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Nanocrystalline silver dressings as an efficient anti-MRSA barrier: a new solution to an increasing problem

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Summary The emergence of multi-drug-resistant strains of bacteria represents a particular challenge in the field of wound management. The aim of the current study was to investigate whether nanocrystalline silver dressings possess the physical properties to act as a barrier to the transmission of methicillin-resistant *Staphylococcus aureus* (MRSA) in the laboratory setting and in a clinical setting. Initially, MRSA suspension and colony culture experiments were performed showing that nanocrystalline silver dressings act as potent and sustained antimicrobial agents, efficiently inhibiting MRSA penetration. Subsequently, a double-centre clinical trial was initiated using nanocrystalline silver dressings as a cover for 10 MRSA colonized wounds in a total of seven patients. By delineating the MRSA load on the upper side of the dressing and the wound bed each time the dressing was changed (i.e. after 1, 24, 48 and 72 h), nanocrystalline silver dressings were found to provide a complete, or almost complete, barrier to the penetration/spread of MRSA in 95% of readings. In addition, 67% of all wound observations showed a decrease in the MRSA load with an eradication rate of 11%. We believe that nanocrystalline silver dressings may become an important part of local MRSA management, with cost benefits to both patients and the healthcare system.

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Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) has become a pandemic problem. The Centers for Disease Control and Prevention's (CDC) National Nosocomial Infection Surveillance System reported that MRSA in US hospitals increased from 2.4% in 1975 to 35% in 1997,[1] with a higher incidence in intensive care units. Until recently, MRSA has been infrequently isolated from the community; however, publications suggest that the incidence of MRSA and other multi-resistant strains is increasing in the community setting,[2] and some deaths from community-acquired MRSA have been reported.[3,4]

Despite World Health Organization (WHO), CDC and national guidelines recommending isolation of MRSA patients, together with special nursing and treatment procedures to prevent and control MRSA infection and transmission, the growing pandemic places a substantial burden on the entire healthcare system. In the light of increasing death rates (in England and Wales, death records with a general diagnosis of *Staphylococcus aureus* infection showed that the proportion due to MRSA increased from 8% in 1993 to 44% in 1998[5]), 4.5-fold-longer periods of hospitalization[6] and increasing costs ($42–$59 million/year for Canadian hospitals[7]), there is an urgent need for new approaches to the management and containment of MRSA transmission/infection.

Acticoat® (Smith & Nephew, Hull, UK), a commercially available silver dressing, consists of silver nanocrystals organized in a coarse columnar structure. When used as a wound dressing, the small silver nanocrystals produce a very large surface area on the lower blue layer providing antimicrobial activity. The absorbent inner core maintains a moist wound environment necessary for the continuous release of silver[8] and advantageous wound-healing conditions.[9] Indications for use include protection against bacterial contamination in burns[10] and chronic wounds.[11]

The aim of the present study was to determine whether the properties of nanocrystalline silver dressings might be used as an active antimicrobial barrier to prevent MRSA transmission and cross-contamination from MRSA colonized wounds and lesions. For this purpose, an in vitro pilot study and a two-centre clinical trial were undertaken to test the potential MRSA barrier and microbial function of nanocrystalline silver dressings.

Patients and methods

Preclinical in vitro assessment

To test the potential MRSA barrier and lytic function of the dressing, a series of eight Columbia agar (bioMérieux, Paris, France) plates (diameter 90 mm/63.6 cm^2) were first inoculated with 0.1 ml MRSA suspensions (MacFarland: 0.5, Colorimeter, Vitek Inc., Loveland, Colorado, USA). A 4×4-cm nanocrystalline silver dressing, moistened with distilled water, was applied immediately to each plate, blue side down, for MRSA solution experiments [sMRSA, Figure 1(A)]. In addition, a series of eight MRSA inoculated plates were incubated at 37 °C to confluent colony growth for 24 h and were subsequently covered with wet dressings, blue side down (MRSA colony experiments, cMRSA). Both sets of plates (sMRSA and cMRSA) were incubated at 37 °C for 1, 24, 48 and 72 h. From the removed dressings, imprints of the upper and lower sides were applied on sterile Columbia agar plates. After 72 h of culture, the number of colonies/plate, representing the MRSA load on the upper and lower sides of the dressing, were directly counted. The area of each plate covered by a dressing (pA) was examined for MRSA growth directly after removal of the dressing. From the areas where no bacteria could be detected visually, smears were taken and cultured in 10 mL of brain heart infusion (bioMérieux) (24 h at 37 °C), and plated on Columbia agar.

