MINIREVIEW

The role of nasal carriage in *Staphylococcus aureus* burn wound colonization

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Abstract

Thermal injury destroys the physical skin barrier that normally prevents invasion of microorganisms. This and concomitant depression of local and systemic host cellular and humoral immune responses are important factors that contribute to colonization and infection of the burn wound. One of the most common burn wound pathogens is *Staphylococcus aureus*. *Staphylococcus aureus* is both a human commensal and a frequent cause of infections ranging from mild to life-threatening diseases. Colonization with *S. aureus* has been associated with delayed wound healing, increased need for surgical interventions, and prolonged length of stay at burn centres. In this minireview, we focus on *S. aureus* nasal carriage in relation to *S. aureus* burn wound colonization and subsequent infection, and its impact on strategies for infection control.

Introduction

The skin or integument covers the entire external surface of the human body and is our principal site of interaction with the surrounding world. Important functions include sensory perception, immunologic surveillance, thermoregulation, and control of insensible fluid loss. It also serves as a protective barrier, preventing internal tissues from exposure to trauma, UV radiation, temperature extremes, hazardous chemicals, toxins, and, not in the least, microorganisms. Thermal injuries of the skin and concomitant depression of local and systemic host cellular and humoral immune responses are important factors that contribute to colonization and infection of the burn wound (Alexander, 1990; Griswold, 1993). Microorganisms colonizing the burn wounds may originate from the patient’s endogenous respiratory and gastrointestinal flora, but may also be transferred to a patient’s skin surface via contact with contaminated environmental surfaces, the hands of health care workers (HCWs) and the air (Wysocki, 2002; Erol et al., 2004; Weber & McManus, 2004). One of the most common burn wound pathogens is *Staphylococcus aureus*. *Staphylococcus aureus* is both a human commensal and a frequent cause of infections ranging from mild to life-threatening diseases. Colonization with *S. aureus* has been associated with delayed wound healing, increased need for surgical interventions, and prolonged length of stay at burn centres (Manson et al., 1992c; Reardon et al., 1998).

Nasal carriage of *S. aureus* plays a key role in the development of *S. aureus* infection. In several recent reviews, the mechanisms, risks, and treatment of *S. aureus* nasal carriage and infection have been described (Kluymans et al., 1997; Nouwen et al., 2001; Peacock et al., 2001; Wertheim et al., 2005a). In this review, we focus on *S. aureus* nasal carriage in relation to *S. aureus* burn wound colonization and subsequent infection, and its impact on strategies for infection control.

General

The skin

The human skin is colonized by a broad variety of microorganisms. Many of these organisms actually provide resistance to pathogenic microorganisms through bacterial interference (Swartz & Weinberg, 1999).
The normal flora of the skin can be thought of as either resident or transient. Resident bacteria are those that normally persistently inhabit an individual’s skin. Grice et al. (2008) recently reported a 16S rRNA gene survey of the resident skin microbiota of the inner elbow regions of healthy humans. They used three sampling methods (swab, scrape, and punch biopsy) to survey the microbiota at different penetration levels of the skin. They reported the same dominant phylotypes of macrobiota at all depths of sampling. Proteobacteria dominated all skin microbiota, followed by Actinobacteria and Firmicutes. Apparently, from the division Proteobacteria the genera Pseudomonas and Janthinobacterium were predominant.

Moist areas and covered skin surfaces such as the axilla, perineum, and toe webs are especially attractive to bacteria. The hair follicles, nail beds, and sweat glands are other areas where bacteria like to reside. Microcolonies of bacteria can also be found at the edges of the squames as halos in the upper loose epidermal surface layers of the skin or the stratum corneum. Several species of bacteria are normally found by culture in human skin including Staphylococcus spp., Micrococcus spp., Peptococcus spp., Corynebacterium spp., Brevibacterium spp., Propionibacterium spp., Streptococcus spp., Neisseria spp., and Acinetobacter spp. (Wysocki, 2002). Not all of these are found on any one individual, but most humans carry strains from at least five of these genera.

Transient bacteria are those species not normally found on a particular person’s skin, but that are lost through daily hygienic measures such as hand washing and bathing. Transient bacteria are acquired through contact with other individuals or exposure to bacteria-laden surfaces.

Data on normal viral flora are scarce, although viruses have been detected in damaged skin or in immunocompromised individuals (Noble, 1983, 1999).

