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Research Article

MRSA in a large German University Hospital: Male gender is a significant risk factor for MRSA acquisition

MRSA in einem deutschen Universitätsklinikum: Männliches Geschlecht ist ein signifikanter Risikofaktor für den Erwerb von MRSA

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Abstract

Background: The continually rising number of hospital acquired infections and particularly MRSA (Methicillin-resistant Staphylococcus aureus) colonization poses a major challenge from both clinical and epidemiological perspectives. The assessment of risk factors is vital in determining the best prevention, diagnosis and treatment strategies.
Materials and methods: We analyzed 798 cases of MRSA in a large German University Hospital over a 7-year period. Data was collected retro- and prospectively including patient age, sex, type of ward and duration of inpatient stay. In addition we analyzed all cases on ICU with regards to cross infection and MRSA genotyping via DNA MicroArray Technology. The years 2004 to 2007 were analyzed with a specific focus on gender.
Results: Male gender is significantly correlated with increased risk of MRSA acquisition ($p<0.001$), the predominant setting for MRSA is on ICU. 75% of the MRSA positive patients are over 50 years of age (average age 59.8 years). The inpatient time was 4.15 times higher in MRSA carriers compared with non-MRSA cases, however this was not significant. MRSA genotyping on ICU showed mainly the subtypes ST 5, ST 22, ST 228, however cross contamination with identical genotypes was only detected in a minority of cases (5 out of 22).
Conclusion: Unlike previous studies which show no or inconclusive evidence of gender as a risk factor, our data confirm that male gender is a significant risk factor for MRSA carrier status. Further research will be required to investigate the aetiology of these findings.

Zusammenfassung

Hintergrund: Die steigende Anzahl von Patienten mit Methicillin resistenten Staphylococcus aureus (MRSA)-Kolonisation oder -Infektion ist unter klinischen, epidemiologischen wie auch ökonomischen Gesichtspunkten ein Problem. Um die Situation des Uniklinikums Dresden (UKD) national einzuordnen, intern zu analysieren und das MRSA-Management weiter zu optimieren, wurde diese Untersuchung durchgeführt.
Methode: In einer retro- und im letzten Jahr der Auswertung prospektiven 7 Jahresstudie (2001 bis 2007) wurden 798 stationäre MRSA-Fälle in Anlehnung an das nationale MRSA-Surveillancesystem MRSA-KISS (Krankenhaus-Infektions-Surveillance-System) erfasst und hinsichtlich Risikofaktoren analysiert. Die Isolate von Patienten der Intensivstationen aus dem Jahr 2007 wurden genotypisiert (Microarray Technology, CLONDIAG®) und Transmissionswege aufgezeigt.
Ergebnisse: Durchschnittlich waren MRSA-Patienten 59,8 Jahre alt und zu 75% älter als 50 Jahre. Eine signifikante ($p<0,001$) Häufung von MRSA konnte im Bezug auf das männliche Geschlecht herausgestellt werden. Die Verweildauer der MRSA-Patienten war im Vergleich zu Patienten ohne MRSA-Nachweis um den Faktor 4,15 höher. Nicht nosokomiale Fälle (n=385) zeigten im Bezug auf den Aufenthaltsort vor der stationären Aufnahme, dass 62,5% aus ihrer häuslichen Umgebung

(nicht Pflegeheime), 26,6% aus medizinischen Einrichtungen und 4,9% aus Pflegeheimen aufgenommen wurden (6% nicht eruierbar). Im nationalen Vergleich mit den MRSA-KISS Referenzdaten ordnet sich das Universitätsklinikum Dresden bezüglich nosokomialer und nicht nosokomialer Inzidenzdichte und MRSA-Last von 2004 bis 2007 jeweils kleiner/gleich des 25%-Quantils ein. Die nosokomialen Fälle pro 1.000 MRSA-Tage sind im nationalen Vergleich über dem 50%-Quantil einzuordnen. Intensivstationen zeigten im klinikinternen Stationsgruppenvergleich die höchsten Inzidenzdichten, die höchste MRSA-Last und die meisten nosokomialen MRSA-Fälle. Die Genotypisierung auf ITS ergab, dass unterschiedliche Epidemiestämme vorkamen (ST 5, ST 22, ST 228). Das Auftreten von genotypisch identischen MRSA konnte in der Minorität der Fälle (5 von 22) nachgewiesen werden.

