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Outbreak of Methicillin-resistant Staphylococcus aureus in a Hospital Center for Children's and Women's Health in a Swedish County

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The objective of this study was to investigate a sudden increase in methicillin-resistant Staphylococcus aureus (MRSA) cases primarily in one maternity ward at the Center for Children's and Women's Health at Linköping University Hospital, Sweden. Approximately 300 individuals including patients, their family members, and healthcare workers were screened for MRSA. The antibiotic susceptibility was tested and isolates polymerase chain reaction (PCR)-positive for the *mecA* gene were *spa* typed. Isolates with the same antibiogram and *spa* type were further whole genome sequenced. Compliance to current cleaning and hygiene routines was also controlled, and environmental samples collected. The results showed that a total of 13 individuals were involved in the outbreak. It was caused by a t386 MRSA strain (ST-1, NCBI-accession AB505628) with additional resistance to erythromycin and clindamycin. All cases were epidemiologically connected to the index patient, who had recently emigrated from a high-endemic area for MRSA. With improved cleaning and better compliance to basic hygiene routines, no further cases were reported. This study demonstrates how rapid an MRSA strain can disseminate in a ward with susceptible patients and insufficient cleaning and hygiene. For a better control of MRSA, clinical cultures and screening samples need to be obtained early and more extensively than according to the current recommendations.

Key words: Infection control; neonates; MRSA; outbreak; t386.

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Methicillin-resistant Staphylococcus aureus (MRSA) is one of the leading causative agents of hospital-associated infections (HAIs) (1). It contributes significantly to increased morbidity and mortality rates, extended hospitalizations, and increased costs, especially in neonates from high-income countries where bloodstream infections are the most frequent infections (2). Sweden is a low-prevalence country regarding MRSA, but since 2012 the number of notified MRSA cases has increased rapidly from an overall incidence of 22 cases per 100 000 inhabitants to 44 cases per 100 000 inhabitants in 2016. In the age group 1 year or younger, the corresponding figures were 77 and 218 per 100 000 inhabitants (3). With the globalization, more frequent international travels and the migrant crisis in Europe in late years the risk of importing MRSA has increased (4, 5).

Newborn infants, and especially those in need of neonatal intensive care, are at increased risk for colonization and infection with MRSA due to an immature immune system (6, 7). Transmission of MRSA to hospitalized neonates may result from direct contact with colonized parents, other relatives, or healthcare workers. It may also occur indirectly by healthcare workers, medical devices, breast milk or from contact with a contaminated hospital environment (8). Community reservoirs have also been implicated, since the carriage rates among patients and visitors have increased, and reports have indicated that community-associated MRSA (CA-MRSA) strains can infect otherwise healthy infants in hospital settings (9).

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In order to prevent the transmission of MRSA, adequate cleaning, compliance to basic hygiene routines (hand washing before and after patient contact, appropriate use of alcohol-based disinfectant, use of barrier equipment when necessary, use of short-sleeved clothing, hands and forearms free from jewelry, and long hair tied back), and a good understanding of the transmission routes are of major importance (8). To discover dissemination, molecular tools are needed. Traditional methods, such as pulsed-field gel electrophoresis (PFGE), multilocus sequence typing (MLST), sequence-based typing of the polymorphic region X of the staphylococcal protein A gene (*spa* typing), and staphylococcal cassette chromosome *mec* (SCC*mec*) typing, may, even when used in combination, fail to detect genetic differences between isolates. As a consequence, the number of MRSA outbreaks has sometimes been overrated (10). In contrast, whole genome sequencing (WGS) has an ultimate resolution power by enabling the sequencing of whole bacterial genomes, thus permitting accurate identification and characterization of bacterial isolates. It is highly likely that WGS will replace currently used molecular genotyping methods in the near future (11).

The objective of this study was to investigate a rapidly increasing number of MRSA cases among newborn infants and their family members primarily in one maternity ward at the Center for Children's and Women's Health at Linköping University Hospital, and to describe the measures taken to control the outbreak.

