Healing outcomes of MRSA-infected wounds with a protocol combining Oakin dressing with elements of de-escalation theory

- **Objective:** This paper presents a novel wound healing protocol for the treatment of MRSA-infected lower extremity wounds of various etiologies, and describes the healing rate at 30, 60 and 90 days.
- **Method:** A total of 40 participants with singular wounds were enrolled and treated with a specially designed protocol, which involves elements of the de-escalation theory together with a wound dressing containing Oakin, in a private practice setting or a wound care center. The primary endpoint was the number of participants who achieved wound closure at 90 days. Data analysed and collected included wound etiology, wound size, gender, healing time by setting, and days to heal overall. Due to the anticipated small cohort of wound types, several statistical calculations were considered, including one-way ANOVA, Pearson correlation, and Levene’s test.
- **Results:** All wounds were classified by etiology: 58% (n=23), diabetic neuropathic ulcers (DNU), 25% (n=10) venous insufficiency ulcers (VU), and 17% (n=7) pressure ulcers (PU). Overall, 35% (n=14) healed within 30 days (22.14 ± 4.47), 60% (n=24) healed in 60 days (31.76 ± 13.02), and 78% (n=31) healed in 90 days (40.81 ± 22.23). After 90 days, the remaining 23% (n=9) of participants were no longer followed.
- **Conclusion:** This clinical evaluation demonstrated the overall effectiveness of this treatment protocol by attaining nearly 80% wound closure within 90 days. This protocol is intended to provide a roadmap for clinicians to follow and adapt to their wound care practice should a high prevalence of MRSA-infected wounds be present.
- **Declaration of interest:** The author has disclosed that he has worked doing clinical case studies for Amerx Health Care Corp. and is on their speaker bureau. The author has also disclosed that he has no financial relationship or vested interest with Amerx Health Care Corp. No funding was provided by the NIH, Wellcome Trust, HHMI, or others.

MRSA infection; Oakin; de-escalation; Amerigel; antimicrobial

The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) strains has been on the rise for several years in the community and is one of the major challenges in wound disinfection. According to the Centers for Disease Control and Prevention (CDC), MRSA was responsible for nearly 70% of all skin infections in the United States in 2010. In addition, approximately 94,000 cases progressed to invasive MRSA infections and was associated with 18,650 deaths. Bamra reported that 75% of all patients with wounds that presented to their emergency department cultured positive for MRSA, demonstrating an area of high prevalence. In those geographic regions of the United States with a high prevalence of MRSA-infected wounds, providers could benefit from implementing a treatment protocol that integrates certain elements or modifications to the de-escalation theory. The de-escalation theory can be defined as the streamlining of empirical antimicrobial therapy based on the culture results for severe infections. The elimination of unnecessary antimicrobial therapy can more effectively target the particular causative pathogens which results in decreased antimicrobial exposure, reduced potential of developing future resistance, and significant cost savings. There is no clear consensus on when to start antimicrobial therapy, however these infections can be limb-threatening and antimicrobial intervention should be initiated well before becoming severe.

The Infectious Diseases Society of America (IDSA) has four classifications of wound infections based upon clinical findings, bioburden, and severity. These Clinical Practice Guidelines also provide recommendations for antibiotic therapy, for example; oral linezolid, minocycline/doxycycline, or trimethoprim/sulfamethoxazole for mild infections should risk factors for MRSA be present. However, should no risk factors for MRSA exist, then different antibiotics are recommended according to the IDSA. Therefore, the presence or absence of risk factors plays a key role in the diagnosis and appropriate selection of antimicrobial therapy (Table 1). While the risk factors listed in Table 1 are
Table 1. Risk factors for MRSA

- Current or recent hospitalisation
- Living in a long term facility
- Invasive devices
- Chronic illness
- Recent antibiotic therapy within the past year (treatment with a quinolone or Cephalosporin can increase the risk of MRSA)
- The patient is of young or older age
- Participating in contact sports
- Sharing towels or athletic equipment
- Weak or compromised immune system
- Living in a crowded or unsanitary condition
- Association with health care workers
- History of MRSA infection/colonisation
- Geographic location