As the blue lower side of a nanocrystalline silver dressing releases silver ions into the covered area, a further experiment was conducted to test whether the released silver ions inhibit MRSA by themselves (post-dressing effect). For this purpose, all test plates initially covered with dressing (1, 24, 48 and 72 h) were stored at 37 °C for a further 72 h without any dressing and MRSA regrowth was quantified. Where no regrowth of MRSA was observed, the areas previously covered with the dressing were re-inoculated with saturated MRSA suspensions in order to exclude the possibility that a lack of nutrients within the agar and/or dried-out bacteria were responsible for the lack of growth. Potential MRSA growth was quantified via direct colony determination after 1 h and every 24 h over a 72-h period. In total, three series of such MRSA re-infection experiments were performed.

Clinical assessment of MRSA-colonized external wounds

Between October 2002 and September 2003, seven patients with 10 wounds (Table I) colonized with MRSA were recruited from two centres (Department of Dermatology, Federal Academic Hospital Feldkirch, Feldkirch, Austria and Department of Dermatology, Wilheminenspital, Vienna, Austria) into an

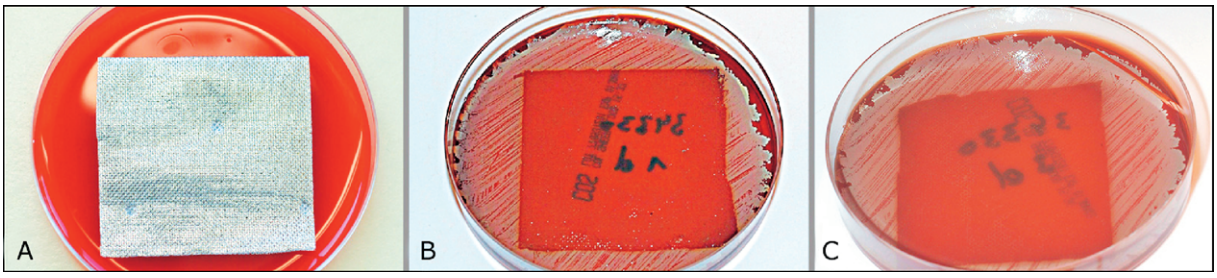

Figure 1 Demonstration of Columbia agar plates with and without a nanocrystalline silver dressing. (A) Dressing applied to a Columbia agar plate, blue side down. Anti-methicillin-resistant *Staphylococcus aureus* effect of the dressing after (B) 24 h and (C) 72 h.

assessment of the nanocrystalline dressing. None of the patients showed local or systemic signs of infection. With the exception of Patients PS and JF, in whom multiple ulcerative lesions were covered with a single dressing (Table I), each dressing was used for a single wound. Before using a dressing, debris and excessive wound fluid were removed with double-distilled water. Dressings were hydrated, placed on wounds and covered with dry gauze [except in one case, where Tielle® (Johnson & Johnson Medical Limited, Skipton, UK) was used]. Dressings were changed at 1 h and then every 24 h for 72 h. When changed at 1, 24, 48 and 72 h, each dressing was sampled for penetration of MRSA by swabbing the upper side of the dressing, and a semiquantitative determination of the MRSA load was made (+ = low load, +++ = high load). In addition, swabs were taken from wounds for assessment of the dressing's anti-MRSA effect before use of the dressing and each time the dressing was changed. Swabbing was performed in a standardized manner, always covering the same dressing site and wound area. Wound-related parameters that might impair the barrier function