MATERIALS AND METHODS

Settings

There are three hospitals in the Östergötland County: one tertiary care hospital (Linköping University Hospital) and two secondary care hospitals (Vrinnevi Hospital, Norrköping and Motala Hospital, Motala). The Center for Children's and Women's Health in Östergötland has about 1000 employees, consists of four departments (The Children and Youth Hospital in Linköping and Motala; Children's and youth clinic in Norrköping; Women's Clinic in Linköping; and Women's Clinic in Norrköping), and has two neonatal wards located in Linköping and Norrköping.

Prior to the outbreak, the maternity ward in Linköping had had two minor MRSA outbreaks (2015: *spa* type t5989, 2016: *spa* type t688). On both these occasions, an insufficient compliance to basic hygiene routines had been observed. All clinics in the Östergötland County undergo monthly observational studies and report the results to the Department of Infection Control and Hygiene, so that the compliance to basic hygiene routines can be followed over time. The design of the maternity ward also contributed to the transmission since there were both single- and multi-bed rooms, and not all rooms were equipped with toilets, showers, and washbasins. Thus, these areas were shared between several patients. In addition, fathers and other family members were free to visit the ward.

Epidemiological investigation

In January 2017, a patient underwent an emergency cesarean section and gave birth to a daughter at Linköping University Hospital. The following day, the patient developed high fever and showed increasing C-reactive protein levels. After five additional days, there were pus and clear signs of inflammation in the incision area. A culture collected 3 days later showed growth of MRSA (*mecA* positive). The patient did not fulfill the local criteria for MRSA-screening, but she had recently emigrated from a high-endemic area for MRSA. In Östergötland, MRSA-screening is recommended if a patient during the six last months has been admitted to a hospital outside Scandinavia or has skin lesions in combination with a long-term visit to a high-endemic MRSA-area. These recommendations are, however, under revision.

The closest family members of the index patient, as well as all mothers and newborn infants admitted to the maternity ward during the same time period as the index patient, were screened for MRSA. Family members of found MRSA cases were also screened. In addition, healthcare workers at the department with known risk factors, such as wounds or eczema, were included in the screening. Cases were defined as patients, their family members, or healthcare workers with carriage of, or infection with, MRSA with the same antibiogram and *spa* type as the index patient. An additional inclusion criterion was that there had to be a connection in time and space with the index patient.

Routines concerning cleaning, basic hygiene, handling of breast milk, and washing of private and hospital clothes were explored. To control the environmental contamination and cleaning efficacy, 100 environmental samples were collected at the maternity ward at Linköping University Hospital during the ongoing outbreak. Sampling was obtained from possible contaminated sites such as mattresses, shelves, chairs, tables, baby dressing tables, gynecology examination tables, keyboards, door knobs, shower head, -wells, and -stools in eight patient rooms; four treatment rooms; four shared areas with toilet, shower, and washbasin; and in the corridor.

Bacterial culturing

The MRSA-screening samples were collected from the nose, throat, groin and, if present, from wounds, eczema, and urine catheters, using ESwabs (Copan Diagnostics Inc., Murrieta, CA, USA) or test tubes for urine. One hundred μL of each MRSA-screening sample was inoculated into Mueller-Hinton broth (Becton Dickinson GmbH, Heidelberg, Germany) supplemented with cefoxitin (4 mg/L, Sigma Aldrich, St. Louis, MO, USA) and aztreonam (20 mg/L, MP Biomedicals, Illkirch, France) and incubated at 35 °C overnight.