Table 2. Wound type and healing time by setting

<table>
<thead>
<tr>
<th>Types of wounds</th>
<th>Enrolled by setting n (%)</th>
<th>Age (years)</th>
<th>Healed at 30 days</th>
<th>Healed at 60 days</th>
<th>Healed at 90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNU</td>
<td>OFC = 10 (43%)</td>
<td>68 ± 12.81</td>
<td>2 (20%)</td>
<td>6 (60%)</td>
<td>8 (80%)</td>
</tr>
<tr>
<td></td>
<td>WCC = 13 (57%)</td>
<td>57.06 ± 11.62</td>
<td>6 (44%)</td>
<td>9 (75%)</td>
<td>10 (81%)</td>
</tr>
<tr>
<td></td>
<td>Total = 23 (58%)</td>
<td>60.75 ± 12.90</td>
<td>8 (35%)</td>
<td>15 (65%)</td>
<td>18 (78%)</td>
</tr>
<tr>
<td>VU</td>
<td>OFC = 3 (30%)</td>
<td>71.67 ± 17.21</td>
<td>1 (33%)</td>
<td>1 (33%)</td>
<td>2 (67%)</td>
</tr>
<tr>
<td></td>
<td>WCC = 7 (70%)</td>
<td>63.43 ± 9.68</td>
<td>2 (29%)</td>
<td>4 (57%)</td>
<td>6 (86%)</td>
</tr>
<tr>
<td></td>
<td>Total = 10 (25%)</td>
<td>65.90 ± 12</td>
<td>3 (30%)</td>
<td>5 (50%)</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>PU</td>
<td>OFC = 4 (57%)</td>
<td>69.33 ± 21.73</td>
<td>1 (25%)</td>
<td>1 (25%)</td>
<td>2 (50%)</td>
</tr>
<tr>
<td></td>
<td>WCC = 3 (43%)</td>
<td>54.25 ± 18.73</td>
<td>2 (67%)</td>
<td>3 (100%)</td>
<td>3 (100%)</td>
</tr>
<tr>
<td></td>
<td>Total = 7 (17%)</td>
<td>60.71 ± 19.95</td>
<td>3 (43%)</td>
<td>4 (57%)</td>
<td>5 (71%)</td>
</tr>
<tr>
<td>Total</td>
<td>OFC = 17 (43%)</td>
<td>69.14 ± 14.45</td>
<td>4 (24%)</td>
<td>8 (47%)</td>
<td>12 (71%)</td>
</tr>
<tr>
<td></td>
<td>WCC = 23 (57%)</td>
<td>58.3 ± 12.27</td>
<td>10 (43%)</td>
<td>16 (70%)</td>
<td>19 (83%)</td>
</tr>
<tr>
<td></td>
<td>Total = 40</td>
<td>62 ± 13.89</td>
<td>14 (35%)</td>
<td>24 (60%)</td>
<td>31 (78%)</td>
</tr>
</tbody>
</table>

Data shown as n (%) and mean ± standard deviation.

OFC = Office setting, WCC = Wound care center

not all inclusive, they should assist the provider to conduct a fairly comprehensive in-depth history.

In March 2012, the IDSA updated their Clinical Practice Guidelines and recommended that all patients with severe infections or select moderate infections with complications be hospitalised initially. Although the IDSA recommendations are specific to diabetic foot infections, they could also apply to other infected wounds on the lower extremity when there are risk factors of MRSA present, to foster limb preservation.

