskan natives [51], men who have sex with men [18,52], drug abusers, and prisoners [53], for whom real outbreaks have been described. During the past 5 years, however, CA-MRSA has obviously become more widely disseminated.

Fridkin et al. [15], who examined 1647 cases of CA-MRSA infection in two large metropolitan areas of the USA, reported an 8–20% frequency of CA-MRSA among non-hospital-related S. aureus infections. This is an agreement with more recent data from Pennsylvania. In Los Angeles, the prevalence of CA-MRSA increased from 29% in 2001 to 64% in 2004 [54]; similar data were reported from San Francisco in 2005 [55], Sylmar in California [56], Georgia [57], and Texas [16].

In Europe, the emergence of CA-MRSA has been a focus of attention since 2003; however, retrospective analyses indicate sporadic cases occurring earlier. Of particular interest is a series of infections with CA-MRSA ST80 in Denmark encompassing 46 individuals in 26 households from November 1997 until June 2003 [58]. The prevalence is obviously still considerably lower than that in the USA, although increasing frequencies are being reported from countries where the incidence of HA-MRSA is quite low, and thus CAMRSA is more the focus of attention, such as The Netherlands and Denmark.

In a study in Germany on 235 dermatology outpatients from the Rhine/Main area attending the ambulatory department of Heidelberg University for treatment of an S. aureus infection, four of nine MRSA isolates were found to be PVL-positive [59]. These patients affected had no previous treatment in the nosocomial setting, whereas for the remaining five of them the acquisition of nosocomial HA-MRSA (ST32 and ST22) due to chronic infections was likely. Altogether, 207 (1.74%) of 12 350 MRSA isolates of various origin sent the German National Reference Centre for typing from 2003 to 2006 were found to be PVL-positive [60].

A study in France in 2003 and 2004 on 238 patients admitted to an emergency department revealed that 93 of them (39%) were positive for MRSA; for 84, at least one hospital stay was documented for a 12-month period prior to this study. PVL-positive MRSA isolates were found in seven (2.9%) of the 93 patients [61]. Among 14 253 patients admitted to Geneva hospital in Switzerland, CA-MRSA prevalence as defined by epidemiological criteria was 0.9/ 1.000 admissions. Five of the MRSA isolates were PVLpositive [10]. Although it was still present at a low level in comparison to the USA, an increasing frequency of CA-MRSA during 2000–2006 was reported from England [62]. Although there is also a recent report about a severe infection with CA-MRSA USA300 from Italy [63], CA-MRSA seems, so far, to be rare in this country [64].

In Denmark, where the prevalence of MRSA is low in general, CA-MRSA ST80 predominates among CA-MRSA isolates belonging to other clonal lineages; epidemiological analysis has indicated that the ST80 isolates have been introduced to Denmark on multiple occasions from the Mediterranean and the Middle East [65].

What Makes the Difference between the USA and Europe?

The difference between the USA and Europe is clearly not a question of different clonal lineages of CA-MRSA; strain USA300, which is most frequent in the USA, has been present in Europe for at least 2 years [60–63,66]. The findings of several studies in the USA indicate that low social standards, with homelessness in the worst case [55,56,67], are, besides professional or leisure sports activities and military service, the main risk factors for the emergence and spread of CAMRSA. This is very probably associated with elevated rates of crime and incarceration. The spread of CA-MRSA in prisons in the USA is well documented, and prior incarceration has been identified as a risk factor [53]. Intravenous drug abuse falls into the same category. Furthermore, sexual activities have to be considered, among heterosexuals [68] as well as among men who have sex with men [52]. Thus, human immunodeficiency virus infection and other sexually transmitted infections, such as syphilis and/or group B streptococcal infection/colonization, which indicate a high level of promiscuity, have been more frequently found among individuals with CA-MRSA infections in the USA [69].

