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Molecular epidemiology of *Staphylococcus aureus* colonization in a burn center

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Abstract

The aim of this study was to investigate carriage of *Staphylococcus aureus* by patients and health care workers (HCW) and to define the genetic relationship of *S. aureus* strains isolated from burn wounds. At admission, 19/55 (34.5%) patients carried *S. aureus* in their nose and/or throat. Of this group, 95% subsequently colonized their burn wounds with *S. aureus*. Molecular analysis showed that in 78% of these cases the burn-wound colonizing strain was identical to the strain carried at admission. Importantly, 23/36 (64%) patients who did not carry *S. aureus* at admission also developed burn-wound colonization. In this group, three dominant genotypes were identified as colonizing strains of burn wounds. These clones represented also the majority (59%) of *S. aureus* strains cultured from the nose and/or throat of health care workers and patients. If patients were admitted to one of the Intensive Care rooms burn wounds of non-carriers were not colonized with *S. aureus* as long as they remained in such isolation. Only patients who carried *S. aureus* at admission developed burn-wound colonization with that genotype they carried in the nose or throat. Both carriage in patients and health care workers and auto-infection play a crucial role in (cross-) colonization events.

Keywords: *Staphylococcus aureus*; Burn-wound colonization; Burn center

1. Introduction

Thermal injury destroys the physical skin barrier that normally prevents invasion of micro-organisms. This provides novel sites of bacterial colonization, infection and clinical sepsis in burned patients. During the first weeks following thermal trauma, the affected sites are colonized with Gram-positive bacteria, including *Staphylococcus aureus*, and as time passes, Gram-negative bacteria become increasingly prevalent and dominant [8,13,17,20,21]. Consequently, patients admitted to burn centers are at increased risk for nosocomial infections, including infections due to *S. aureus*.

Several studies have shown that the rate of burn-wound colonization with *S. aureus* varies significantly (14–83%), depending on total body surface area burned, the age of the patient and, more importantly, with the type of care provided by the burn center health care team [1,14,15,20]. Colonization with *S. aureus* is often associated with delayed wound healing, an increase in the need for surgical interventions and prolongation of stay at the center [8,15]. Transmission of *S. aureus* occurs often and involves both patients and persons in close contact with them [6]. Nasal and pharyngeal colonization of patients as well as health care workers (HCWs) in burn centers appear to play an important role in *S. aureus* colonization of burn wounds [1,19]. However, detailed molecular epidemiological analysis of the dynamics of *S. aureus* carriage and transmission in burn units has not yet been presented.

We performed an epidemiological survey on staphylococcal colonization of burn wounds. The study was performed in a single dedicated burn center. Data on clinical practice were recorded and regular surveillance culture, specific for *S. aureus*, was performed for patients and personnel. Longitudinally collected strains of *S. aureus* were genetically characterized in order to elucidate the dynamics of wound colonization and possible transmission routes.

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2. Patients and methods

2.1. Setting

The study was performed in the Burn Center at the Martini Hospital, Groningen, The Netherlands. The burn center is a closed unit including a dedicated operating theater. It consists of four rooms with two beds each, and two Intensive Treatment (IT) rooms with one bed each, accommodating a total of 10 patients. In the whole burn center an air-flow with positive air pressure is maintained; each IT-room has its own laminar down-flow with positive air pressure. When the patient is alone in the IT-room, the ventilation rate is 30 air changes per hour. If there are health care workers or visitors in the IT-room, the ventilation rate is raised to 80 air changes per hour. At the burn center, a dedicated team of HCW ($n = 46$), which have no other healthcare duties outside the burn center, takes care of the patients. Patients remain at the burn center during the entire hospital stay. However, occasionally patients may be moved from room to room within the burn center.

2.2. Patients and health care workers

During a period of 31 weeks, from September 1997 to May 1998, all patients hospitalized at the burn center, were included in this study. At admission, burn wounds were sampled at least once and nose and throat swabs were taken in order to assess staphylococcal carriage. During hospital stay, all burns were sampled weekly. At regular 2 month-intervals, nasal and pharyngeal swabs were taken for *S. aureus* screening from those HCW, who were at that period present at the burn center. To study whether clonal types of *S. aureus* circulate persistently among HCW, a short screening period of 1 week was implemented approximately 19 months after the study period.

