Staphylococcus aureus epidemiology and control:

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Chapter 2.1

Meticillin-resistant *Staphylococcus aureus* epidemiology and transmission in a Dutch hospital

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Abstract

The application of the Search & Destroy (S&D) policy in Scandinavian and Dutch hospitals is associated with low rates of meticillin-resistant *Staphylococcus aureus* (MRSA). The objective of this study was to describe the MRSA epidemiology and transmission in a Dutch hospital. The descriptive study was performed in a teaching hospital with approxiamtely 40,000 admissions a year. In this hospital the MRSA S&D hospital has been applied for several decennia. MRSA epidemiology was studied during the years 2001 through 2006. The transmission rate in this hospital was determined using 1) patient's history, 2) relation in time and place to other patients or health care workers, and 3) molecular typing (PFGE and *Spa*).

Ninety-five persons were identified as MRSA carriers, i.e. 82 patients and 13 health care workers. The annual MRSA incidence increased with more than 300 percent during the study period, which was entirely caused by animal-related MRSA. Twenty-three percent of the patients acquired MRSA in a foreign hospital, 26% via animals, 16% by nosocomial transmission, 4% in another Dutch healthcare institute, 10% in the community via a known MRSA positive person and in 22% the source was unknown. For HCW, 69% of MRSA was due to nosocomial transmission, 15% was related to working in a foreign hospital and in 15% HCW got colonised via a MRSA positive partner or relative. The transmission rate of 0.30 (22 secondary cases/73 index cases) indicates that the spread of MRSA was under control during the study period, so the S&D policy should be continued.

Introduction

Since the eighties, The Netherlands en Scandinavian countries have applied a Search & Destroy (S&D) policy to control MRSA, which is outlined in the national guidelines of the Dutch Working Party on Infection Prevention (WIP). Screening of patients considered at risk for MRSA, isolation of both MRSA positive and suspected patients, desinfecting rooms and contact tracing are the main aspects of this policy. Carriers of MRSA are treated with antibiotics, which is described in the guidelines of the Dutch Working Party on Antibiotic Policy (SWAB). The S&D policy in The Netherlands and Scandinavian countries is associated with low endemic MRSA levels. The percentage of *S. aureus* bacteraemia caused by MRSA in these countries is very low (≤ 1%), contrary to other European countries that have reached percentages up to 50 percent.[1]

The objective of this study was to describe the MRSA epidemiology and transmission in a large Dutch teaching hospital.

Methods

Setting

An observational prospective survey was performed during 2001 through 2006 in the Amphia hospital, a teaching hospital with 1370 beds, which is located in the southwestern part of The Netherlands. All medical specialties are present. The hospital serves a population of approximately 440,000 inhabitants. During the study period, on average 38,943 patients were admitted annualy to this hospital with 282,585 patient days per year (mean numbers over 2001 through 2006). This hospital has applied the S&D policy for several decennia. Patients at risk for MRSA were selected on admission. All patients were asked on admission whether they belonged to one of the MRSA risk categories, i.e. treatment in a foreign hospital or direct exposure to pigs/veal calves. This question was also asked to all patients that visited the outpatient's clinic.

Collection of Data

Data of all patients and health care workers (HCW) that were found carrying MRSA during the years 2001 through 2006 were prospectively recorded in a data base. When a MRSA positive patient or HCW was found, extensive contact tracing among patients and HCW was performed to identify possible transmission. Samples from nose, throat, perineum were taken from all contact persons. Furthermore, samples from wounds and sputum were taken when present and an urine sample was taken from patients with an urinary tract catheter. The following items from all MRSA positive patients and HCW were recorded in the data base: patient identification number, date of birth, date of first

MRSA positive culture, MRSA PFGE type and S*pa* type, MRSA source, whether MRSA was found by targeted screening or by coincidence, number of screened contact patients and HCW (both unprotected and protected contacts), number of secondary cases, number of days that MRSA positive HCW were suspended from work, whether MRSA treatment was given and if so, whether MRSA was eradicated (follow up period was at least 1 year). To collect these data, files of the infection control department and the laboratory information system were used. Based on these data the annual MRSA incidence, MRSA sources and the nosocomial MRSA transmission rate were determined.