CA-MRSA can spread rapidly if purulent skin lesions are not treated in an appropriate manner, owing to a lack of sufficient access to healthcare. All of these factors may be present in particular large urban communities in the USA [70]. There are very probably similar communities in some larger European cities; with respect to infectious diseases, the situation in large Russian cities has to be mentioned. Under these circumstances, we cannot exclude the possibility of a spread of CA-MRSA similar to that in the USA.

Widespread Dissemination of Particular Clonal Lineages or Frequent de novo Evolution of CA-MRSA?

An essential prerequisite for answering this question is molecular typing. For nearly three decades, phage typing was broadly used in S. aureus epidemiology, and became increasingly difficult to interpret in the case of tracing and discrimination of MRSA. By the early 1990s, SmaI macrorestriction (pulsed-field gel electrophoresis) had been introduced, and this method represents the current reference standard with respect to discriminatory power [71]. Clusters of SmaI patterns are widely congruent with clonal lineages as defined by multilocus sequence typing (MLST) [72], which is based on allelic polymorphisms of seven housekeeping genes [73]. MLST lineages widely reflect the evolution of the population structure of S. aureus [38]. Spa-sequence typing, which is based on the repeat polymorphism of the X-region of the spa gene, is nearly as discriminatory as SmaI macrorestriction patterns [74]. When spa types are grouped by use of the BURP algorithm [75], these clusters are fairly congruent with clonal complexes as obtained from BURST analysis of MLST findings [72]. There are a few exceptions in the case of recombinational exchange of large chromosomal regions containing the spa gene (e.g. in HA-MRSA ST239) [76].

When, however, spa types of particular CA-MRSA clonal lineages are attributed to clonal lineages by means of the BURP algorithm, different clonal lineages can be grouped together, such as CA-MRSA ST80 with CA-MRSA ST1, methicillin-resistant S. aureus (MSSA) ST15, MSSA ST097 and MSSA ST07, and CA-MRSA ST30 with MRSA ST398 [77]. PCRs for arcA (ST8), seh (ST1) and etd (ST80) are helpful for unambiguous attribution of the most frequent CA-MRSA isolates to clonal lineages, and can be performed in routine clinical bacteriology laboratories [78].

The most frequent spa types among CA-MRSA are shown in Table 1, and the clonal lineages from which HA-MRSA and CA-MRSA have evolved are shown in Fig. 2.

CA-MRSA strains may have evolved: (i) from already existing PVL-positive MSSA by acquisition of SCCmec elements; (ii) from HA-MRSA by acquiring further genes, enabling them to cause invasive SSTIs and to spread more efficiently outside the hospital (e.g. lukS-PV/lukF-PV-containing phage); or (iii) by acquisition of SCCmec and other genes from so far ‘innocent’ MSSA clonal lineages.

Examples of (i) are obviously CA-MRSA ST30 (USA400) [79]; MLST and spa sequence typing suggest possibility (ii) for CA-MRSA ST5 and ST22, although a more detailed genome-wide analysis of single-nucleotide polymorphisms indicates convergent evolution [80]; and examples of (iii) are CA-MRSA ST1, ST8, ST59, ST80, and ST152.

What Can We Learn from Genomics?

At present, the genomes of 11 MRSA and MSSA clinical strains, of both community and hospital origin, and those of two bovine strains, have been deposited in the GenBank database. Of particular interest with respect to evolution and features characteristic of CA-MRSA are comparisons of the genomes of CA-MRSA and HA-MRSA of the same clonal lineage, as well as with their most probable MSSA ancestor.

At present, high-throughput sequencing technologies are becoming increasingly available, and will make essential contributions to the elucidation of evolutionary relationsships, as already performed for salmonellae [81].

Comparative whole genome sequencing of ten isolates from the widely disseminated CA-MRSA USA300 clone revealed very recent diversification rather than convergence [82].