Environmental samples were collected with ESwabs (n = 89) (Copan Diagnostics Inc., Murrieta, CA, USA) or contact plates with tryptic soy agar (n = 11). The ESwab samples were inoculated onto urinary tract infections

(UTI)-agar plates (Oxoid AB, Malmö, Sweden) and thereafter into Mueller-Hinton broth (Becton Dickinson GmbH) supplemented with cefoxitin (4 mg/L, Sigma-Aldrich) and aztreonam (20 mg/L, MP Biomedicals). The UTI-agar plates were incubated at 35 °C for approximately 48 h. After an overnight incubation at 35 °C, the broths were inoculated onto MRSA Chromagar plates (CHROMagar, Paris, France) and incubated at 35 °C overnight. Bacteria were identified to the species level using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) with a MALDI Biotyper 3.0 (Bruker Corporation, Karlsruhe, Germany).

PCR

The DNA was prepared by heating the bacterial suspension at 95 °C for 15 min in a ThermoMixer (Eppendorf, Hørsholm, Denmark). Primers and probes included in the polymerase chain reaction (PCR) were nuc-4 (TCAAGTCTA AGTAGCTCAGCAAATGC), nuc-5 (GAAGTTGCACTA-TATACTGTTGGATCTTC), *mec*A-F (ACTTCACCAGG TTCAACTCAAAA), *mecA*-R (TATGTTATCTGATGATT CTATTGCTTG), nuc-probe (6-FAM-TCACAAACAGA-TAACGGCGTAAATAGAAGTGGTTCT-BHQ1), and *mecA*-probe (JOE-ATCGATGGTAAAGGTTGGCAAA AAGATAAATC-BHQ1) (sequences given in 5′-3′) (Eurofins Biotech, Constance, Germany). The PCR mixture consisted of 2 μL of the DNA preparation together with 2 μL MRSA-PCR primer/probe-mix (10 ×, with a final concentration of 0.4 μM for primers and 0.2 μM for probes), 4 μL QuantiFast Pathogen PCR + IC kit (Qiagen, Germantown, MD, USA), 1 μL $MgCl_2$ (25 mM), and 11 μL RNase-free water (Qiagen, Germantown, MD, USA) in a final volume of 20 μL. The PCR was performed in a Rotor-Gene 3000 thermal cycler (Corbett Robotics, Mortlake, Victoria, Australia) with the following protocol: an initial denaturation/activation at 95 °C for 5 min, followed by 40 cycles of two steps consisting of annealing at 95 °C for 15 s and extension at 60 °C for 30 s. For each run, a positive control (CCUG strain 35601) carrying the nuc- and *mecA* genes and two negative controls (non-inoculated cefoxitin broth and no template broth) were processed along with the patient samples. Carriage of the *mecA* gene was verified with GeneXpert, using the Xpert SA Nasal Complete kit (Cepheid, Sunnyvale, CA, USA), according to the manufacturer's instructions. *Nuc*- and *mecA*-positive samples were inoculated onto DNase Test Agar (Neogen, Lansing, MI, USA) and MRSA Chromagar plates (CHROMagar, Paris, France). They were thereafter incubated overnight at 35 °C.

Antibiotic susceptibility testing

Antibiotic susceptibility testing was performed with the disk diffusion method, according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST, www.eucast.org). Included antibiotics were penicillin G, oxacillin, cefadroxil, cefuroxime, cefotaxim, imipenem, erythromycin, clindamycin, tobramycin, fusidic acid, rifampicin, moxifloxacin, and linezolid (Oxoid AB). Constitutive or inducible resistance to clindamycin was determined with the D-shaped disk diffusion method (12).

The minimal inhibitory concentration (MIC) for vancomycin was determined using E-test (bioMérieux, Marcy l'Etoile, France). Isolates were classified as susceptible, indeterminant, or resistant according to the EUCAST species related breakpoints.

spa typing

Bacterial DNA was extracted in a BioRobot EZ1 system by using the EZ1 DNA tissue kit (Qiagen). *spa*-specific primers T7-*spa*-1113f and Sp6-*spa*-1514r (Eurofins Biotech, Constance, Germany) were used to amplify the polymorphic region X of the *spa* gene in PCR with a 2720 Thermal cycler (Applied Biosystems, Thermo Fisher Scientific, Waltham, MA, USA). The size and intensity of the PCR product were thereafter controlled in the automatic gel electrophoresis instrument QIAxcel by using the QIAxcel DNA High Resolution kit (Qiagen). Amplified DNA was sequenced at Eurofins MWG Operon (Eurofins Biotech). The resulting sequences were analyzed in BioNumerics version 6.6 (Applied Maths, Sint-Martens-Latem, Belgium) with access to Ridom SpaServer (13).