Schlussfolgerung: Zusätzlich zu den vom Robert-Koch-Institut publizierten Risikofaktoren hat sich in der eigenen Patientenklientel das männliche Geschlecht als signifikanter Risikofaktor darstellt. Die MRSA-Belastung ist im Stationsgruppenvergleich auf den Intensivstationen besonders groß. Aufenthaltsort nicht nosokomialer MRSA-Fälle vor Hospitalisation ist mehrheitlich die häusliche Umgebung. Die durchschnittliche Verweildauer von MRSA-Patienten ist höher als die anderer Patienten. Die Genotypisierung stellt eine sinnvolle Maßnahme dar um die Transmissionskette von MRSA zu verstehen und gezielt Hygienemaßnahmen einzuleiten.

Introduction

Over the past two decades the number of nosocomial infections has risen steadily [1]. Methicillin-resistant Staphylococcus aureus (MRSA) has been the main focus of attention due to its obvious direct and indirect consequences for all involved parties [2], [3], [4]. Patients with MRSA have a significantly longer in-hospital stay, a worse prognosis and higher mortality. They also instigate higher costs in their diagnosis and therapy, are subject to social stigma and suffer from greater psychological stress [5], [6], [7], [8], [9], [10], [11], [12].

The prevalence of resistant *S. aureus* has shown a dramatic increase worldwide since 1990 [13], [14]. In Germany the ratio of MRSA to Methicillin susceptible *S. aureus* (MSSA) blood cultures has risen from 1.7% to 21% in 15 years (1990–2005), putting Germany to a mid position amongst all EU countries with the steepest rise in MRSA infections. Furthermore, the development of further resistant pathogens seems imminent due to documented Vancomycin Resistant Staphylococcus Aureus (VRSA) cases in countries neighbouring Germany [15], [16], [17]. The aim of this study was to analyse a representative cohort of inpatients with MRSA, to identify risk factors for MRSA acquisition, transmission pathways and particularly affected specialties. Furthermore we aimed to audit the prevalence of MRSA in an East-German University Hospital as compared to the national situation [9].

Material and methods

All data originates from a Saxonian University hospital with 1,250 beds and treats 50,000 in-patients per year. The study period was 7 years between 01.01.2001 and 31.12.2007. Data from the first 6 years were collected retrospectively and the last year prospectively. Patients were screened for MRSA in keeping with the modified guidelines outlined by the Robert Koch-Institute in the presence of at least one risk factor (Table 1). Processing of specimens was undertaken by the Institute for Microbiology and Hygiene of the Technical University Dresden, Germany. Specimens taken from patients on the intensive care units at the University Hospital in the year 2007 were analysed and sent for genotyping.

Individual specimens were plated on Columbia blood agar (Oxoid, Wesel, Germany) and incubated overnight at 37 °C. Single colonies were used for further subculturing. Screening for clumping factor and coagulase was performed using Pastorex Staph-Plus (Bio-Rad, Munich, Germany) and rabbit plasma (Becton-Dickinson, Heidelberg, Germany). Routine susceptibility tests were performed using the VITEK I system (bio-Mérieux, Nürtingen, Germany) as recommended by the manufacturer. Methicillin resistance was confirmed by detection of penicillin-binding protein 2' (PBP2') using an agglutination assay (MRSA-screen; Innogenetics, Ghent, Belgium). Penicillinase activity was detected using the BBL DrySlide Nitrocefin test (Becton Dickinson). The identified MRSA were plated on Columbia blood agar (Oxoid, Wesel, Germany) and incubated overnight again.

Genotyping was undertaken with DNA microarray technology (CLONDIAG Chip Technologies GmbH) as described previously [18], [19].

In case of a positive MRSA result the patient was isolated in keeping with the protocol of the Robert Koch-Institute (isolation in one-bed-room, use of protective clothing, basic hygienic actions, screening as explains above, use of one way masks, isolation lifted after three negative

Table 1: Risk factors with screening as consequence
Microbiological screening comprises swabs of vestibules nasi, throat and wounds (including eczema and chronic wounds).