The comparison of the genomes of CA-MRSA USA300 from the USA and of HA-MRSA COL from Europe, which both belong to lineage ST8, revealed that there are no pronounced differences in gene content besides the arginine catabolic mobile elements (ACME) gene cluster on an SCCmec element and lukS-PV/lukF-PV, which are both present in CA-MRSA USA300. Likewise, comparison of recently obtained clinical MRSA USA300 and MSSA isolates of lineage ST8, both originating from Houston, Texas, revealed only subtle genetic genomic differences, with respect to the ACME cluster, the SCCmec element, a region containing genes for a number of conserved hypothetical proteins, and 32 non-synonymons single-nucleotide polymorphisms [83].

The ACME gene cluster in CA-MRSA USA300 encodes enzymes representing an additional arginine decomposition pathway, with arginine deiminase (ArcA) as a key enzyme. This might contribute to depletion of arginine as a source for NO production by granulocytes, as well as to enhanced colonization on epithelia by neutralizing lower-pH environments (ammonia production). There are recent data that demonstrate a difference in survival of isogenic USA300 ACME-positive and ACME-negative derivatives in a rabbit infection model [84].

Although lukS-PV/lukF-PV is a genetic marker for CAMRSA, the exact role of PVL in the pathogens, as suggested by a study on necrotizing pneumonia [85], remains to be shown in more detail. As shown in a recent study on gene expression directly in human tissue, PVL, together with other secreted toxins, has a high level of expression during superficial and invasive CA-MRSA infections [86].

As shown at least for CA-MRSA ST1 USA400, ST8 USA300, and ST59, strong expression of small, phenolsoluble molecules (PSMs) is probably another important characteristic of CA-MRSA. These peptides have a remarkable ability to recruit, activate and subsequently lyse human neutrophils, and their role in bacteraemia, as well as in SSTIs, has been demonstrated just recently in murine models [87].

Are There Efficient Methods for Infection Control in Cases of CA-MRSA Infection?

As described above, risk factors for acquisition and transmission that confirm the basic principle of transmission of S. aureus by contact have been identified. A study in New York has shown that nasal carriage of CA-MRSA among household members of patients with CA-MRSA infections is much more frequent than among the general population [88]; also, family outbreaks of CA-MRSA infections have been reported [89]. Most of the risk factors described above do not apply to young children, for whom CA-MRSA infections have also been reported [90]. Starting from a few cutaneous infections which were recognized too late or not sufficiently treated, CA-MRSA can efficiently spread among groups of children through play and sports activities.

Besides routine social interactions, CA-MRSA is obviously transferred by physical interactions among athletes in competitive sports [50], and exercises among military personnel [91]. The acquisition and subsequent transmission of CA-MRSA is facilitated when it comes into contact with non-intact epithelium, and minor superficial injuries of skin, such as abrasions and lacerations, are more frequent among the groups mentioned above.

Furthermore, transmission of CA-MRSA by sexual contacts, both among men who have sex with men and among heterosexual individuals, has been reported. Besides nasal colonization, colonization of the genital area can be important as a potential CA-MRSA reservoir [68]. Transmission is also likely if infected individuals share personal items, such as clothing, towels, razors, and sports equipment.

For these reasons, improvement of personal hygiene is an essential prerequisite for prevention. This includes hand washing with soap and warm water, and the use of antibacterial hand sanitizers and hand gels. Individuals in group facilities should regularly shower with soap and warm water when finishing their activities, and they should not share items, as mentioned above.

Early detection of CA-MRSA by routine clinical examination is very important; therefore, bacteriological investigation should be performed, along with surgical treatment (incision and draining) of SSTIs.

Individuals affected by potentially cutaneous CA-MRSA infections should avoid direct contact with non-colonized/ non-infected individuals in families, sport teams, schools, and military facilities. Affected patients and family members should be checked for nasal colonization with CA-MRSA, and in case of positive results, sanitation should be performed, preferentially by nasal application of mupirocin ointment, in combination with chlorhexidine body wash.

When CA-MRSA SSTIs persist, worsen, and/or recur, despite appropriate surgical intervention, additional systemic antimicrobial therapy is necessary. CA-MRSA can be resistant to other alternatives, such as doxycycline in the case of ST80, to erythromycin (this includes potential resistance to clindamycin when coded by erm genes), and to moxifloxacin in the case of ST8.