WGS

All isolates with *spa* type t386, belonging to patients with an epidemiological connection with the index patient, were sent to The Public Health Agency of Sweden for WGS. An additional isolate (*spa* type t386, but with a different antibiogram and no clear connection with the index patient in space) was included for control.

Genomic DNA was sequenced by using the Ion Torrent S5 XL platform (Thermo Fisher Scientific). Two hundred ng of genomic DNA was sheared for 12 min and Ion Xpress Barcode adapters were ligated by using the Ion Xpress Plus Library kit for the AB Library Builder System (Thermo Fisher Scientific). Fragment libraries were pooled and purified by using Agencourt AMPure XP beads clean-up (Beckman Coulter Inc., Atlanta, GA, USA). The libraries were then clonally amplified, prepared, and loaded on a 530 chip by using the Ion Chef system (Thermo Fisher Scientific) to produce templates for sequencing. The loaded chip was subsequently transferred to the Ion S5 XL instrument for sequencing.

The raw data were mapped by using the CLC assembly cell (Qiagen) to a reference genome (in-house) specific for the sequence type. Variants were called for each position in the genome. Variants were filtered, all positions with <10× coverage or >10% minority calls in one or more samples were removed. The proportion of remaining positions to the reference genome sixe was reported as the fraction of shared genome. Called bases at all variable positions were arranged in a multiple sequence alignment, and the alignment was filtered for recombination. Minimum spanning trees (MSTs) were built by using MSTgold and visualized using GVEdit. Distances were reported as number of single nucleotide polymorphisms (SNPs).

RESULTS

Outbreak cases

Approximately 300 individuals were screened for MRSA. Of these, 12 fulfilled the case criteria. Like the index isolate, these 12 case isolates belonged to *spa* type t386, consisting of three repeats (07-23-13) according to Ridom SpaServer (13). Apart from

their resistance to beta-lactams, they were all resistant to erythromycin and clindamycin (Table 1). Furthermore, all the included cases had epidemiological connections to the index patient since they had been located in rooms near each other and/or shared toilet, shower, and washbasin.

The daughter, husband, and parents-in-law of the index patient were all colonized with the outbreak strain. The mother-in-law had stayed at the maternity ward together with the index patient to take care of her newborn granddaughter. From this family, the outbreak strain was further transmitted to eight individuals (four newborn infants and four family members) belonging to four other families, including one newborn who was transferred from Linköping to the neonatal ward in Norrköping where one of the other newborns became colonized. The latter patient was colonized with MRSA in the nose on a single occasion and was thereby signed off as a transient carrier (Table 1).

Results of WGS

Twelve of the isolates (92%), including the index isolate, were designated SNP variant A (ST-1, NCBI-accession AB505628). Nine of these (75%) had identical SNPs, whereas three isolates (25%) differed from the index patient with one SNP. The remaining isolate, belonging to the husband of the index patient, differed from the index patient with seven SNPs (closely related) and was designated A1. The additional isolate (*spa* type t386 but with a different antibiogram and no clear connection with the index patient in space) differed from the index patient with 77 SNPs and was thereby considered unrelated and designated SNP variant B (Fig. 1 and Table 1).

The outbreak strain did not carry genes encoding toxic shock syndrome toxin-1 (TSST-1) or Panton–Valentine leukocidin (PVL).