MRSA incidence

All patients were asked on admission whether they belonged to one of the MRSA risk categories, i.e. treatment in a foreign hospital or direct exposure to pigs/veal calves. This question was also asked to all patients that visited the outpatient's clinic. The patients that confirmed this question were screened and isolated. Based on the laboratory results the annual numbers of screened patients, MRSA positive patients and MRSA positive HCW were determined. Furthermore, the MRSA incidence among patients during the six-year study period was calculated on the base of the total number of MRSA positive patients and was expressed per 100,000 patient days and 100,000 admissions.

Strain typing and source determination

The source of MRSA was based on both the patient's history and strain typing. MRSA strains from all patients and HCW were typed by the Dutch National Reference Centre (RIVM, Bilthoven, The Netherlands). Two different typing methods were used:

1. PFGE: Pulsed Field Gel Electrophoresis

Chromosomal DNA was digested with the restriction-enzyme *SmaI*.[2,3] Macro fragments were separated in a changing electrical field. The generated 'DNA-fingerprints' were analysed and stored using BioNumerics software (Applied-Maths, Sint-Martens-Latem, Belgium). Strains were compared with each other in dendrograms using the Dice similarity coefficient and the Unweighted Pair Group Method using Average (UPGMA) cluster method.

2. Spa typing

The polymorphic X-region of the protein A-gene (*Spa*) was amplified by PCR. PCR products were sequenced to determine the strain specific variable numbers of repeats of 24 to 27 specific base pairs.[4,5] Bionumerics software or Ridom StaphType software (Ridom GmbH, Germany) assigned a number to these repeats, forming an allele profile. This profile was converted into a *Spa* type, which was used for clustering.[5] The genetic relation between strains was shown in minimal spamming trees (MST) using Bionumerics software.

The MRSA source was determined for both MRSA positive patients and HCW. First, it was investigated whether the MRSA positive case could be classified as index or secondary (MRSA due to nosocomial transmission) case. When a MRSA positive case found in the hospital could be linked in time (overlap in dates of patient days with a maximal interval of 30 days) and place (overlap in wards including adjacent wards) to an index patient or HCW and the MRSA strain was identical to the strain of the index, the source of the case was classified as nosocomial transmission. When no link in time and place was found, the MRSA positive case was classified as index case. For these index cases a stratification in sources was made, i.e. MRSA related to a foreign hospital, to another Dutch healthcare institute, to transmission in the community via a known MRSA positive person, to animals or MRSA with unknown source. MRSA was classified to be related to a foreign hospital when the MRSA positive patient had recently been treated in a hospital abroad. For HCW, both admission and working in a foreign hospital were included. MRSA was related to animals when the patient or HCW had direct contact with living pigs or veal calves or was living on a pig/veal calf farm and the strain was non-typeable with PFGE. MRSA was classified to be related to transmission in another Dutch healthcare institute when the above mentioned criteria for nosocomial transmission were applicable for this institute. When patients or HCW were colonised by MRSA via partners, friends or other people in the community, the source was classified as community transmission.

Nosocomial MRSA transmission

After source determination, the numbers of patients and HCW colonised by MRSA due to nosocomial transmission were identified. To calculate the transmission rate, the number of patients and HCW who were colonised by MRSA due to nosocomial transmission was divided by the number of index cases.

Results

MRSA incidence

The annual number of screened patients who belonged to a MRSA risk category was obtained from the Laboratory Information System, which was introduced in 2004. No reliable estimates could be obtained about the first three years of the study period. For 2004, 2005 and 2006, the numbers of patients screened on admission or during a visit to the outpatient department were 161, 164 and 252, respectively. 15 (9.3%), 10 (6.1%) and 32 (12.7%) of these patients were MRSA positive. From 2001 through 2006, 95 persons were identified to carry MRSA, i.e. 82 patients and 13 HCW (see table 1). The most prevalent specialties of the patients at the time the first MRSA was cultured, were surgery (24.4%), internal medicine (19.5%), paediatrics (13.4%), orthopaedic

Table 1: Demography of MRSA positive patients and Health Care Workers.