**Thermal injury of the skin, pathogenesis, and aetiology of burns’ infection**

Several important physiological functions of the skin are severely compromised by thermal injury. Disruption of the skin can result in infection, fluid loss, hypothermia, scarring, and compromised immunity (Wysocki, 2002). Breaches in the skin barrier are the main hallmark of thermal injury. The body attempts to maintain homeostasis by initiating a process of contraction, retraction, and coagulation of blood vessels immediately after a burn injury. Three distinct zones of a burn wound have been described by Jackson (1953). The zone of coagulation comprises the dead tissue that forms the burn eschar that is located at the centre of the wound nearest to the heat source. The zone of stasis comprises tissues adjacent to the area of burn necrosis that is still viable, but remains at risk for ongoing ischaemic damage due to decreased perfusion. Finally, the zone of hyperaemia comprises normal skin with minimal cellular injury showing vasodilatation and increased blood flow as a response to injury (Gibran & Heimbach, 2000; Roth & Hughes, 2004) (Fig. 1).

A superficial (first degree) burn, the least serious type, is one in which the epidermis of the skin has been burned slightly. These burns produce pain, redness, and swelling of the skin. In partial-thickness (second degree) burns, the dermis is partially destroyed, causing pain, redness, swelling, and blistering. These wounds can become infected more easily than superficial burn wounds. Damage from full-thickness (third degree) burns extends into the hypodermis, causing destruction of the full thickness of the skin, including its nerve supply; the skin becomes whitened, blackened, or even charred. Full-thickness burns leave scars and may cause persisting loss of function and/or sensation. For both partial- and full-thickness burns, if the percentage of the total body surface area (TBSA) exceeds 15%, resuscitation fluids are required; at TBSA > 25%, the patient is at risk of frank shock.

Because of the importance of the skin as a barrier to the host’s microbial invasion, it is not surprising that the risk of subsequent burn wound colonization and infection, and subsequent systemic infection correlates with the size of burn injury (Sheridan, 2000; Santaniello et al., 2004).

The extent of a burn wound, expressed as the percentage of the TBSA that is burned, and the depth of the burn wound are the most important predictors of clinical outcome. The percentage of TBSA affected is used to calculate the patient’s fluid and nutritional needs, which can be enormous for those with severe burns. Burn depth, on the other hand, dictates subsequent local and surgical treatment of burn wounds. An estimate of the percentage TBSA can be made by a method in which the patient’s own hand is used as a complementary, readily available template (Miller et al., 1991). The entire palmar surface area of the hand (including the fingers) is c. 1% of the TBSA. Another method to estimate the percentage of TBSA is using, for example, a Lund–Browder chart (Lund & Browder, 1944). The Lund–Browder system uses fixed percentages for the feet, arms, torso, neck, and
contaminated external environmental surfaces, the hands of gastrointestinal flora, but the bacteria may also be colonized with a variety of microorganisms (Wysocki, 2002; Erol et al., 2004). Microorganisms colonizing the burn wounds originate from the patient’s endogenous skin, respiratory, and gastrointestinal flora, but the bacteria may also be transferred to a patient’s skin surface via contact with contaminated external environmental surfaces, the hands of HCWs, and even air (Wysocki, 2002; Erol et al., 2004; Weber & McManus, 2004).

Immediately following injury, predominantly Gram-positive bacteria (e.g. *S. aureus*, coagulase-negative staphylococci, *Enterococcus* spp.) from the patient’s endogenous flora or the external environment start to colonize the burn wound (Gibson & Thompson, 1955; Wysocki, 2002; Barret & Herndon, 2003). Endogenous Gram-negative bacteria from the gastrointestinal flora (e.g. *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Enterobacter* spp.) also rapidly colonize the burn wound surface in the first few days after injury (Manson et al., 1987, 1992a, b; Ramzy et al., 2000). Wound colonization by yeasts and fungi usually occurs later due to the clinically imposed selective powers of broad-spectrum antibiotic therapy (e.g. *Candida* spp. and *Aspergillus* spp.) (Burdge et al., 1988; Desai & Herndon, 1988; Ekenna et al., 1993). The most common burn wound pathogens are *S. aureus* and *P. aeruginosa*. This review focuses on *S. aureus*.