1. Patients with MRSA in history
2. Patients coming from facilities with high MRSA rates
3. Patients having contact with MRSA positives (e.g. staying in one room)
4. Skin ulcers, gangrene, chronic wounds, deep soft tissue infections
5. Burning injuries

Table 2: Disciplines and their subgroups

Surgical wards	Other surgical wards	Medical wards	ICU
General Surgery, Traumatology, Vascular Surgery, Heart- and Chest Surgery	Orthopaedics, Otolaryngology, Ophthalmology, Urology, Gynaecology, Paediatric Surgery, Oral and Maxillofacial Surgery, Neurosurgery, Dermatology	Neurology, Psychiatrics, Psychosomatic, Radiology, Nuclear Medicine, Paediatrics, Geriatrics, Palliative Care	All subtypes of ICU

samples being taken at 24 h intervals) and the MRSA case was recorded. Data recording included age at first MRSA presentation, gender, and hospital acquired versus community acquired infection, time of inpatient stay, ward and location settings previous to admission. Wards were subdivided into intensive care, general surgical and medical wards and other surgical wards (Table 2). National comparison was performed in accordance with the criteria and standards outlined by the MRSA-KISS study [20]. For statistical reasons the differentiation of gender could only be performed in the years 2004 to 2007. An MRSA case was defined as a patient testing positive for MRSA during the hospitalisation. Recurrent admissions were classified as new cases. Using these standards we were able to identify 1,079 MRSA cases, 74% of which were inpatients (n=798), 25.98% outpatients and 0.02% day cases. Only inpatients were included in this study. $P<0.001$ was taken as the level of significance.

Results

798 cases were identified during a 7-year time period (Figure 1). Patients with MRSA were between 50 to 74 years with a median of 60 years (Figure 2). Male to female ratio showed a significant predominance ($p<0.001$; χ^2-Test) of the male gender (Figure 3). Most patients were admitted directly from their own home (62.6%) prior to admission followed by other medical facilities (26.5%) and more rarely nursing homes (4.9%). MRSA positive patients had a 4.15 times longer in-hospital stay (not significant; $p>0.001$). ICU had the highest MRSA prevalence (Figure 4). ICU had the highest MRSA prevalence, except for the year 2007 when the surgical wards had the highest MRSA rates (cases per 1,000 patient days). Despite the higher MRSA rates in ICU, we were able to observe a reduction of MRSA cases per 1,000 inpatient days as compared to the surgical wards where this rate continually increased (Figure 4). We also detected a correlation of hospital acquired infection rate per 1,000 inpatient days with MRSA inpatient days ($k=0.99$). Genotyping of MRSA samples from ICU (2007 only) showed the Barnim-(ST 22) and Rheine-Hessen (ST 5) as well as South German (ST 228) strains only. Between three and five subtypes of the main strain were sampled for genotyping, respectively (Table 3). Of note, the anaesthetic ICU was only affected by two different subtypes of the South German strains.

Discussion

Two thirds of MRSA patients were above 50 years of age in keeping with the current literature [21], [22], [23]. However, age as an independent risk factor has not been registered in the literature or with the Centers for Disease Control and Prevention (CDC) or with the Robert Koch-Institute. Older people have more risk factors [24]. In addition they are the largest patient subgroup in hospitals, which could be seen as a confounder (Table 1). Further research will be required to investigate this [25], [26]. In contrast to previous studies that showed no or no significant gender predominance we were able to demonstrate that male sex is a significant risk factor ($p<0.001$) for MRSA [27], [28], [29]. We attribute this to the fact that most risk factors, which predispose individuals to acquiring MRSA, were mainly possessed by men rather than women. Van Landeghem et al. [30] stated that diabetes mellitus related terminal renal failure, requiring dialysis, was more common in men (59%), which added to the risk profile. Invasive devices were a further factor such as bladder catheters. In nursing homes only 5% of women but 30% of men were catheterised. Similarly, due to obvious patho-anatomical considerations we would assume