	Patients (n=82)	Health Care Workers (n=13)
Age at first MRSA positive culture		
Mean	49.7	35.8
Minimum	0.1	19.0
Maximum	90.6	55.8
Median	54.9	35.3
Females / males	33 / 82	10 / 3
Dutch nationality / foreign nationality	71 / 11	12 / 1
Treatment		
Not treated	61.0 % (50/82)	8% (1/13)
Treated	39.0 % (32/82)	92% (12/13)
Total number of treatments	41.0	15.0
Treatment data of all patients/HCW (n=82/13)		
Mean	0.5	1.2
Median	0	1.0
Minimum	0	0
Maximum	3.0	3.0
Treatment data of patients/HCW with MRSA eradication therapy (n=32/12)		
Mean	1.3	1.3
Median	1.0	1.0
Minimum	1.0	1.0
Maximum	3.0	3.0
Treatment results		
MRSA free after first treatment, which was topically applied	25% (8/32)	83% (10/12)
MRSA free after first treatment, which was systemically administered	9.4% (3/32)	N.A.
MRSA free after second treatment (topical or systemical)	15.6 (5/32)	8% (1/12)
MRSA free after third treatment (systemical)	3.1% (1/32)	8% (1/12)
No eradication	34.4% (11/32)	N.A.
Unknown MRSA status after treatment	12.5% (4/32)	N.A.
MRSA free without eradication therapy	30.5% (25/82)	8% (1/13)

surgery (7.3%) and pulmonology (6.1%). Other specialties, such as cardiothoracic surgery, neurology and cardiology, represented less than 5%. From thirty (37%) patients, MRSA positive samples were obtained from other places than the nose, throat and perineum, i.e. MRSA was cultured from wounds, urine and sputum. No MRSA positive blood samples were found. The other 52 patients and all 13 HCW were colonised, but not infected, with MRSA in the nose, throat or perineum. The annual MRSA incidence in patients and HCW is shown in figures 1 en 2, respectively. During the study period, the MRSA incidence among patients was 5/100,000 patient days (82/1,695,514) or 35/100,000 (82/233,661) admissions.

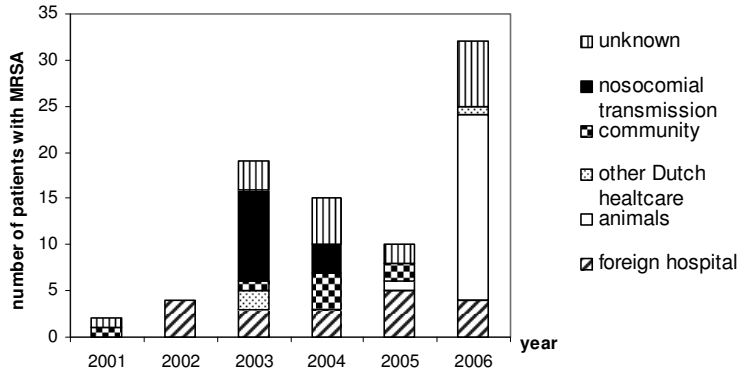

Figure 1. MRSA incidence and sources in patients, 2001 through 2006.

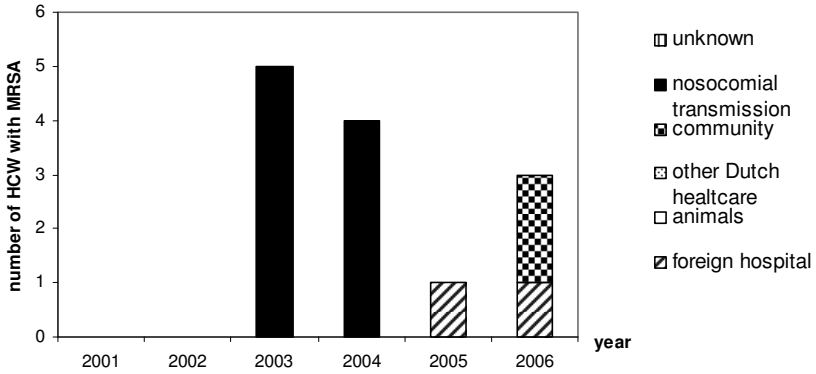

Figure 2. MRSA incidence and sources in health care workers, 2001 through 2006.