2.3. Decontamination regimens

Adults with more than 20% total burned surface area (TBSA) and children with more than 15% TBSA received a regimen of selective decontamination (SDD) of the digestive tract, from 0 days post-burn till 5 days after last surgical intervention. The SDD regimen comprised co-trimoxazole (500 mg, given three times daily), colistine (200 mg, given four times daily) and amphothericin B (0 days post-burn 500 mg, four times daily and there after 500 mg, two times daily).

2.4. Microbiological methods

Samples of nasal and pharyngeal flora were collected from patients and HCW. The nasal vestibule of both the right and left nares were swabbed with a sterile swab, and the flora of the throat was sampled with another sterile swab. Swabs were inoculated on 5% sheep blood agar (Oxoid, Haarlem, The Netherlands) and incubated overnight at 37 °C. Bacteriological examination of the burn wound was performed at least once a week. Burn wounds were sampled using 10 cm^2 contact plates with blood agar. These contact plates were placed on the burn surface on a spot for a few seconds under aseptic conditions, after which they were incubated overnight at 37 °C. Presumptive *S. aureus* colonies were tested for slide coagulase and DNAse activity (Oxoid). Coagulase and DNAse positive strains were identified as *S. aureus* and stored in skim milk (Oxoid, Haarlem, The Netherlands) at −70 °C.

2.5. Pulsed field gel electrophoresis (PFGE)

The protocol for the preparation of chromosomal DNA was modified from that described by Bannerman et al. [2]. *S. aureus* isolates were grown overnight at 37 °C in 9 ml BHI-broth (Oxoid). The culture was brought to a density of 8 McFarland; cells of 0.7 ml of this suspension were harvested by centrifugation, 6500 rpm for 2 min (MSE Microfuge, Beun de Ronde, Abcoude, The Netherlands). After washing with 1 ml sterile TEN buffer (0.1 M Tris–HCl, 0.1 M EDTA, 0.15 M NaCl) cells were re-suspended in 0.3 ml autoclaved EC-buffer (6 mM Tris–HCl, 1 M NaCl, 0.1 M EDTA, 0.5% Brij-58, 0.2% deoxycholate, 0.5%). Three microliter of 1 mg/ml lysostaphin (Sigma, St. Louis, USA) dissolved in 20 mM NaAc and 0.3 ml 2% agarose (Molecular Biological Certified Agarose, Bio-Rad, Veenendaal, The Netherlands) were added to the cell mixture. After brief vortexing, 100 μl of this suspension was pipetted immediately in a plug mould and incubated for 1 h in 3 ml EC-buffer at 37 °C. The EC-buffer was decanted, replaced by 1 ml autoclaved TE-buffer (10 mM Tris–HCl, 5 mM EDTA) and the tube was incubated for 1 h at 55 °C. The plug was washed four times with 3 ml TE-buffer at room temperature with gentle shaking.

Restriction-endonuclease digestion was performed by placing a small slice (3 mm × 5 mm) of the plug in 125 μl restriction buffer A (Roche Diagnostics Corporation, Indianapolis, USA) containing 20 U *Sma*I (Roche Diagnostics). After incubation for 2 h at 25 °C with gentle shaking the slice was brought into a well of a 1.4% agarose gel (Molecular Biology Certified Agarose, Bio-Rad). The gel was prepared in 0.5 × TBE (45 mM Tris–HCl, 45 mM Borate, 1.0 mM EDTA pH 8,0). Bacteriophage lambda DNA concatemers (Bio-Rad, The Netherlands) were used as molecular size standards and placed in each sixth well in the gel. ATCC-strains 25923 and 29213 were used as controls for the total procedure. The running parameters of the CHEF-DR II system (Bio-Rad) were as follows: block 1 switching from 1 to 10 s for 3 h, followed by block 2 switching from 5 to 40 s for 17 h, all at 6 V/cm and 13 °C. Gels were stained with 0.5 μg/ml ethidium bromide (Sigma–Aldrich, Zwijndrecht, The Netherlands) and photographed.

2.6. Interpretation of PFGE banding patterns

The software package Molecular Analyst (Bio-Rad) was used to analyze and group PFGE patterns (0.8% position tolerance, Dice, UPGMA). Interpretation of the grouped PFGE-patterns was performed visually according the guidelines of Tenover et al. [18]. A clonal type consists of a group of identical *S. aureus* strains, including closely related subtypes.

2.7. Statistical analysis

The Chi-square test, Fisher exact test and Survival-analysis (Taron-Ware) were used to compare proportions, a *P*-value of <0.05 indicating statistical significance.