Environmental cultures

No MRSA was found in the environment. However, several of the environmental samples showed heavy growth of various bacteria. Growth of *S. aureus* was e.g. found at nine different locations: inside a baby bassinet, around beds, on a visitor's chair, on a shelf placed over a diaper changing table, on a mattress used for neonatal jaundice

Table 1. *spa* type, single nucleotide polymorphism (SNP) variant and antibiotic susceptibility (OX stands for oxacillin, DA for clindamycin, E for erythromycin, FD for fusidic acid, LZD for linezolid, RD for rifampicin, and TOB for tobramycin) of investigated isolates

Patient	Hospitalization time	Placement	spa type	WGS SNP variant[1]	Antibiogram						
					OX	DA	E	FD	LZD	RD	TOB
Newborn	20170107–20170119	Maternity ward, Linköping	t386	A	R	R	R	S	S	S	S
Mother (index)	20170106–20170119	Maternity ward, Linköping	t386	A	R	R	R	S	S	S	S
Father			t386	A1 (7)	R	R	R	S	S	S	S
Mother-in-law			t386	A	R	R	R	S	S	S	S
Father-in-law			t386	A (1)	R	R	R	S	S	S	S
Newborn	20170115–20170117	Maternity ward, Linköping	t386	A	R	R	R	S	S	S	S
Father			t386	A	R	R	R	S	S	S	S
Newborn	20170112–20170119 20170119–20170220	Neonatal ward, Linköping Neonatal ward, Norrköping	t386	A	R	R	R	S	S	S	S
Mother	20170112–20170114	Maternity ward, Linköping	t386	A	R	R	R	S	S	S	S
Father			t386	A	R	R	R	S	S	S	S
Newborn (transient carrier)	20170116–20170309	Neonatal ward, Norrköping	t386	A	R	R	R	S	S	S	S
Newborn	20170108–20170114	Maternity ward, Linköping	t386	A (1)	R	R	R	S	S	S	S
Mother	20170108–20170114	Maternity ward, Linköping	t386	A (1)	R	R	R	S	S	S	S
Unrelated	20170123	Infection reception, Linköping	t386	B (77)	R	S	S	S	S	S	S

[1]Difference in SNPs from the index patient shown in brackets.

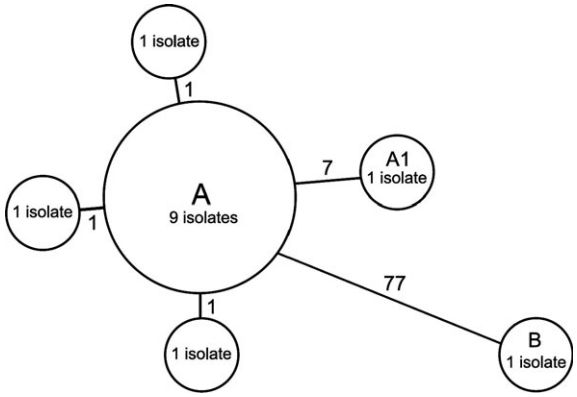

Fig. 1. Minimum spanning tree created from whole genome single nucleotide polymorphisms, created in MST gold v2.4.

phototherapy, and on a plastic stool placed in one of the showers used by the mothers.

Control measures

Control measures were immediately taken by the Department of Infection Control and Hygiene. These included improved compliance to basic hygiene and cleaning routines, disposal of all furniture that was impossible to disinfect, total stoppage of the use of a washing machine intended for parents to neonates but used for almost anything, changed routines concerning breast pumps/milk and the usage of common areas, and MRSA-screening of all patients at the involved wards before discharge. These measures were followed by information to the staff about disinfection procedures and basic hygiene, leaflets for visitors in the most frequently spoken languages about basic hygiene routines, and a regular collection of environmental samples. Once the new rules were implemented, no more cases were reported and the observational studies showed a better compliance to basic hygiene routines. None of the colonized individuals developed an infection caused by MRSA during the following 12 months.