There remain a number of options for empirical oral therapy with substances for which resistance is still infrequent or absent in CA-MRSA and that reach sufficient concentrations in skin and in the secretions of the upper respiratory tract [92,93]. Although successful co-trimoxazole treatment of CAMRSA SSTIs has been reported [51], one should keep in mind that this antibacterial is only bacteriostatic in the case of staphylococci. Other alternatives are new antistaphylococcal agents such as linezolid, tigecycline, and daptomycin [93,94].

Furthermore, possible side effects and drug interactions have to be considered, such as the contra-indication for rifampicin in human immunodeficiency virus-infected patients treated with proteinase inhibitors, and the development of haematological or renal side effects resulting from the use of co-trimoxazole.

The rather complex approach to the prevention and treatment of SSTIs caused by S. aureus was found to be successful in the case of an outbreak of furunculosis with MSSA (clonal lineage ST121) in northern Germany in 2005 [95], and a decolonization programme was also found to be efficient in controlling the dissemination of CA-MRSA ST80 in Denmark [58].

Emergence of Livestock-Associated MRSA in Humans in the Community

MRSA of clonal complex CC398 (eight MLST types, most frequent spa types t011, t034, t108, t571, and t2974) is obviously widely disseminated among pigs in European countries with high-density pig farming, such as The Netherlands [96], Denmark [97], and Germany [98], but also in Canada and in the USA [99]. Besides pigs, MRSA ST398 has also been isolated from veal calves [100], horses [101,102], and dogs [103]. Thus, animal association has also to be taken into consideration in the epidemiological analysis of SSTIs with MRSA. Further steps of adaptation to humans should be carefully monitored, as suggested by the emergence of a cluster of infections with PVL-positive MRSA ST398 in a Chinese hospital [104].

Of particular interest is the question of dissemination to humans exposed to MRSA-colonized animals, to their family members, and then to the community. Nasal colonization of exposed humans is frequent, and although it is less frequent, there is obviously transmission to family members of farmers [105]. Although rare in relation to PVL-positive CA-MRSA, MRSA CC398 is able to cause severe SSTIs in humans who need surgical intervention and, in some cases, even those who need hospitalization [106–108].

Transparency Declaration

The author declares no conflict of interest in conjunction with this review.

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Figures and Tables

Figure 1. Use of clear definitions: grouping of methicillin-resistant Staphylococcus aureus (MRSA) according to epidemiological origin. CA-MRSA, community-associated MRSA; HACMRSA, healthcare-associated community-onset MRSA; HA-MRSA, healthcare-associated MRSA; ICU, intensive-care unit; LA-MRSA, livestockassociated MRSA.