3. Results

3.1. S. aureus carriage among burn-wound patients

From September 1997 through May 1998, 55 patients were admitted to the burn center and all were included in the analysis. The bed occupancy was 20–90% (mean 54%). All the four rooms with two beds each were occupied 29 weeks. Twenty-one out of fifty-five (38%) of the patients had been admitted to another health care center prior to transfer to the burn center. The remaining patients were admitted without prior treatment in another hospital. Cultures taken at the time of admission revealed that 19 (35%) patients carried *S. aureus* in their nose and/or throats (5 nose and throat, 2 throat only and 12 nose only). In 18/19 (95%) of these carriers their burn wounds became colonized with *S. aureus* with an average interval of 5 days after admission [1–19]. Molecular fingerprinting showed that in 14/18 (78%) of these wound colonization events the colonizing strain was identical to the strain carried in nose or throat at the time of admission (Fig. 1).

The majority of patients that did not carry *S. aureus* at the time of admission also developed wound colonization with this bacterial species during their stay in the burn unit. However, their risk of acquiring *S. aureus* burn-wound colonization was less when compared to the rate of colonization observed among the nasal *S. aureus* carriers (23/36 (64%) versus 18/19 (95%), $P = 0.012$) (Fig. 1). When *S. aureus* strains, isolated from wounds of patients that were non-carriers at admission but nonetheless did acquire *S. aureus* wound colonization during their stay at the center, were genotyped, three dominant genotypes (A, B and C) were identified. In 16 out of the entire group of non-carriers ($n = 36$; 44%) burn wounds became colonized with clones A ($n = 4$), B ($n = 7$) or C ($n = 5$).

Five out of 22 patients (23%) who had been hospitalized in another health care center prior to admission to the Groningen' Burn Center, carried genotype B ($n = 2$), C ($n = 2$) or D ($n = 1$) in the nose.

3.2. S. aureus carriage among personnel

During the inclusion period, the carrier rate among burn center personnel varied between 35 and 45%. Genotyping of the strains cultured from personnel regularly showed identity with patients' strains. Thus, the same dominant genotypes A, B and C represented the majority of *S. aureus* strains cultured from health care workers, i.e. 17/22 (77%), 15/23 (65%) and 13/18 (72%) of the strains collected at the three sampling times. When re-screened in January 2000, i.e. some 19 months after the last patient had been discharged from the center, clones A, B and C were found to persist in the noses of many health care workers in the burn center, although one new clonal type (designated Z) of *S. aureus* seemed to have gained a foothold among personnel in the center at that time (Table 1).

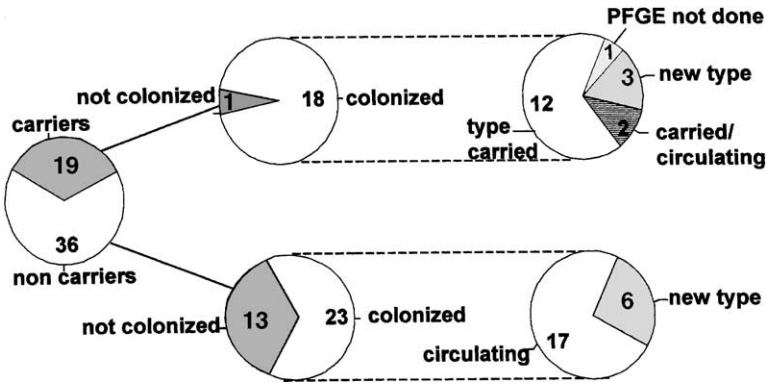

Fig. 1. *S. aureus* burn-wound colonization of carriers and non-carriers of *S. aureus* during their stay at the burn wound center. Represented are the number of patients who colonized the burn wound with the same genotype carried in the nose or throat (type carried), with genotypes isolated from HCW and/or patients at the burn center (circulating) or with clonal types which were not isolated from HCW and patients in the burn center (new type).

Table 1
S. aureus carriage rates among healthcare workers (HCW)

Screening period	HCW[a], *n*	Carriers, *n* (%)	Clonal type carried					
			A, *n* (%)	B, *n* (%)	C, *n* (%)	Z, *n* (%)	AJ, *n* (%)	Other types *n* (%)
October 1997	49	22 (44)	8 (16)	6 (12)	3 (6)			5 (10)
December 1997	66	23 (35)	8 (12)	5 (7)	2 (3)	1 (2)		7 (11)
March 1998	44	18 (41)	7 (16)	3 (7)	3 (7)		1 (2)	4 (9)
January 2000	49	26 (53)	7 (14)	3 (6)	4 (8)	4 (8)	2 (4)	6 (13)

The HCW were repeatedly screened for *S. aureus* carriage.