Strain typing and source determination

One patient carried two different strains, so 96 MRSA strains were included. Based on PFGE typing 33 different types of MRSA were identified, i.e. eight clusters of two or more identical PFGE strains and 25 types containing one single PFGE strain. The largest clusters consisted of 28 strains (PFGE type 55) and of 25 strains that could not be typed with the enzyme *SmaI*, the enzyme used for PFGE typing (non-typeable (NT)-strains). Twenty-one (84%) of these NT-MRSA were found in patients that had direct exposure to pigs or veal calves. The other four NT-MRSA were found in two adoption children and two patients who did not belong to any known risk group. Based on both the absence of a link between some persons from the same PFGE cluser and the increase of NT-MRSA, a second typing method was performed, i.e. *Spa* typing. The strains from 4 HCW colonised by nosocomial transmission (PFGE 55) and from a patient with a single PFGE strain were not available for *Spa* typing, so 91 of the 96 MRSA strains were typed with *Spa*. They comprised 32 different PFGE types and 27 different *Spa* types were found. Some PFGE types showed several *Spa* types and visa versa. *Spa* typing of the 8 PFGE clusters

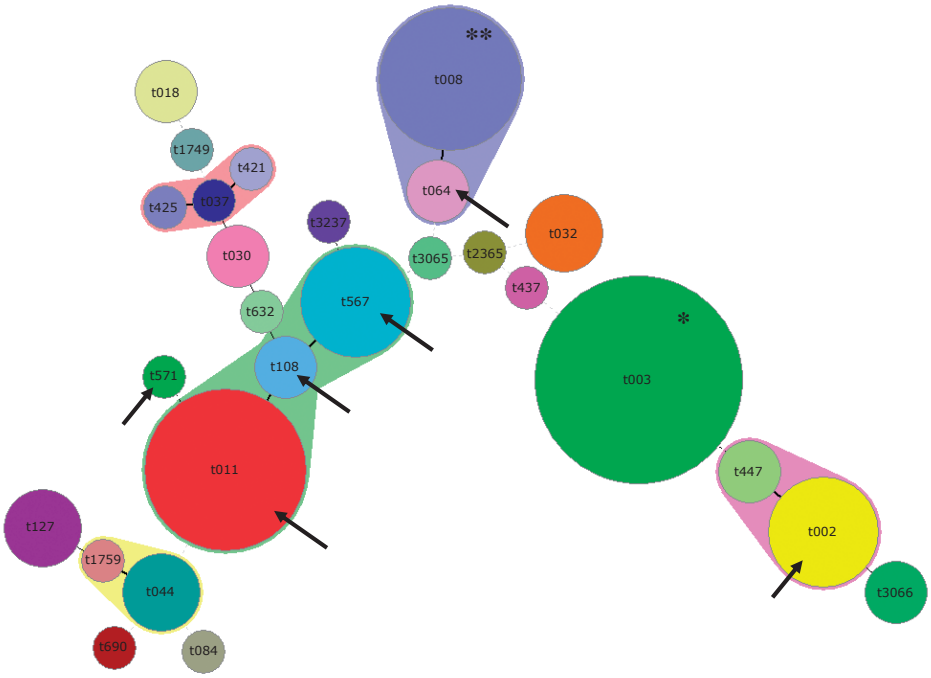

Figure 3. Genetic relation between different Spa types shown in minimal spamming trees (MST). The animal related strains are indicated by an arrow. *t003 consisted of the oubreak strain (PFGE type 55) and a single other strain. **t008 consisted of 4 PFGE strain types.

identified 15 different *Spa* types, so 7 additional types were found. PFGE cluster 55, the most prevalent PFGE type, showed three different *Spa* types, i.e. t002 (n=1), t003 (n=22), and t447 (n=1), which are closely related (figure 3). The strains that could not be typed with PFGE showed six different *Spa* types, i.e. t002 (n=1), t011 (n=12), t064 (n=2), t108 (n=2), t567 (n=6), and t571 (n=1). Patients with exposure to pigs showed all these *Spa* types, except for t002. All 3 positive calf farmers were colonised with *Spa* type t011 and a calf farmer's daughter carried t002, which showed no genetic relation with the other animal-related *Spa* types (figure 3).