### Patient’s demographics

Very young children and the elderly have an increased risk of being burned and they have worse clinical outcomes compared with patients in other age groups (Hunt & Purdue, 1992; Burn Foundation, 1999; McGill et al., 2000; Pruitt et al., 2002). In the United States, approximately two-thirds of children who required emergency care for burn-related injuries sustained thermal injuries, while children < 4 years are particularly prone to scald injury (National Safe Kids Campaign, 2002). Obese adults, AIDS patients, and those who have an underlying medical condition such as diabetes have also been shown to suffer higher morbidity and mortality (Dyer, 1988; Gottschlich et al., 1993; Mele et al., 1998; McCampbell et al., 2002; Mzezewa et al., 2003; Memmel et al., 2004; Sjöberg et al., 2004).

Individuals with deliberate self-inflicted burn injuries and the disabled have been shown to have more severe injuries and, on average, longer hospital stays than those with accidental injuries (Baker et al., 1992; Backstein et al., 1993; Pham et al., 2003).

### Microbial colonization of the burn wound

The burn wound surface is a protein-rich environment consisting of avascular necrotic tissue that provides a favourable niche for microbial colonization and proliferation (Manson et al., 1992b; Barret & Herndon, 2003; Nasser et al., 2003; Erol et al., 2004). The avascularity of the eschar results in impaired migration of host immune cells and restricts delivery of systemically administered antimicrobial agents to the area. Therefore, topical burn treatment is essential; the gold standard in topical burn treatment is silver-sulphadiazine (Ag-SD), a useful broad-spectrum antibacterial agent.

Although burn wound surfaces are sterile immediately following thermal injury, these wounds will soon be colonized with a variety of microorganisms (Wysocki, 2002; Erol et al., 2004). Microorganisms colonizing the burn wounds originate from the patient’s endogenous skin, respiratory, and gastrointestinal flora, but the bacteria may also be transferred to a patient’s skin surface via contact with contaminated external environmental surfaces, the hands of HCWs, and even air (Wysocki, 2002; Erol et al., 2004; Weber & McManus, 2004).

Several longitudinal studies reported that *S. aureus* nasal carriage patterns differ between individuals; 10–35% of individuals carry *S. aureus* persistently, 20–75% carry intermittently, and 5–50% never carry *S. aureus* in the nose (Gould & Mckillip, 1954; Goslings & Buchli, 1958; Maxwell et al., 1969; Armstrong-Esther, 1976; Höfler et al., 1978; Hu et al., 1995; Riewerts Eriksen et al., 1995). Furthermore, the number of *S. aureus* cells in the nose is significantly higher in persistent carriers than in intermittent carriers (White, 1961; Nouwen et al., 2004b), resulting in an increased risk of *S. aureus* infections in the first category of individuals (White, 1963; Calia et al., 1969; Bruun, 1970). Persistent carriers are often colonized by only one single strain over extended periods, up to 10 years, while intermittent carriers carry many different strains over time (Gould & Mckillip, 1954; Hu et al., 1995; Riewerts Eriksen et al., 1995; VandenBergh et al., 1999).

### Staphylococcus aureus

*Staphylococcus aureus* is a common bacterium that often resides quite harmlessly on the skin or in the nose of a healthy person. However, a breach in the skin or a weakened immune system can trigger *S. aureus* to cause minor skin infections or sometimes even life-threatening diseases. *Staphylococcus aureus* cells also contaminate the inanimate environment when excreted from the body of (persistent) carriers. Staphylococci are known to survive on inanimate surfaces (e.g. surfaces and medical equipment) for weeks or even months (Scott & Bloomfield, 1990; Neely & Maley, 2000; Wagenvoort et al., 2000).

### Staphylococcus aureus carriage

*Staphylococcus aureus* colonizes the skin and mucosal surfaces of humans and also of several animal species. The anterior nares of the nose are the most frequent carriage site for *S. aureus* (Williams, 1963; Kluytmans et al., 1997). Other sites that can harbour this organism are the skin in general, the perineum, the gastrointestinal tract, and the pharynx (Williams, 1963; Armstrong-Esther, 1976; Rimland & Roberson, 1986; Wertheim et al., 2005b). Less frequently, *S. aureus* can be cultured from the vagina (Guinan et al., 1982) and axilla (Williams, 1963; Dancer & Noble, 1991).