Table I Patient characteristics, methicillin-resistant *Staphylococcus aureus* (MRSA) load of each wound immediately prior to application of a nanocrystalline silver dressing, and dressing-related MRSA barrier properties

Patient	Diagnosis	Location	Size[a]	MRSA[b] wound[c]	MRSA dressing upper site			
					1 h	24 h	48 h	72 h
BW1	Diabetic ulcers	Left heel	4.5 cm	+++	no	no	no	no
BW2		Right sole	3 cm	+++	no	no	no	no
PS1	Atopic eczema	Left lower arm	1.5 cm[d]	+++	no	no	no	no
PS2		Right lower arm	1.5 cm	+++	no	no	no	n.a.
JF	CREST syndrome	Left lower leg	2.5/ 12 cm[e]	+++	no	no	no	no
NL1	Venous ulcers	Left lower leg	n.a.	++	no	no	no	no
NL2		Right lower leg	n.a.	+	+	no	no	no
KHA	PAOD	Left lower leg	18 cm	+++	no	no	++	+
KHE	Traumatic ulcer	Cranium	4.5 cm	+++	++	no	+	no
EM	Cicatricial ulcer	Right lower leg	3 cm	+++	no	no	no	no

no, no MRSA detection; n.a., not analysed; PAOD, peripheral arterial occlusion disease.
[a] Initial wound size as outlined from photographic documentation.
[b] Semiquantitative delineation of the MRSA count ranging from no MRSA to +++ positive (high load).
[c] MRSA colonization status of wounds immediately before the dressing was used.
[d] Disseminated, multiple ulcers covered by one large dressing.
[e] Two ulcers covered by one large dressing.

of the dressing were also recorded. The status of wounds (e.g. amount of granulation, fibrinous and necrotic tissue), amount of exudate, quality of wound borders and behaviour of the dressing (i.e. tight or loose adhesion) at 1 h and at every dressing change were defined in detail.

Results

In vitro assessment

Total clearing of bacteria on the plate was seen in sMRSA cultures after 1 h and was maintained up to 72 h [Figure 1(C) and Table II]. On cMRSA plates, reduction of MRSA to below detection levels was recorded at 24 h (Table II). The 48- and 72-h cultures [Figure 1(C)] of cMRSA plates were also MRSA-free. With regard to the barrier function, we revealed only 17 colonies in the upper side of the dressing in sMRSA plates, but confluent growth in cMRSA plates after 1 h. After 24, 48 and 72 h, cMRSA cultures decreased to undetectable MRSA levels (Table II). Based on the absorbent effect of the dressing, the lower side always yielded the higher level of bacteria, with undetectable levels of MRSA in 72-h cultures only. Taken together, nanocrystalline silver dressings always worked faster in the sMRSA setting than in the cMRSA plates. When finally cultured without a dressing for a further 72 h, neither sMRSA nor cMRSA cultures showed any recolonization of areas previously covered by a dressing. Even in the second series of experiments where post-dressing areas were inoculated with freshly saturated MRSA solution, 11 of the 12 different culture conditions (triplicate experiments at 1, 2, 4, 48 and 72 h) showed no regrowth of bacteria (except on one occasion, 0.5 cfu/cm^2 after 1 h).

Table II Methicillin-resistant *Staphylococcus aureus* (MRSA) solution and MRSA colony plates incubated with a nanocrystalline silver dressing

s/c MRSA plates (h)	UpA	loA	pA
1	17c/cg	cg/cg	e/1.000c
24	e/e	6c/40c	e/e
48	e/e	8c/7c	e/e
72	e/e	e/e	e/e

upA, upper side of the dressing; loA, lower side of the dressing; pA, dressing-covered areas of plates; s, solution; c, colonies; cg, confluent growth; e, eradication.