[a] Besides the dedicated team at the Groningen' Burn Center also another health care workers (therapeutists, psychologists and dieticians), may enter the center to take care of the patients.

3.3. Intensive care versus regular treatment

Nine patients were hospitalized in one of the two single bed IT-rooms. Three of these patients were already carrier at their admission in the IT-room; two of them colonized their burn wounds with the genotype they carried in the nose or throat. One patient did not colonize the burn wound with *S. aureus*. Six other patients entered the IT-room without *S. aureus* as evidenced by negative cultures from nose, throat and burn wound at the time of admission. These six patients remained free of *S. aureus* burn-wound colonization for as long as they remained nursed in the IT-room. However, upon transfer to one of the standard non-IT-rooms in the burn center, the burn wound of five patients colonized with *S. aureus*, usually with one of the prevalent clones also found among personnel (see Fig. 2).

Three of the nine patients received the SDD regimen. Burn wounds of two of these patients were colonized during stay in the IT-room with *S. aureus*. These patients were already carrier at their admission in the IT-room and colonized their burn wounds with the genotype they carried in the nose or throat.

Colonization of the burn wound with *S. aureus* was less for patients treated at IT-rooms when compared to the colonization of the burn wound of patients treated at standard rooms ($P = 0.011$). In IT-rooms 50% of the patients had no burn-wound colonization after 21 days, in standard rooms 50% of the patients had no burn-wound colonization after 8 days ($P = 0.032$). Colonization of the burn wound with *S. aureus* by patients who were no nasal *S. aureus* carriers with treatment at IT-rooms was less frequently seen as compared to standard rooms ($P = 0.009$).

4. Discussion

Burn wounds lack the normal physical barrier provided by intact skin. In burn wounds, molecules such as fibronectin, fibrinogen, collagen and many others are exposed at the wound surface [7]. Many bacterial species harbour specific receptors for such molecules and, hence, burn-wound surfaces are easily colonized by bacteria. *S. aureus* encodes many proteins that specifically interact with human cellular matrix components. These microbial surface compounds recognizing adhesive matrix molecules (MSCRAMMS) enable *S. aureus* to be one of the most common microbes found to be colonizing burn wounds [10]. Prevention of this colonized state is important and adequate identification of the source of the *S. aureus* strains is mandatory in this respect. Colonization of the nose, skin or wound of an individual can give rise to contamination. In addition, the environment (through air, bandages, clothes, bed linen, dust, etc.) may become contaminated as well. In the end this may lead to new cases of colonized wounds. Recent studies have demonstrated, that transmission via the hands of contaminated health care workers is a very important determinant of the spread and persistence of pathogens [4,5,9]. Changing dressings and bed making generates dust and airborne micro-organisms. A recent study showed that 15 min after bed making the number of *S. aureus* containing particles is significantly higher than during the resting period [16]. These airborne *S. aureus* cells can colonize the burn wound and can be inhaled. Inhalation of such particles is likely to play a role in *S. aureus* colonization of the nares.

Admission *S. aureus* carriage state was a predictor of *S. aureus* colonization: 95% of carriers but only 64% of non-carriers later developed *S. aureus* colonization. Strain typing of paired admission and subsequent clinical isolates in 18 patients with acquired burn-wound colonization with *S. aureus* indicated that 14 (78%) became only colonized with a strain identical with their admission isolate. Other studies also show that *S. aureus* carriage state is a predictor of subsequent development of *S. aureus* colonization and infection in burn and non-burn patients [19,23].

Strain typing of the 'burn center acquired' isolates (i.e. patients cultured negative on admission who later developed *S. aureus* colonization) showed different strains with three genotypes predominant. An important finding of our study is the predominance of these same three genotypes among health care workers at our burn center. Taylor et al. [19] showed in their study no predominating strains in the 'burn center acquired' isolates and strains isolated from health care workers.