Table 3: MRSA strains and their genotype detected by microarray technology

Name of MRSA strain	Gene specifics of strain
(ST 22) Barnim 1	agr_I/ST22-MRSA IV, Barnim/EMRSA-15, [entC/L-, ermC-, IEC+]
(ST 22) Barnim 2	agr_I/ST22-MRSA IV, Barnim/EMRSA-15, [entC/L-, ermC+, fnbB-/n.a.]
(ST 22) Barnim 3	agr_I/ST22-MRSA IV, Barnim/EMRSA-15, [entC/L+, entB, ermC+]
(ST 22) Barnim 4	agr_I/ST22-MRSA IV, Barnim/EMRSA-15, [entC/L+, ermC+, IEC+]
(ST 288) South-German 1	agr_II/ST228-MRSA I, South-German EMRSA [mer-, ermA-, normal egc, lukD/E+, bbp-, clfA+]
(ST 288) South-German 2	agr_II/ST228-MRSA I, South-German EMRSA [mer+, ermA+, normal egc, lukD/E+, bbp+, clfA-]
(ST 288) South-German 3	agr_II/ST228-MRSA I, South-German EMRSA [mer+, ermA+, truncated egc, lukD/E-, bbp+, clfA+]
(ST 5) Rheine-Hessen 1	agr_II/ST5-MRSA II, Rheine-Hessen/EMRSA-3 [entA-N315-, entDJR+, blaZ+, ermA+, aadD+]
(ST 5) Rheine-Hessen 2	agr_II/ST5-MRSA II, Rheine-Hessen/EMRSA-3 [entA-N315+, entDJR-, blaZ-, aadD-]
(ST 5) Rheine-Hessen 3	agr_II/ST5-MRSA II, Rheine-Hessen/EMRSA-3 [entA-N315+, entDJR-, blaZ-, aadD+]
(ST 5) Rheine-Hessen 4	agr_II/ST5-MRSA II, Rheine-Hessen/EMRSA-3 [entA-N315+, entDJR+, aadD+, ermA+]
(ST 5) Rheine-Hessen 5	agr_II/ST5-MRSA II, Rheine-Hessen/EMRSA-3 [entA-N315+, entDJR+, blaZ+, aadD-]