Clinical assessment

Based on the experimental design, i.e. swabs from the upper side of the dressing and the wound, a total of 39 measurable observations were obtained from 10 wounds of seven patients. Immediately prior to application of the dressing, all wounds with the exception of Patient NL showed $+++$ MRSA (Table I). Over the entire 72-h observation period, the dressing showed active barrier properties in all covered wounds (Table I) without any $+++$ MRSA breakthrough on the upper side. No bacterial penetration through the dressing was observed in seven sites over the entire observation period. One wound had minor colonization of the upper side of the dressing after 1 h, but then changed to a sustained MRSA-free dressing surface thereafter. In two patients, single $++$ penetrations were found, subsequently reduced to MRSA loads or even eradicated. Taken together, the dressing presented an absolute (34 observations) or almost absolute (three observations) MRSA barrier in 95% of all readings. With regard to the direct anti-MRSA effect of the dressing within the wound, nine sites of six patients (36 observations) were evaluated. Eleven percent (4/36) showed a complete clearing of MRSA, while 56% (20/36) of wounds showed a $+$ to $++$ reduction, demonstrating that nanocrystalline silver dressings form a 67% effective anti-MRSA device in an in vivo setting.

Discussion

MRSA contamination or colonization of wounds in any setting represents a significant threat to both the affected patient and to other patients in terms of cross-infection. Based on in vitro analyses, the current study clearly demonstrated that nanocrystalline silver dressings work as an efficient barrier against MRSA. In addition, dressings were highly active against MRSA and were found to have sustained bactericidal activity, even after removal of the dressing. In this context, it is important to mention that sMRSA cultures achieved more pronounced results in all experiments, and these are much closer to the in vivo situation than cMRSA plates.

In the clinical trial, nanocrystalline silver dressings exhibited a highly effective and reliable barrier to the spread of resistant organisms into the wider environment. Notably, the $++$ MRSA penetrations were limited to two wounds (Table I), while no penetration at all was observed in seven wounds during the entire observation period. Taking into account that one incomplete barrier

site was located on the scalp and the other affected almost the whole circumference of the lower leg, one might speculate that difficulties of accurate adhesion/bandage rather then dressing-related deficiencies permitted the transmission of MRSA. Notwithstanding these considerations, wound care specialists now use the product in clinical practice to prevent infection by environmental bacteria/fungi.[10,11]

The MRSA barrier function may have significant benefits. Current guidelines[12–14] for the management of MRSA recommend standard contact precautions (e.g. handwashing, masking and appropriate handling of laundry), eradication of MRSA from the nasopharynx and isolating the patient. These procedures are often difficult to implement, often fail to control or prevent cross-contamination and are costly, both in monetary terms and psychologically for the patient. In contrast, the use of nanocrystalline silver dressings proved to be easy, cost-effective and had a high degree of confidence. Consequently, in patients with MRSA-colonized wounds, the use of dressings as antimicrobial barriers in association with decontamination of carrier sites may become an attractive new procedure in the field of infection control. The principle of locally enclosing MRSA offers a number of potential advantages. First, silver-containing dressings protect staff in the hospital as well as relatives and home-care nurses in the community setting from acquiring MRSA. In addition, the use of local MRSA barriers also reduces the hazards of standard procedures in hospitals, such as transfer of MRSA patients to examinations. The most significant development would be the demonstration that patients with external MRSA-colonized wounds no longer need isolation. Such a decision would reduce the burden on the patient, decrease the hospital costs substantially and reduce the logistical problems for small healthcare units such as rehabilitation centres.

Overall, this study has shown for the first time that nanocrystalline silver dressings provide an effective barrier to MRSA cross-contamination with further local anti-MRSA properties. Particularly in diabetics or patients with peripheral arterial occlusion disease where systemic antibiotics often fail to reach peripheral infections, the antimicrobial effect of such dressings may enhance effective antibiotic treatment and reduce therapeutic regimens.

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