Perhaps more than any other medical specialty, wound care providers are in a unique position to lessen the unnecessary use of systemic antibiotic agents to treat skin or soft tissue infections. In many situations, the application of one of the various topical antimicrobials or specialty antimicrobial wound dressings should preclude a “knee-jerk” reaction of randomly prescribing systemic antibiotic therapy. Provided the patient is not systemically ill, does not have other comorbidities that would support additional empirical antibiotic therapy, and is able to notify the wound care provider of any deterioration or progression to a more serious condition, a primary broad-spectrum antimicrobial wound dressing should provide sufficient local antimicrobial therapy. While the choice of antibiotics is important, so should the choice of a topical antimicrobial dressing.

Antimicrobial agents used in current wound dressings include polyhexamethylene biguanide, ionised silver, iodine, and natural tannins. Oakin, a natural tannin harvested from oak extract (Amerigel Wound Dressing, Amerx Health Care Corp., Clearwater, FL), exerts bactericidal and fungicidal activity against 51 pathogens, including MRSA and VRE. An in vitro time-kill study demonstrated that the Oakin wound dressing eliminated 99.2% of MRSA within the first 6 hours and sustained that kill rate for the remainder of the 24 hour test. Moore and Perkins compared the antimicrobial efficacy of Oakin to three wound dressings containing silver. Their findings suggested that there were no substantial differences in antimicrobial efficacy between Oakin and ionic silver. The Oakin antimicrobial dressings are indicated for stage I-IV pressure ulcers, venous stasis ulcers, diabetic skin ulcers, first and second degree burns, wounds with dehiscence, and wounds healing by secondary intention. These dressings are intended to be used on hydrogel appropriate wounds defined as: dry wounds requiring moisture, wounds with no exudates, or wounds with low amounts of exudate.

This paper presents a pilot study to assess the viability of a MRSA wound healing protocol intended for use in multiple settings including a wound care center or private practice. The proportion of participant’s wounds healed by 90 days would be a primary endpoint to suggest the potential overall effectiveness of the protocol. This protocol gives the wound care provider a step by step process to follow when evaluating and managing a new patient presenting with a chronic wound. For purposes of this paper, chronic is defined as a non-healing wound of at least 90 days duration.

Method

Each participant or their legal representative signed an informed consent form prior to enrolment. Consent for the study was strictly voluntary and participants were advised that they could decline or drop out of the study at any time. Participants were advised that the risks of being involved in the study were expected to be the same or less than the risk of a non-study participant. These risks included allergic reaction or infection. Cultures were taken from those that individuals presenting with the classic clinical signs of infection including, erythema, ede-
Adult individuals 18 years of age and older with a single, chronic, hydrogel-appropriate, infected lower extremity wound with risk factors present for MRSA (Table 1) were considered eligible, pending culture results. Those eligible were evaluated and treated according to the protocol which included sharp wound debridement, wound culture, antibiotic therapy when appropriate, and daily dressing with the Oakin antimicrobial hydrogel. When the wound culture results were received, the antibiotics were assessed to ensure that adequate coverage was provided for the identified pathogens. Oral antibiotics were added and adjusted depending on the participant’s allergies, comorbidities, vascular status, drug resistance where wounds were not improving, insurance coverage (i.e. Linezolid) and the participant’s ability to pay for the antibiotics.

Those eligible with a wound culture positive for MRSA were enrolled as a participant and then followed for a 12 week period. Any individual with a serious wound infection requiring intravenous antibiotics or hospitalisation was excluded from enrolment. For purposes of this paper, a serious wound infection would have indicators such as odour, serous exudate, delayed healing, friable granulation tissue, discolored granulation tissue, pocketing of the wound base, and wound breakdown.15

Each participant’s wound was assessed, measured and photographed. Debridement was performed every 7–10 days at the wound care center and every 10–14 days at the office setting. Participants and/or their caregivers were shown the necessary steps to perform daily dressing changes and were also provided with a standardised wound care instruction sheet. The Oakin antimicrobial dressings used for this clinical evaluation were one ounce (30 gram) tubes or the individually wrapped, sterile 2” x 2” saturated gauze dressings that were provided free of charge to the participants.