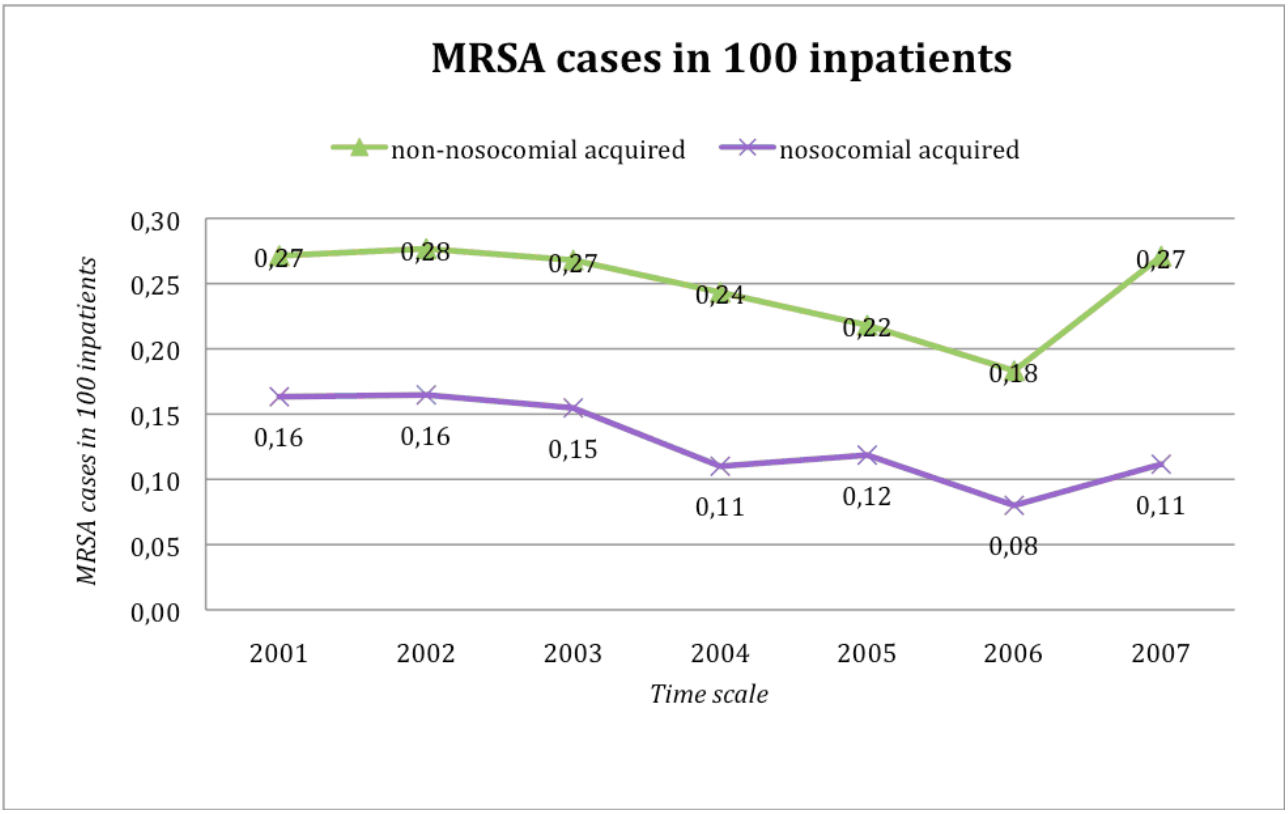

Figure 1: Nosocomial and non-nosocomial MRSA cases in 100 inpatients

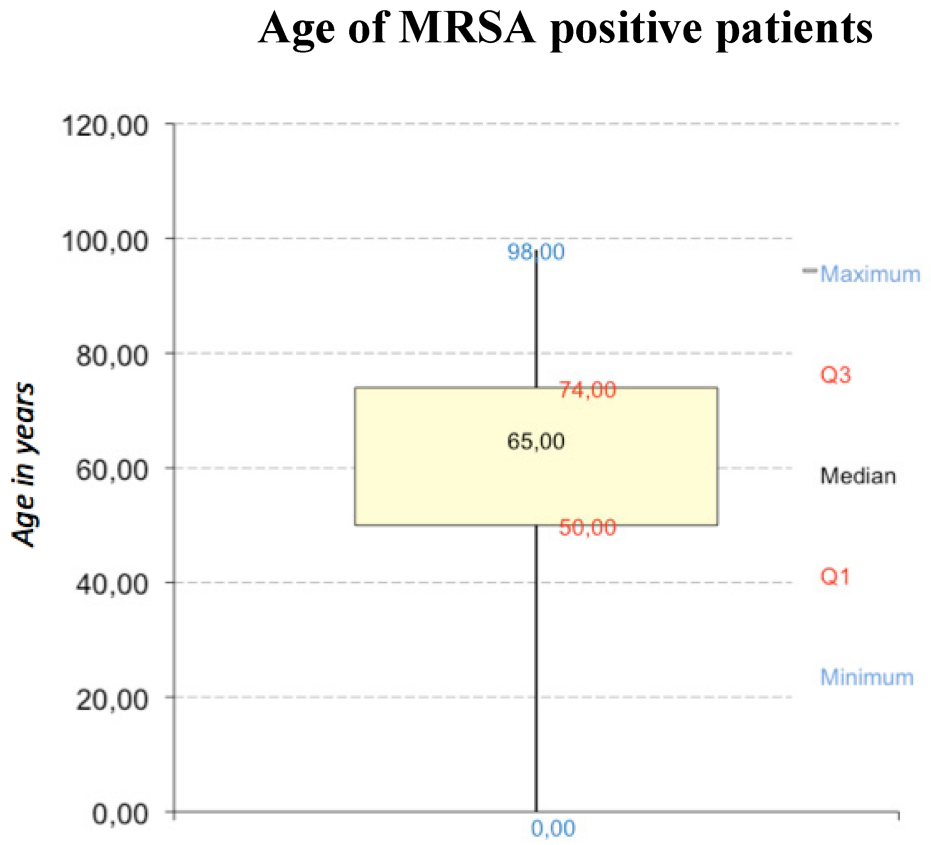

Figure 2: Age of 798 MRSA-Positives (Box-Whiskers-plot graphic)