Nasal carriage of *S. aureus* plays a key role in the development of *S. aureus* wound colonization. Our current data identify two important common sources for *S. aureus*

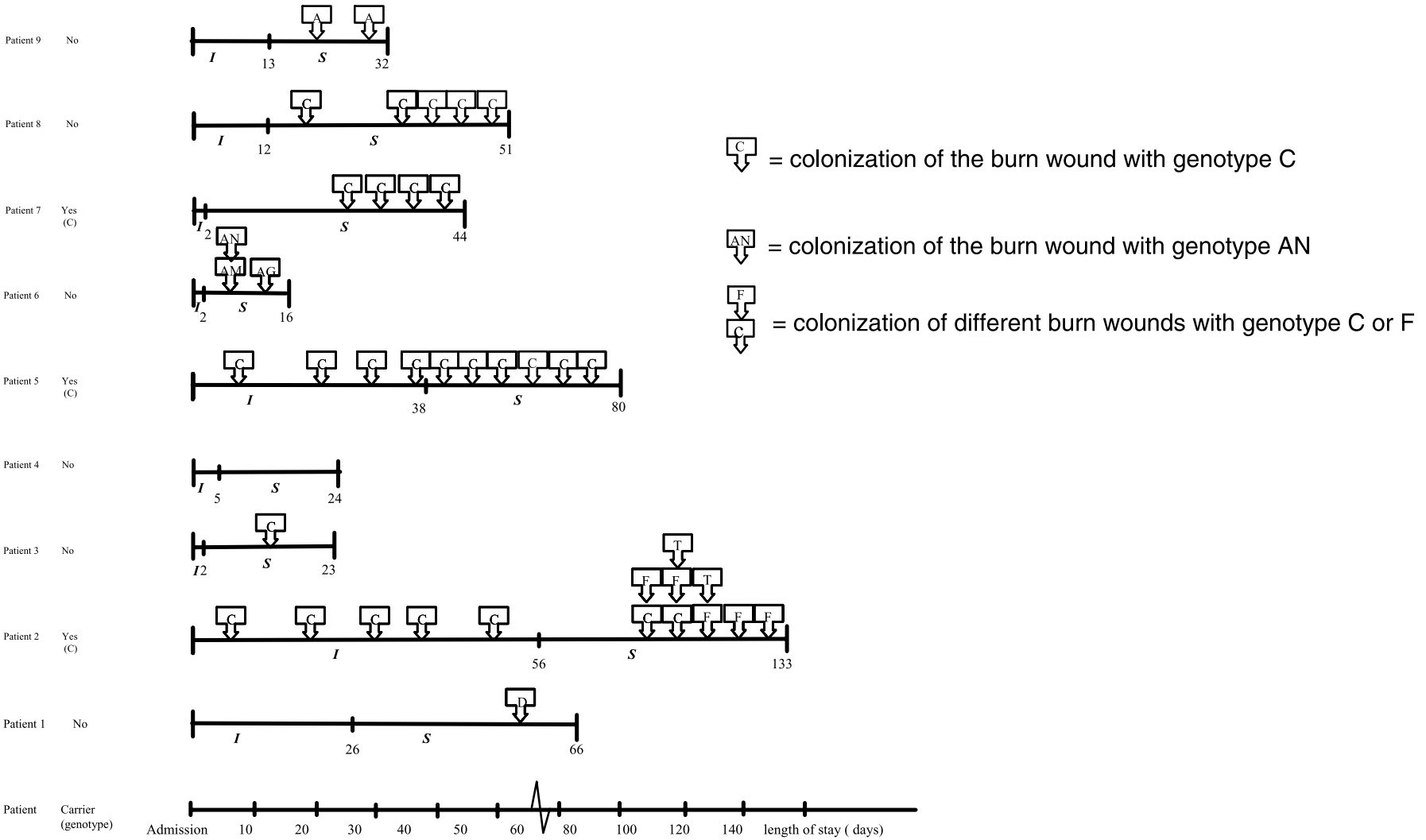

Fig. 2. Time lines of nine patients admitted to the IT-rooms at the burn center. Each line represent a patients from the moment of admission to the time of discharge. Note that all nine patients were admitted to an IT-room (*I*) and, only later, transferred to a standard room (*S*). Each moment of *S. aureus* burn-wound colonization is given as boxes.

burn-wound colonization in the Groningen' Burn Center. One important source is the patient him- or herself in case of *S. aureus* carriage prior to the thermal trauma. In these cases, colonization can be classified as *endogenous*. The other source of colonization, and quantitatively at least as important, are the health care workers of the burn unit. Especially patients that do not carry *S. aureus* at the time of admission, are prone to become 'infected' with staphylococci through contact with the persons that take care of them. In these cases, the colonization can be classified as exogenous or as cross-colonization. Environmental cultures were not taken during this study. Airborne transmission only seems important in the acquisition of nasal carriage [22].