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Determinants of S. aureus nasal carriage

Regarding the occurrence of S. aureus nasal carriage, both bacterial and host factors play a role. Hydrophobic interactions and surface charge are forces probably involved in mediating staphylococcal binding to epithelial cells (Car ruthers & Kabat, 1983; Schwab et al., 1993; Shuter et al., 1996). Specific nonproteinaceous staphylococcal cell wall components (Aly et al., 1980; Carruthers & Kabat, 1983), surface proteins (van Belkum et al., 1997), microbial surface components recognizing adhesive matrix molecules (Epsersen & Clemmensen, 1982; Foster & Mcdevitt, 1994; Patti et al., 1994), and staphylococcal factors facilitating interactions with mucus components (Sanford & Ramsay, 1989; Sanford et al., 1989) are important in colonization efficacy. Hundreds of S. aureus virulence factors and putative virulence genes have been described, including those involved in adherence to human tissue, evasion of the immune response, and regulation of virulence gene expression (Projan & Novick, 1997).

The fact that different nasal S. aureus colonization patterns can be discerned suggests a clear host influence. A study in which volunteers (noncarriers and persistent carriers) were artificially inoculated with a mixture of S. aureus strains showed that noncarriers quickly eliminated the inoculated S. aureus strains, whereas persistent carriers primarily reselected their original resident strain from the inoculation mixture (Nouwen et al., 2004a). The authors concluded that host factors substantially codetermine the S. aureus carriage state in an individual. This conclusion is supported by other studies that showed that S. aureus carriage rates vary between different ethnic groups, with higher rates in white individuals, in men, and lower rates in elderly individuals (Williams, 1963; Armstrong-Esther, 1976; Riewerts Eriksen et al., 1995; Parnaby et al., 1996; Cole et al., 2001; Peacock et al., 2003; Herwaldt et al., 2004). Increased carriage rates are found in hospitalized patients (Goslings & Buchli, 1958; Shooter et al., 1958; Williams et al., 1959; Noble et al., 1974; Paul et al., 1982; Kluytmans et al., 1997; Nouwen et al., 2001). Another recently discovered nasal determinant is smoking status: current smoking was negatively associated with nasal S. aureus carriage (van Belkum et al., 2009). Emonts et al. (2008) showed that persistent carriage of S. aureus is influenced by genetic variation in host inflammatory response genes; the interleukin-4 – 524 C/C host genotype was associated with an increased risk of persistent S. aureus carriage, whereas C-reactive protein haplotype 1184C, 2042C, 2911C was overrepresented in individuals who were not colonized. van den Akker et al. (2006) reported that the genotype-dependent variation in the sensitivity to glucocorticoids is associated with tolerance toward staphylococcal nasal colonization.

The noncarrier state may, in part, be explained by the phenomenon of bacterial interference; when an ecological niche is already occupied by other bacteria, such as coagulase-negative staphylococci, newly arriving wild-type S. aureus cannot replace the resident bacterial population (Shinefield et al., 1966, 1971, 1974; Hu et al., 1995). Bacterial interference between S. aureus and Streptococcus pneumoniae in the nasopharynx of children was documented recently (Bogaert et al., 2004). Uehara and colleagues artificially implanted a strain of Corynebacterium spp. into the nares of 17 S. aureus carriers. After 15 inoculations, S. aureus was completely eradicated in 71% of the carriers. Thus, Corynebacterium spp. interfered with S. aureus (Uehara et al., 2000).

Finally, underlying diseases have been associated with a higher S. aureus nasal carriage rate and infection rate as reviewed by Kluytmans et al. (1997) and Nouwen et al. (2001).

What are the risks of S. aureus nasal carriage for patients with burn wounds?

The nose is regarded as the ecological niche from where S. aureus can spread to other parts of the body. In 1959, the first reports were published that investigated the relation between nasal carriage and the development of surgical wound infection. Furthermore, phage typing determined that a clonal relation was often found between nasal strains and infectious strains (Luzar et al., 1990; Zimakoff et al., 1996). Further studies showed a significant risk for development of autologous wound infections by nasal carriers (White, 1963; Kluytmans et al., 1997). Hence, S. aureus carriage has been identified as a risk factor for the development of infections in various settings.

The burn wound itself and the accompanying immunosuppression are two major factors that predispose burn patients to colonization and infection (Bhat & Milner, 2007; Calum et al., 2009). Several studies have shown that the rate of burn wound colonization with S. aureus varies considerably. The risk of colonization seems to be determined, at least in part, by the TBSA, the age of the patient, and nasal and pharyngeal S. aureus carriage of patients as well as of their HCWs (Taylor et al., 1992; Adeniran et al., 1995; Vindenes & Bjerknes, 1995; Reardon et al., 1998). Colonization of burn wounds with S. aureus has been associated with delayed wound healing and prolonged length of stay at the burn centre (Manson et al., 1992c; Reardon et al., 1998).