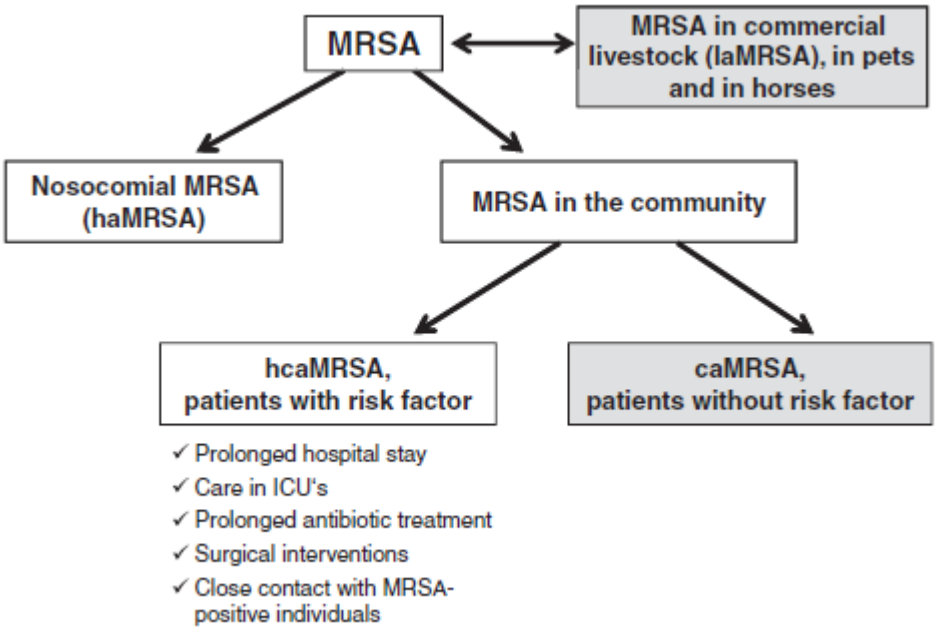
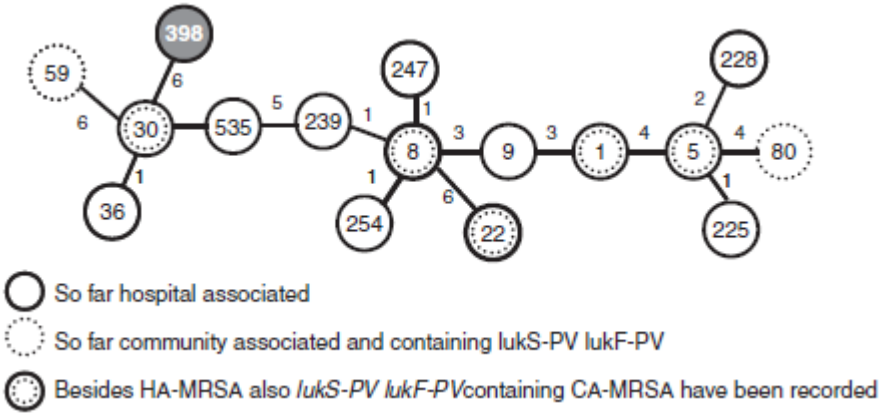


Figure 2. Probable genetic relatedness of methicillin-resistant Staphylococcus aureus (MRSA): simplified minimum tree spanning tree based on multilocus sequence typing profiles (seven housekeeping genes). CA-MRSA, community-associated MRSA; HA-MRSA, healthcare-associated MRSA; SNP, singlenucleotide polymorphism.



Each clonal lineage represents a subpopulation of isolates with a common ancestral core genome, several SNP polymorphisms in various house-keeping genes suggest subclones. Examples show that different subclones have acquired different SCC*mec* elements at different times and on different occasions.

Table 1. Typing characteristics and geographical dissemination of community-associated methicillin-resistant Staphylococcus Aureus

MLST, ST	spa types	SCCmec	Further markers	Resistance phenotypes	Geographical dissemination
1	t175, t1383	IVa	*seh*	OXA	USA, sporadic in several European countries
5	t002	IV		OXA, GEN	The Netherlands, Switzerland, Germany, Slovenia
8	t008	IVc	*arcA, msrA, mphB*	OXA, ERY, CIP, MFL	USA, Europe, Asia
22	t310	IVa, IVh		OXA, ERY, CLI, CIP, MFL	Scotland, Germany
30	t021 t019	Iva		OXA	Oceania, USA, Baltic area, Denmark, UK, sporadic in other European countries
59		IV		OXA	Europe, Asia, North America
80	t044, t131, t343	IVh	*etd*	OXA, TET, FUS, KAN, (CIP)	All Europe, North Africa
152	t355, t1123	V		OXA, GEN	Slovenia, Kosovo

arcA, arginine deiminase; etd, exfoliative toxin D; mphB, macrolide phosphotransferase B; msrA, macrolide efflux; seh, staphylococcal enterotoxin; CIP, ciprofloxacin; CLI, clindamycin; ERY, erythromycin; FUS, fusidic acid; GEN, gentamicin; KAN, kanamycin; OXA, oxacillin; MFL, moxifloxacin; TET, tetracycline; MLST, multilocus sequence typing; ST, sequence type.