The participants were scheduled to be reassessed at 30, 60 and 90 day intervals or until wound closure based on measurements of LxWxD was achieved. Parameters measured include proportion healed at 30, 60 and 90 days, wound aetiology, wound size, and days to heal overall. Due to the anticipated small subject sizes, several different statistical calculations would have to be incorporated including, one-way ANOVA, Pearson correlation, and Levene’s test. The proportion of wounds healed by 90 days would be a primary endpoint in determining the overall effectiveness of the protocol.

**Results**

A total of 40 adult participants with a single, chronic, hydrogel-appropriate, lower extremity wound with positive culture results for MRSA were enrolled. Their wounds were classified by aetiology: 58% (n=23) diabetic neuropathic ulcers (DNU), 25% (n=10) venous insufficiency ulcers (VU), and 17% (n=7) pressure ulcers (PU). 43% (n=17) were seen in the private practice/office (OFC) setting and 57% (n=23) were seen in the wound care center (WCC) setting. Of the 31 participants healed within 90 days, 71% (n=12) of the OFC setting healed in an average of 51.78 ± 25.76 days and 83% (n=19) of the WCC setting healed in an average of 36.32 ± 19.50 days. (Table 2)

A one-way ANOVA was conducted to evaluate the different types of wounds and days to healing. The independent variable, type of wound, included 3...
groups: DNU, VU, and PU. The dependent variable was the number of days to healing. A preliminary analysis evaluating the homogeneity of variances assumption, using Levene's test, indicated no significant difference in variances among groups (F[2,28]=0.61, p=0.55). The ANOVA indicated no significant differences (F[2,28]=0.23, p=0.79), in mean healing time among DNU (39.89 ± 19.97), VU (43.50 ± 21.83), and PU (34.80 ± 24.40; Table 2).

The relationship between days to healing and wound size was evaluated using a Pearson correlation. However, the relationship between days to healing and wound size was non-linear; therefore a quadratic transformation of wound size was used for the correlation (Fig 2).

A correlational analysis was conducted to evaluate the strength of the positive quadratic relationship between wound size and days to healing. After a quadratic transformation of wound size a one-tail Pearson correlation coefficient was computed, r=0.37, p=0.02. The relationship was statistically significant. Wound size and days to healing were moderately correlated. (Fig 2). Overall, 35% (n=14) healed within 30 days (22.14 ± 4.47), 60% (n=24) healed in 60 days (31.76 ± 13.02), and 78% (n=31) healed in 90 days (40.81 ± 22.23; Fig 3).

Of all participants, 10% did not receive any empiric therapy and were treated only with the Oakin antimicrobial wound dressing. The author considered these four wounds to be mildly infected and did not prescribe antibiotic therapy initially. By the time the culture results were received, the wounds had improved substantially, considering the results were positive for MRSA. Based on the author’s observations, it was apparent that the Oakin wound dressing was providing sufficient local antimicrobial therapy, therefore no empiric antibiotics were necessary and the four wounds achieved closure uneventfully. The Oakin antimicrobial dressings were well tolerated and no participants reported or developed an allergic or adverse reaction, nor were any clinically observed.

Of the 40 enrolled, 45% (n=18) were male and 55% (n=22) were female, ranging in age 28 to 91 years (62.00 ± 13.89). The mean for men 41.63 ± 23.71, was not significantly different from the mean for women 38.27 ± 20.31 (F[1,29]=0.18, p=0.68). A second correlational analysis was conducted to evaluate the strength of the relationship between age and days to healing. A two-tailed Pearson correlation coefficient was computed, indicating no significant relationship between age and days to healing (p=0.95).

Case Studies

Case one
A 91-year old Caucasian male was referred from the wound centre with a right lower leg stasis ulcer with MRSA infection (Fig 4a). It was treated with periodic debridement and topical Mupirocin for 18 months. The wound underwent sharp debridement, and was covered with Oakin antimicrobial gauze dressing. Culture tests showed that the wound was positive for MRSA. Following treatment, the patient’s wound rapidly progressed to closure. A culture swab was negative for MRSA in one week. The wound healed in 14 days (Fig 4b).