Clinical effect of burn wound colonization

Burn wound colonization describes the presence of microorganisms in a wound that appears to be clinically uninfected. Following colonization, the organisms on the surface start to penetrate the burn eschar to a variable extent, depending on their invasive capacity, local wound factors, and the degree of patient’s immunodepression (Hansbrough, 1987). Noninvasive burn wound infection involves microbial growth in the wound or eschar with purulent...
drainage and diffusion of microbial products into the surrounding viable tissue. This can cause a systemic response in the patient. Invasive burn infection describes microbial growth in the wound or eschar with invasion into and necrosis of the surrounding and potentially viable tissue (Weber et al., 1997).

Infection of burn wounds with *S. aureus* increases the risk of sepsis and multiorgan failure. Furthermore, infection of burn wounds can lead to hypertrophic scarring. A hypertrophic scar is ‘a widespread red, raised, sometimes itchy scar that remains within the borders of the injury’ (Bláha & Pondilícek, 1997). These scars can be disfiguring and even painful. If such scars are situated across joints, the almost inevitable contractures can impair function and result in painful fissures. Burn scars may have a dramatic influence on a patient’s quality of life. They have been associated with anxiety, social avoidance, depression, a disruption in normal daily activities, the onset of sleep disturbances, and all of the consequent difficulties in returning to normal life after physical rehabilitation. The factors involved in pathological scar formation are still under debate, and their complexity, especially with burn scars, is well known. Some studies suggest that genetics plays an important role in the pathogenesis of scarring (Deitch et al., 1983; Castagnoli et al., 1990a, b; Lewis & Sun, 1990; Stella et al., 1998; Santucci et al., 2001; Desmoulière et al., 2005). It seems that local factors such as burn depth, the presence of infection in the wound bed, and healing delay are also relevant (Deitch et al., 1983). Concerning the causes of postburn pathologic scarring, it has been hypothesized that hypertrophy is a systemic inflammatory disease of central origin, regulated by local influence factors (Stella et al., 1998). Some studies have pointed out the key role played by lymphocytes and the skin’s immune system in general in the maintenance of a continuous activated inflammatory state of hypertrophic tissue (Castagnoli et al., 1990a, b; 1997; Cracco et al., 1992). A delay in re-epithelialization increases the risk of wound infection and prolongs the inflammatory phase, consequently leading to eschar abnormalities (Singer & McClain, 2002).

Hypertrophic scars are particularly common following burns; however, the prevalence of hypertrophic scars is unknown. A limited number of groups studied the prevalence of hypertrophic scars and found prevalences ranging from 32% to 67% (Table 1). Infection increases the likelihood of hypertrophic scarring. Baker et al. (2007) showed that there is a significant association between bacterial colonization of burn wounds and hypertrophic scarring. The association between colonization and hypertrophic scars was significant for several genera, namely *Staphylococcus* spp., faecal *Streptococcus* spp., *Pseudomonas* spp., *Proteus* spp., *Enterococcus* spp., and *E. coli*. Colonization may elicit a subclinical inflammatory response, which may increase the stimulus to the formation of hypertrophic scar tissue (Baker et al., 2007).

### Table 1. Overview of studies that illustrate the prevalence of hypertrophic scars in patients with burns

<table>
<thead>
<tr>
<th>Reference</th>
<th>Publication date</th>
<th>Patients (n)</th>
<th>Scars (n)</th>
<th>Patients with hypertrophic scars, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2008</td>
<td>705</td>
<td>–</td>
<td>340 (44)</td>
</tr>
<tr>
<td>B</td>
<td>2003</td>
<td>110</td>
<td>–</td>
<td>74 (67)</td>
</tr>
<tr>
<td>C</td>
<td>2007</td>
<td>–</td>
<td>127</td>
<td>51 (40)</td>
</tr>
<tr>
<td>D</td>
<td>1999</td>
<td>779</td>
<td>–</td>
<td>249 (32)</td>
</tr>
<tr>
<td>E</td>
<td>1990</td>
<td>–</td>
<td>–</td>
<td>(50)</td>
</tr>
</tbody>
</table>

A, Gangemi et al. (2008); B, Bombaro et al. (2003); C, Baker et al. (2007); D, Dedovic et al. (1999); E, Spurr & Shakespeare (1990). –, no data given.