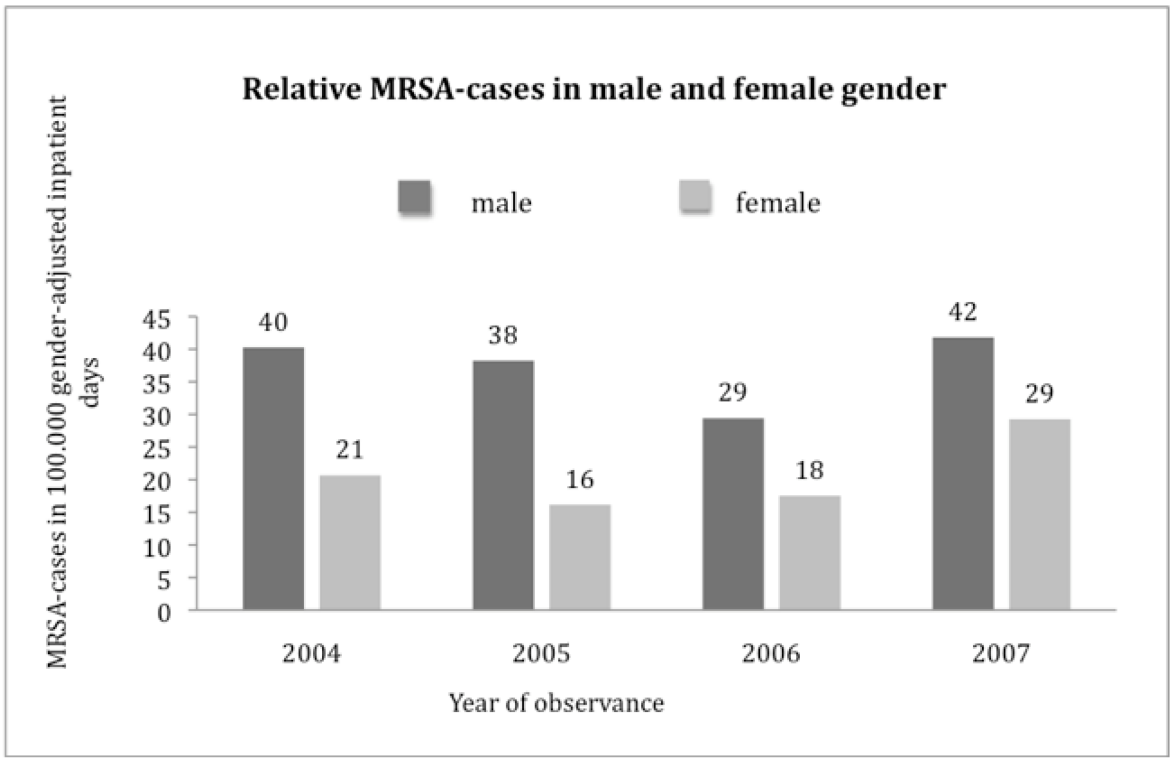

Figure 3: Relative distribution of MRSA positives selected by gender

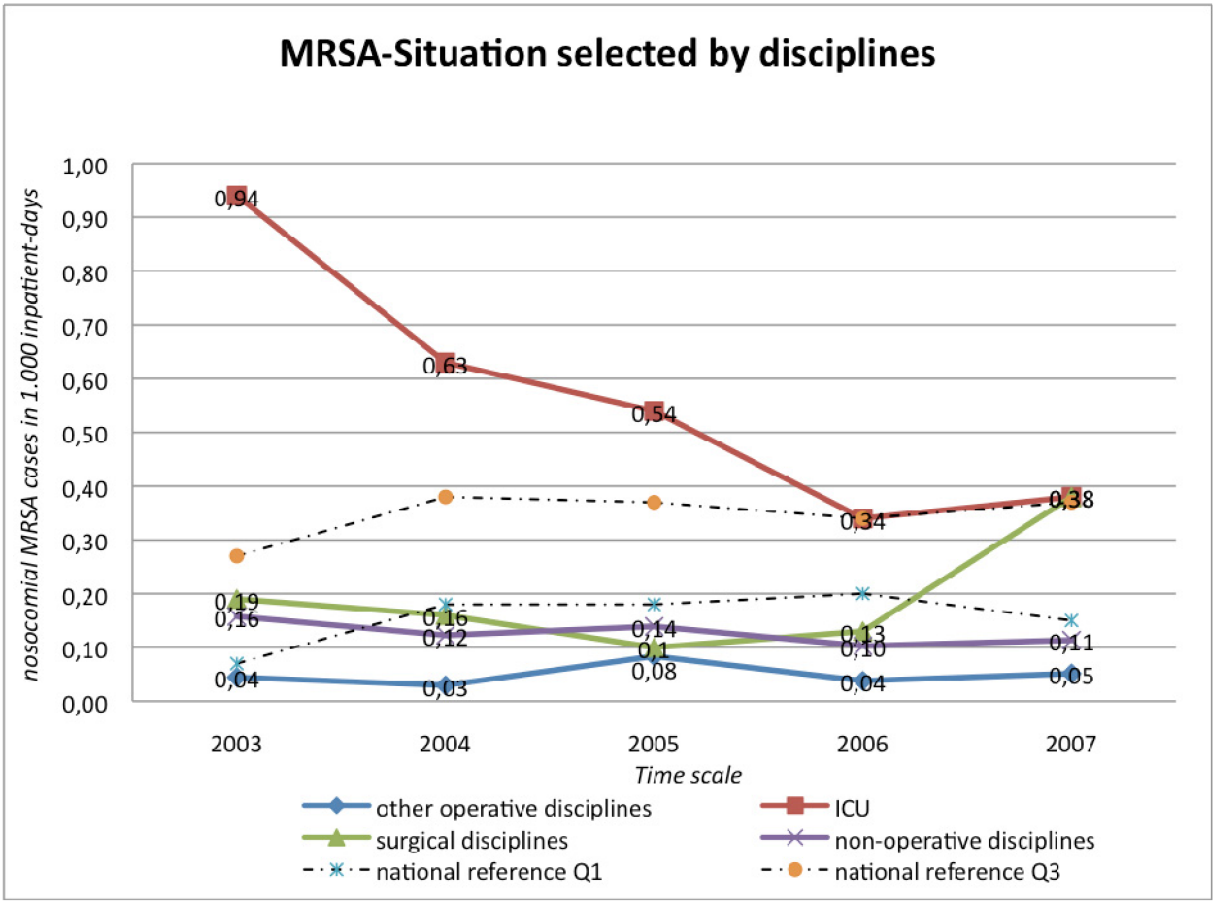

Figure 4: Nosocomial MRSA cases in 1,000 inpatient-days, selected by ward-type

that in the general community more men than women are catheterised [31]. Hornberg et al. argue that peripheral vascular disease in diabetics is four times more common in men, leading to delayed wound healing with prolonged or repeated hospital inpatient days. Both factors add to the MRSA risk profile [8], [32].

The increase in hospital days among MRSA patients is in keeping with the literature. This tendency decreased during our observation time [1], [9], [17], [21]. MRSA infections not acquired in hospital (n=385) showed that the pre-hospital residence was their own home in 62.5% of the cases, medical facilities in 26.6% and only 4.9% were from nursing homes (6% could not be traced). These numbers show a high prevalence of MRSA patients in presumed "non-risk" areas.

The East German University Hospital Dresden can be seen (regarding *all* MRSA cases per 1,000 inpatient days) under the 25% percentile between 2004–2007 compared to the national average monitored by the MRSA-KISS study. The hospital acquired MRSA rate per 1,000 *MRSA days* is comparably high on national comparison. Further data will be necessary to evaluate this.

The highest infection rate among the hospital wards was seen on the intensive care units followed by the surgical wards (Table 2). Medical wards were third and minor surgical wards last, in keeping with the current literature [33], [34], [35].