DISCUSSION

In the present study, an outbreak of MRSA at a Center for Children's and Women's Health in Sweden was suspected and confirmed. Apart from the infected index case, four newborn infants and eight family members were colonized with an erythromycin- and clindamycin-resistant MRSA strain of *spa* type t386 (Table 1). With prompt infection control measures, including improved cleaning and hand hygiene, the outbreak was stopped and no more cases of the t386 MRSA strain were observed at any of the wards of the Center for Children's and Women's Health after February 2017. However, the maternity ward in Linköping has not yet performed the recommended renovations in order to avoid shared toilets, showers, and washbasins.

During the last couple of years, Östergötland, as well as other regions of Sweden, has experienced an increased incidence of MRSA and other multiresistant bacteria, partly as a result of imported multiresistant strains. Between 2014 and 2016, the number of patients colonized with MRSA in Östergötland increased 43% (the database of the Clinical Microbiology Laboratory at Linköping University Hospital). To protect susceptible patients, such as neonates, it is important to identify carriers of multiresistant bacteria as early as possible. An important group to pay attention to in this context are the refugee mothers, especially if they have fled from or traveled through high-endemic areas for multiresistant bacteria (4). Unfortunately, established hospital routines are not quite adapted to the new situation, and there is often a delay when it comes to both diagnosis and adequate treatment. In this case, it took twelve days. During this time period, the index patient was put at risk, and one infected neonatal was transferred between the neonatal wards in Linköping and Norrköping. The Public Health Agency of Sweden recently published new screening recommendations (14). According to these recommendations, patients, who have stayed in a highly endemic area for at least two coherent months within the last 6 months before their arrival to Sweden, should be screened for multiresistant bacteria. Even with this new criterium, our index patient would have escaped the screening. Since not everybody can be screened, it is important to always keep multiresistant bacteria in mind and collect samples early in the infectious process. A recent study shows that the prevalence of multiresistant bacteria carriage and infection is elevated among migrants and highlights the importance of detecting these patients to prevent transmission (5).

spa type t386 has been a relatively rare finding in the Östergötland County, with the first four cases reported in 2013. Since then, a total of 22 patients have been identified, of whom 13 belonged to this MRSA outbreak. In Sweden, the incidence of MRSA strains of *spa* type t386 has significantly increased since 2008 when the first case was reported. Until 2016, 317 additional cases have been identified (3). According to the Ridom SpaServer (13), most t386 cases are reported from northern Europe and Sweden in particular.

The national method used for epidemiological typing of *S. aureus* is *spa* typing. Although one of the

isolates in this study was designated *spa* type t386, it was unrelated to the outbreak strain with a difference of 77 SNPs (Fig. 1 and Table 1). This demonstrates the importance of using complementary molecular genotyping methods, or just WGS, when investigating outbreaks (15). In comparison to *spa* typing and other commonly used molecular genotyping methods, WGS is a better method for detecting minor but essential genetic differences between isolates. Furthermore, WGS yields more information about the isolates than just the genetic relatedness. Bacteria can be simultaneously genotyped and profiled to determine their antibiotic resistance and virulence potential. The outbreak strain did not carry two of the more important virulence factors, i.e., TSST-1 and PVL. There are, however, a number of existing challenges restricting the use of WGS. Analysis of WGS data can be complex and requires specialist knowledge and skills in bioinformatics. Furthermore, there is no standardized interpretation of results into genetically indistinguishable, related, or unrelated isolates, although studies have suggested that differences ranging from 23 to 40 SNPs are indicative of epidemiological linkages between individuals (11, 15). The resulting SNP variants are arbitrary for each analysis and should, as always, be compared with available epidemiological data.

In conclusion, a suspected MRSA outbreak caused by *spa* type t386 and involving 13 patients at a Center for Children's and Women's Health was confirmed. The intervention was successful, but the outbreak could probably have been avoided if the patient's diagnosis had not been delayed. To protect vulnerable patient groups, it is necessary to be more pro-active, collect samples for culture as early as possible during infections, and keep a high hygienic standard.

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