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**Fig. 2. Schematic representation of different routes to acquire *Staphylococcus aureus* colonization.**

**Staphylococcus aureus reservoirs and transmission routes**

Important sources of *S. aureus* in burn centres are colonized burn wounds and carriage sites of patients and personnel. These are the places where the microorganisms multiply, and from these they are transmitted to other patients, HCWs, and the air and surfaces in the inanimate environment. The principal *S. aureus* transmission route is most likely from patient to patient via transiently contaminated hands of the HCWs who have acquired the microorganism by direct patient contact or by handling contaminated materials (Mortimer et al., 1966; Mulligan et al., 1993). Compliance rates of HCWs in hand hygiene are known to be around 50%, which essentially is too low to effectively block transmission (Kampf & Kramer, 2004).

In Fig. 2, a number of possible transmission routes are schematized. Colonization of the nose, skin, or wound in a given individual can give rise to additional contamination of individuals and the environment. In the end, this may lead to newly colonized noses and wounds. The risk of acquisition is influenced by the colonization status of other patients (Bonten et al., 1998). This has been demonstrated...
for methicillin-resistant *S. aureus* (MRSA) (Merrer et al., 2000), vancomycin-resistant enterococci (Puzniak et al., 2002), and *Enterobacteriaceae* (de Man et al., 2001).

**Prevention of colonization and infection**

Measures to prevent and treat infections are essential for the survival of patients with extensive burns. In patients with less extensive burns, infections may increase morbidity, length of hospital stay, and the risk of hypertrophic scarring.

**Hygienic measures**

Preventing the spread of *S. aureus* at a burn centre can be partly achieved by (1) the layout of the burn centre and the use of a dedicated operating theatre, (2) the implementation of contact precautions (HCWs wear masks, gowns, and gloves while in contact with the patients; these covers are removed and the hands are washed after finishing contact with the patient), (3) cohort nursing (i.e. grouping patients of a given colonization status, with designated HCWs, which is targeted at a minimum ratio of 1:1 of nursing staff to patients), (4) strict aseptic techniques for changing dressings, (5) hand disinfection and location of hand disinfectant (alcohol 70% isopropanol/ethanol) dispensers near all beds, and (6) timely closure of the burn wound.

Laminar airflow techniques have been shown to decrease the infection rate in a number of infection-prone patient populations (Levine et al., 1973; Demling et al., 1978).

**Decolonization strategies**

**Topical antibacterial treatment: silver and cerium**

The gold standard in topical burn treatment is Ag-SD, a useful broad-spectrum antibacterial agent for treatment of burn wounds. Silver has been used to treat wounds for a very long time (Klasen, 2000a, b) and has proven to be very effective in controlling infections. The silver ion is a highly reactive ion, readily binding to negatively charged proteins, RNA, DNA, chloride ions, and other moieties. This explains its broad spectrum of antibacterial activity. Ag-SD was introduced in 1968 (Klasen, 2000b). Ag-SD acts on the bacterial wall and binds relatively strongly to DNA (Klasen, 2000b). It was shown to significantly lower mortality in severely injured patients (Fox, 1968, 1975). Later in 1976, cerium (belonging to the lanthanides or rare earth elements) was added to the ointment as various studies had shown that cerium, in combination with Ag-SD, enhanced the antibacterial effect (Hermans, 1984; Boecxkx et al., 1985; Ross et al., 1993). Cerium forms a yellow-green, leathery eschar over the wound site, providing a barrier against bacterial colonization and infection (Boecxkx et al., 1985, 1992; Lorenz et al., 1988; Cameron, 1997). Some studies suggest a major effect of cerium in binding and denaturing the immunosuppressive lipid protein complex generated by burned skin (Peterson et al., 1985; Sparkes, 1997; Deveci et al., 2000; Allgöwer et al., 2008). Thus, cerium-based burn wound topical therapies appear to limit local inflammation and systemic immunosuppression. However, topical agents reduce the microbial overgrowth, but they seldom prevent further colonization with other potentially invasive bacteria and fungi.

Although it was originally thought that treatment with silver did not lead to the development of resistance, recently, resistance to silver compounds has been described (Silver, 2003). In addition, silver has been shown to display cytotoxic effects on cultured keratinocytes, which might hamper the use of this compound in combination with tissue-engineered skin substitutes (Duc et al., 2008).