In keeping with literature, ICU's are known to provide the highest risk for nosocomial infection. The elevated risk of MRSA within the ICU is most likely to be due to the preselected cohort of patients with a larger number in risk factors and comorbidities [6], [36], [37], [38], [39]). Other factors involve the increased inpatient time, the use of invasive devices, high prevalence of multiresistant bacteria and increased use of antibiotics [40], [41], [42]. Genotyping of MRSA strains on ICU showed Rheine-Hessen- (ST 5), Barnim- (ST 22) and South German (ST 228) strains (Table 3), representing three of the four most common types in Germany. Horizontal infection was only seen in a minority of cases. Persistence of MRSA on the ward was observed independently of patient contacts. This highlights the importance of Panton-Valentine-Leukozidin and the relationship of staff and medical equipment [12], [24].

Conclusion

MRSA is a challenging problem under clinical and epidemiological perspectives. In this study we were able to demonstrate that male gender is significantly correlated with an increased risk of MRSA acquisition ($p<0.001$), the most predominant setting for MRSA being the intensive care unit. 75% of MRSA positive patients are over

50 years of age. The inpatient time was 4.15 times higher in MRSA carriers compared to MSSA cases, however this was not significant. MRSA genotyping on ICU showed mainly the subtypes ST 5, ST 22, ST 228. Cross contamination with identical genotypes was only detected in a minority of cases (5 out of 22).

Unlike previous studies which show no or inconclusive evidence of gender as a risk factor, our data confirm that male gender is a significant risk factor for MRSA carrier status. Further research will be required to investigate the aetiology of these findings.

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