In burn units, patients and personnel may continuously present new clones to the center. Besides the transmission routes also the clonal nature of *S. aureus* populations may play an important role. Apparently, some strains are much more successful colonizers than others and are well-equipped to induce colonization. Persistent carriers often carry a single strain [3], whereas intermittent carriers can be colonized with unrelated strains over time. This suggests that bacterial factors could be involved [11]. In this study, clones A, B, C, and later Z turn out to be most efficient in colonizing patients and healthcare workers. Apparently, these clones have a selective advantage making them colonization prone.

An another important finding of our study is that the Intensive Treatment rooms, as defined in this study, can prevent cross-colonization in a burn center. This is in agreement with van Rijn et al. [24] who showed the effectiveness of bacteria-controlled nursing units in preventing cross-colonization with resistant bacteria in severely burned children. Thompson et al. [25] evaluated the effect of a closed unit on infection rates. They found a significant decrease in the incidence of infection during treatment in these units.

Our study shows that at this dedicated burn center only treatment in the IT-rooms, as defined in this study, can prevent cross-colonization with *S. aureus*. A constant laminar down-flow, a high ventilation rate and other preventive procedures (including sterile coats, gloves, and gowns), during all contacts with HCW prevent burn wounds from cross-colonization. The SDD-regimen did not prevent the colonization of burn wounds with *S. aureus*. At standard rooms, the same preventive procedures as used at IT-rooms, are carried out only during changing of dressings of burn wounds of patients with more than 5% total body surface area burned. After all HCW–patient contacts, hand cleansing is carried out using an alcohol-based hand-rub solution. Strict hand hygiene policies may already achieve some success in the battle against the transmission of *S. aureus* [12].

Due to physical and financial constraints, it is not possible to hospitalize all patients at IT-rooms. Until new strategies have been developed to minimize transmission of *S. aureus*, we propose a few useful clinical actions that can be taken at burn centers in order to lower the number of burn-wounds colonized with *S. aureus*. The endogenous transmission route could be blocked by nasal mupirocin treatment of all patients at admission. Nasal mupirocin has an important role to play in the prevention of *S. aureus* infection by eliminating nasal carriage of this organism. Topical mupirocin has been used widely for the clearance of nasal *S. aureus* carriage particularly during outbreaks [26,27]. It has been shown to reduce the rate of nasal carriage and clinical infection in surgical and dialysis patients and in human immunodeficiency virus (HIV) disease [28–31]. Mackie et al. [32] found a reduction in *S. aureus* wound colonization using nasal mupirocin and selective decontamination of the digestive tract in extensive burns.

Doebelling et al. [33] described the long-term efficacy of intranasal mupirocin ointment. They found that a single brief treatment course was effective in reducing nasal *S. aureus* carriage for up to 1 year. Several studies reported the short-term efficacy of 91–100% [34–36]. Dupeyron et al. [34] found a re-acquisition rate of 18%. Martin et al. [30] noted the re-colonization rate in a population of HIV-patients increased over time (27, 45 and 71% at 2, 6, and 10 weeks, respectively). Re-colonization is dependent upon epidemiological pressure and mupirocin should not be used as the sole method for infection control [37]. Mupirocin resistance has been reported in the literature following lengthy courses or when applied to large wounds of areas [27,38]. To avoid resistance one could decide to avoid repeated applications and to treat patients once. Cross-colonization events can be reduced by strict hand hygiene, by changing of dressings of burn wounds under a laminar down-flow, and finally by disinfection of the inanimate environments after changing dressings and bed linen.

On the basis of our results, we believe the routine practice of taking only one nasal swab at burn center admission could identify those patients who are at high risk for subsequent development of staphylococcal colonization. We also saw that strains cultured from health care workers regularly showed identity with patients' strains. Finally, we can say that Intensive Treatment rooms, as defined in this study, can prevent burn wounds from *S. aureus* cross-colonization. Further studies, including quantification of transmission routes, incidence, risk factors and interventions, are required to fully elucidate the transmission dynamics of *S. aureus* at burn centers.

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