**Selective decontamination of the digestive tract (SDD)**

SDD is a prophylactic strategy to reduce infectious morbidity and mortality in granulocytopenic patients and in immunocompromised patients (Guiot & Furth, 1977; Sleijfer et al., 1980; de Vries-Hospers et al., 1981). The efficacy of SDD in burned patients is defined in a number of studies (Jarrett et al., 1978; Mackie et al., 1992; Manson et al., 1992b; Barret et al., 2001; de la Cal et al., 2005). Manson et al. (1992b) showed that SDD limits the colonization of burn wounds with microorganisms originating from the gastrointestinal tract. The efficacy of SDD has been evaluated in patients with severe burns in one prospective and in one historically controlled trial (Jarrett et al., 1978; Mackie et al., 1992). Jarrett et al. (1978) studied the efficacy of SDD prospectively and found that infections were reduced by 50% in the SDD group as compared with the control group. Mackie et al. (1992) found that the incidences of respiratory tract infections (27.3% vs. 6.5%) and mortality (21.2% vs. 3.2%) were reduced in the SDD group. de la Cal et al. (2005) performed a double-blind, placebo-controlled study at a single centre; patients with burns ≥20% of TBSA and/or suspected inhalation injury were enrolled and assigned to receive SDD or placebo for the total duration of treatment in the burn intensive care unit (ICU) (N = 117 enrolled, 107 analysed). Treatment with SDD was associated with a significant reduction in mortality in the burn ICU. The incidence of pneumonia was significantly higher in the placebo group: 30.8 and 17.0 pneumonias per 1000 ventilation days (P = 0.03) in the placebo and the SDD group, respectively.

Barret et al. (2001) studied the efficacy of SDD in decreasing the bacterial colonization of the aerodigestive tract and burn wounds, and the incidence of septic complications in severely burned children in a prospectively randomized double-blind study (N = 23). Colonization rates of the wound, sputum, nasogastric aspirates, and faeces...
were similar. Pneumonia, sepsis, and other complications had similar incidences in both groups. They concluded that SDD is not effective in decreasing bacterial colonization and infectious episodes in severely burned paediatric patients. The efficacy of SDD in severely burned patients in decreasing bacterial wound colonization requires further study.

Elimination of nasal S. aureus carriage

Mupirocin (pseudomonic acid) is a topical antibiotic agent produced by Pseudomonas fluorescens. It displays a strong activity against most Gram-positive bacteria, including MRSA, although it is also active against some Gram-negative bacteria, including Neisseria spp., Haemophilus spp., and Mycoplasma spp. (Sutherland et al., 1985). Mupirocin inhibits bacterial protein synthesis by reversible binding to bacterial isoleucyl-tRNA synthetase (IleS) (Ward & Campoli-Richards, 1986; Cookson, 1990). Mupirocin has been used primarily for skin infections and for the prevention and the topical treatment of infections by MRSA (Ward & Campoli-Richards, 1986; Cookson, 1990). During the last decades, mupirocin has been the agent of choice for the eradication of nasal and percutaneous colonization by S. aureus in patients undergoing peritoneal dialysis (Pérez-Fontán et al., 1993; Bernardini et al., 1996; Thodis et al., 1998; Casey et al., 2000), haemodialysis (Boelaert, 1994), cardiothoracic surgery (Kluytmans, 1998), and HIV infection (Martin et al., 1999).

Clinical trials with mupirocin have consistently shown that this agent temporarily eliminates nasal carriage of S. aureus in surgical patients and patients undergoing haemodialysis (Kluytmans et al., 1996a,b). Moreover, nasal mupirocin was proven to be effective in eliminating nasal carriage of MRSA during outbreaks in a variety of clinical settings, including nursing homes (Cederna et al., 1990) and neonatal units (Davies et al., 1987). However, some clinical studies found little or no efficacy of mupirocin in preventing nosocomial infections (Kalmjejer et al., 2002; Perl et al., 2002; Wertheim et al., 2004). Wertheim et al. (2005b) showed that mupirocin is effective in overall decolonization of nasal carriers, but less effective in decolonizing extranasal sites.

Decolonization therapy includes a 5-day course of mupirocin nasal ointment applied twice daily. It has been reported to result in elimination rates of 91% directly after therapy, 87% after 4 weeks, and 48% after 6 months (Doebbeling et al., 1993).