Case two
A 66-year-old Caucasian female presented with a non-healing ulcer over the left lateral malleolus (Fig 5a). The patient had a previous ulcer of the 5th toe with revascularisation. Radiographs were negative for osteomyelitis, but a wound culture was positive for MRSA. The patient was prescribed oral Linezolid (600mg). Sharp wound debridements were per-
formed every 2 weeks, and Oakin wound dressings were changed daily (Fig 5b). Revascularisation was performed 2 days after the initial visit. The wound steadily progressed to closure, and the full course of empirical therapy was completed. The wound healed in 71 days (Fig 5c).

**Discussion**

The protocol for this article was designed by the author and utilised on patients in clinical settings in geographical areas known to have a high prevalence of MRSA. All participants presented with non-healing, static or deteriorating infected lower extremity wounds which were suspected to be positive for MRSA based on risk factors prior to having any culture results. Missed appointments, poor glycaemic control, and non-adherence to treatment were noted among participants just as they would occur in a typical private practice or wound care center in the real-world.

Debridement is an important component in wound bed preparation and plays a critical role in wound healing. The primary purpose of debridement is to remove non-viable or necrotic tissue in a healable wound because this tissue is a pro-inflammatory stimulus and a culture medium for bacterial growth.14–16 Methods of debridement include: autolytic, sharp, laser, mechanical, enzymatic, and biosurgical using maggots.14,15 For this paper, sharp debridement was performed with a sterile scalpel and/or curette. The results of this article show nearly 80% of wounds were healed within 90 days using this unique treatment strategy. The concept of de-escalation is not often described in the context of MRSA-infected wounds.

**De-escalation theory**

The origin of the de-escalation theory and practice was first used in the hospital setting for the treatment of pulmonary infections.17,18 The de-escalation theory was first discussed for the treatment of MRSA-infected diabetic foot wounds by Rogers and Bevilacqua.19,20 Their algorithm focused on the
empiric treatment of limb threatening moderate to severely infected diabetic foot wounds. Certain elements from their algorithm were combined and incorporated into the protocol for this article. Empiric therapy points to consider include:

- Cultures of presumed infected sites should always be obtained prior to administration of any antibiotics.
- Initial empiric therapy should be chosen based on most likely pathogen(s), cost-effective therapy, and impact on development of resistance.
- The patients’ natural flora may be altered by previous antibiotic courses and recent therapy should be taken into account when choosing initial empiric therapy.
- Greater severity of illness or severely immunocompromised state may warrant broader initial empiric coverage.

Oakin technology

The Oakin antimicrobial wound dressings were chosen for this article because of their efficacy against MRSA. Furthermore, the lack of the need for antibiotics (which may potentially lead to resistance with overuse) is a distinct advantage of the Oakin dressing.

Acute wounds

In geographical regions experiencing a high prevalence of MRSA, acute wounds such as those healing by secondary intention and presenting with the clinical signs of infection should be considered positive for MRSA until culture results are obtained. We hypothesize that the protocol used in this study would also be appropriate for the treatment of acute wounds at risk for MRSA infection.

Conclusion

Overall, nearly 80% of wounds healed within 90 days. The dressings were well tolerated and no participants reported any adverse reactions to the Oakin dressings. These data suggest that this protocol is efficacious for treating individuals with chronic lower extremity MRSA-infected wounds. It can’t be determined from this small study whether the Oakin or antibiotic or combination therapy were synergistic and responsible for the wound closure. The results were not intended to compare the effectiveness of one treatment modality or combination thereof. Additional studies with larger patient populations and other interventions should be undertaken. Instead, this protocol should serve as guidance for wound care providers to follow and adapt to their setting where a high prevalence of MRSA-infected wounds exist. This clinical evaluation further validates the therapeutic benefit of the Oakin antimicrobial dressings.

References