Based on patient's history and strain typing the MRSA source was determined (figures 1 and 2). Twenty-three percent (19/82) of the patients acquired MRSA in a foreign hospital, 26% (21/82) via animals, 16% (13/82) by nosocomial transmission, 4% (3/82) in another Dutch healthcare institute, 10% (8/82) in the community (related to a previously identified carrier) and in 22% (18/82) the source was unknown (figure 1). In total 13 HCW got colonised during the study period, i.e. 69% (9/13) was due to nosocomial transmission, 15% (2/13) was related to working in a foreign hospital and in 15% (2/13) HCW got colonised via a MRSA positive partner or friend (figure 2).

Nosocomial MRSA transmission

In 2003 and 2004 two outbreaks occurred, both caused by the same MRSA type (PFGE 55, *Spa* t003). The first patient with this type was a patient who had been treated in a hospital in Turkey a month before he was admitted to the Amphia. However, his MRSA risk was not recognised on admission and therefore he was not treated with adequate isolation precautions for several days. Thirteen patients and 9 HCW were colonised by nosocomial transmission during these two outbreaks. In 2001, 2002, 2005 and 2006, no nosocomial transmission occurred. The transmission rate during the study period was 0.30 (22 secondary cases / 73 index cases).

Discussion

In the Amphia hospital, before 2006 the MRSA prevalence was relatively low. In 2006 a sudden and strong increase of MRSA carriage was found that was caused entirely by the emergence of animal-related MRSA, as reported previously (figure 1).[6] Combined PFGE- and Spa analyses of all MRSA strains found in the years 2001 through 2006 showed that in one PFGE cluster several Spa types can be found, and visa versa. Spa typing showed a better relation between MRSA positive persons than had been shown by PFGE typing before. For example all persons involved in the MRSA outbreak caused by PFGE type 55 showed the same Spa type (t003), while persons who were also colonised with type 55 but not related in time and place to the outbreak, showed other Spa types (t002 and t447), which were closely related to t003. Another example is a patient who got recolonised after eradication. Although PFGE typing showed two different strains (albeit with minor differences), the Spa type of the second MRSA was the same as the first one, which indicates a decolonisation failure or recolonisation from the same MRSA source. Another advantage of Spa typing over PFGE are the unambigious results. Also, Spa typing differentiated the large number of NT strains. They belonged to six different Spa types and these Spa types had already been found to be related to animal farming.[7-9] Figure 3 shows that most nontypeable strains were related to each other (t011, t108, t567 and t571). Two other nontypeable strains (t002, t064), were not closely related, indicating a separate descent. These NT MRSA were found in an adopted child, a veterinary surgeon and a calf farmer's daughter. All MRSA related to pigs or veal calves were tetracyclin resistant, while MRSA related to other sources were not. There is no other correlation between susceptibility patterns and sources of strains. There were few infections caused by MRSA in the patients involved in this study in general and no serious infections at all. For example, none of the patients developed a bacteraemia. Therefore we cannot draw conclusions about strains and clinical outcome based on these data.

At the moment there is a discussion going on about the burden of disease due to MRSA related to pigs or veal calves. There are indications that the burden of disease caused by this clonal group of MRSA is less than from other MRSA's, while others debate this. At the moment this is being studied in The Netherlands, but it is too early to draw conclusions.