Mackie et al. (1994) showed that supplementing the SDD regimen with intranasal mupirocin for patients with TBSA > 30% was effective in eliminating the endogenous bacterial reservoirs. This study showed an overall decline in the incidence of bacterial wound colonization in patients treated with SDD and nasal mupirocin. In this group, the incidence in S. aureus wound colonization was significantly decreased when compared with the historic control group with patients who were treated with SDD only (24% and 65%, respectively).

A few studies have been published in which the effect of prophylactic antibiotic use in burn centres was described. Ergün et al. (2004) observed no reduction in the rate of wound infection in a group of patients who were treated with antibiotic prophylaxis, when compared with the control group. Ugburo et al. (2004) concluded that systemic antibiotic prophylaxis is of no value in controlling burn wound-associated sepsis, and might even favour the growth of P. aeruginosa in the burn wounds. Durtschi et al. (1982) showed that routine administration of prophylactic penicillin does not protect against cellulites or burn wound sepsis.

In a very recent review (Lee et al., 2009), it was concluded that the available evidence does not support the role of systemic antibiotic prophylaxis in the management of paediatric burns. However, they also commented on the fact that there is a lack of comprehensive evidence to address this pressing issue.

Novel therapies for staphylococcal infections

Until recently, severe staphylococcal infections were primarily treated with antibiotics. This treatment became progressively more difficult because some strains developed or acquired resistance to multiple antibiotics, including vancomycin (Tenover et al., 2004). Staphylococcal infections with multi-drug-resistant S. aureus may lead to serious clinical problems. These problems require new therapies and prevention strategies. Over the past decade, several therapies have been suggested in the literature. First of all, experimental bacteriophage-mediated prophylaxis in mice and rabbits demonstrated a preventive effect of phages against local and systemic staphylococcal infections (Wills et al., 2005; Capparelli et al., 2007). Ahmad (2002) proposed a treatment of infections of the burn wound with a cocktail of phages specific for opportunistic pathogens that is sprayed on the burn wound. However, before applying phage therapy in humans, its possible adverse side effects on the physiology, biochemistry, and immune system must be studied. Also, at present, rapid clearance in the spleen, the inability to kill intracellular bacteria, and stimulation of neutralizing antibodies still represent objections to the use of bacteriophage therapy (Lederberg, 1996; Sulakvelidze et al., 2001; Westwater et al., 2003). Recently, however, Capparelli et al. (2007) showed that S. aureus A170 phage M3a lacks these shortcomings and is capable of lysing MRSA cells in mice.

Secondly, nasal carriage of S. aureus is a risk factor for subsequent colonization and infection (White, 1963; Kluytmans et al., 1997). Nasal S. aureus eradication, therefore, is urgently recommended when the colonizing strain is MRSA or a multi-drug-resistant S. aureus strain. Nowadays, MRSA...
carriers are treated with mupirocin to eliminate carriage. However, this can lead to the development of resistance. The nasal cavity can be colonized with various other microorganisms such as *Staphylococcus epidermidis* or species of corynebacteria (Uehara et al., 2000). Two other recent studies showed that carriage of *S. pneumoniae* suppressed the *S. aureus* carriage rates in healthy children (Bogaert et al., 2004; Regev-Yochay et al., 2004). Hence, when properly investigated, microbial interference could be an option as a novel prophylactic management of infections.

Finally, another therapy protective against *S. aureus* infections is mucosal vaccination. Narita et al. (2008) showed recently that intranasal immunization with mutant toxic shock syndrome toxin-1 could elicit a protective effect against nasal colonization as well as systemic *S. aureus* infection in a mouse model.

Each of the above-mentioned novel therapies might contribute to the reduction of *S. aureus* carriage and/or *S. aureus* infections in patients in general and in patients with burn wounds in particular. However, additional research is required before further development of these therapies. In the future, infected burn wounds might be topically treated with one or more of the innovative therapies identified above.

**Conclusion**

This review has summarized the impact of nasal *S. aureus* carriage on burn wound colonization and the effect of several prophylactic measures on *S. aureus* burn wound colonization and infection. Despite a variety of infection control measures, i.e patient cohorting and contact precaution at burn centres, *S. aureus* is still frequently encountered in burn wounds.

Multiple *S. aureus* reservoirs and routes of transmission may exist and each contributes to the epidemiology and pathogenesis of *S. aureus* colonizations and infections in a dedicated burn centre. However, little is known about the relative contribution of each of the potential reservoirs and routes of transmission in the colonization and infection of patients with burns. More intervention studies should be performed to elucidate the transmission dynamics of *S. aureus* at burn centres.

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**References**


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