In this observational study, a low MRSA incidence among patients was described, i.e. 5/100,000 patient days (82/1,695,514) or 35/100,000 admissions (82/233,661). In contrary, Kuehnert mentioned a MRSA infection incidence of 3.95 per 1,000 hospital discharges in the USA, which was based on the data in the National Hospital Discharge Survey from 1999 to 2000.[10] The incidence found in our study was more than 100 times lower than the MRSA incidence found in the USA. It must be noted that in the USA calculation, only the MRSA infection rate was included while we took both colonisation and infection into account. During this six-year study period, nosocomial transmission of one MRSA type occurred in the inpatient clinic and no nosocomial transmission was observed in the outpatient clinic. At first consideration the outbreak may be considered as a failure of Search and Destroy. However, this is not the case. Search and Destroy relies on active screening of high risk groups and subsequently applying control measures to limit the spread of MRSA. Unfortunately, not all carriers belong to known risk groups. The outbreak that we described was caused by a carrier of MRSA that had not been identified upon admission. Subsequently, the strain spread to patients and health care workers. When the outbreak was detected, Search and Destroy was used to control it. This means that all contacts were traced and cultured and if found to be positive they were isolated. This resulted in control of the outbreak. Therefore this can be considered as an 'unintended' experiment showing that MRSA also spreads in The Netherlands if no control measures are applied. When spread occurs, Search and Destroy is an effective strategy to control it again. That's why it is important to continue the S&D policy. For the outpatient clinic another conclusion was drawn. During the study period 16 outpatients were found to be MRSA carrier after they had visited the outpatient clinic. So, during their visit no isolation measures had been applied. 211 health care workers were screened subsequently and none of them was found to be MRSA positive. Based on these results the policy for outpatients was adjusted. No additional control measures are taken anymore for MRSA carriers. It is important to realize that the general infection control precautions for all patients are still recommended. To monitor this adjustment all health care workers and medical doctors who are working on the outpatient clinic are screened twice a year. So, the risk for MRSA transmission from inpatients is higher than from outpatients, probably because of the more intense contacts between inpatients and HCW.

The best way to study the effectiveness of the S&D policy is the comparison of the use of this strategy with a similar setting were no control measures are taken. This

study is not feasible in the Netherlands, because all Dutch hospitals apply the S&D policy according a National guideline, just like other Dutch health care institutes, e.g. nursing homes, rehabilitation centres and home care. The hospital described in this paper is located about 10 miles from the Belgian border. In Belgium Search and Destroy is not used (except some hospitals). Almost all hospitals in Belgium have much higher MRSA rates.[1]

It is difficult to translate the relevance of the findings in our low prevalence setting to countries with a high incidence of MRSA. In any case it will be more difficult to apply a S&D policy in a country with a high incidence because there are much more patients to be screened and isolated. Nevertheless, a mathematical model developed by Bootsma and colleagues showed that S&D will be effective in high prevalence settings as well.[11]

Up till now we have been able to identify which patient groups have to be screened upon admission because they are at increased risk for MRSA. Therefore, we don't need to screen all patients, which results in a relatively low number of screenings. It is possible that not all patients-at-risk were identified and screened. However, we expect that more patients with MRSA positive clinical samples would have been found when many patients-at-risk were missed. All patients-at-risk are isolated until screening results become available. The proportion of admissions that belongs to a risk group is relatively low, approximately 0.5%. The proportion for both admissions and outpatient visits is even rarer (0.025% in 2004 and 0.026% in 2005). However, it has increased to 0.040% in 2006 due to the emergence of a new reservoir of MRSA related to pig-farming and to the increase in patients with MRSA that do not belong to known risk groups.[6] The latter probably represents the emergence of MRSA in the community. Further research to identify determinants for community associated MRSA carriage is essential for a successful continuation of the S&D strategy. Only then the control measures can be adapted to this new threat.

In concusion, MRSA was introduced in the hospital by both patients and HCW. This introduction of MRSA cannot be prevented, but the S&D policy is applied to prevent subsequent nosocomial tranmissions. The transmission rate of 0.30 indicates that the spread of MRSA was under control during the study period, so the S&D policy is effective and should be continued. The emergence of new reservoirs of MRSA outside of the hospital are potential treats to the S&D strategy and should be identified as soon as possible.

Acknowledgment

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