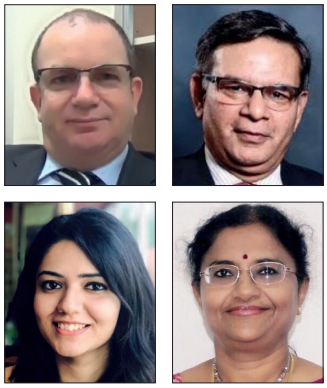
Management of burn patients with Technology Lipido-Colloid with silver sulphate to fight local infection and restore the healing process



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Burn wounds are predisposed to infection and topical antimicrobial preparations are used both to prevent and treat infection. The choice of topical antimicrobial should be based on the ability of the agent to inhibit microorganisms that may be harmful within the wound bed and on the host. Silver is indicated when a local negative impact of bacterial colonisation is suspected and/or confirmed, because it has a broad antimicrobial effect. Technology Lipido-Colloid (TLC) is a matrix containing hydrocolloid and lipophilic substances that has been shown to promote the proliferation of fibroblasts and to be atraumatic for patients. TLC-Ag incorporates silver sulphate (3.5%) into the TLC matrix. When it is in contact with the wound, the dressing releases a constant supply of antibacterial silver. This article will discuss the use of antimicrobials in burn wound management, show the evidence for the TLC-Ag antimicrobial healing matrix and portray outcomes of cases of burns patients in India who have been managed with TLC-Ag.

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Wound infection has been defined as a proliferation of microorganisms leading to a response that can be either locally within the wound (local infection), around the wound (spreading infection) or systematically (systemic infection) (International Wound Infection Institute, 2016).

Contamination is the occurrence of non-proliferating microorganisms which do not invoke a host response, while colonisation denotes that microorganisms are present with limited proliferation, but still not evoking a host response (Eberlein and Assadian, 2010). Local infection is where microorganisms migrate deeper in the wound and proliferate enough to initiate a host response, which presents with mild signs of infection (Siddiqui and Bernstein, 2010). Spreading infection is the invasion of microorganisms into the surrounding tissue and may also involve deep tissue, muscle, fascia, organs or body cavities, causing signs and symptoms beyond the wound, while systemic infection is where the microorganisms spread in the whole body via the vascular or lymphatic system, invoking an systemic inflammatory response and includes organ dysfunction (Leaper et al, 2012).

The World Union of Wound Healing Societies (2008) consensus document states that the risk of infection is increased by any factor that debilitates the patient, impairs immune resistance or reduces tissue perfusion.

This brings us to the dilemma of whether clinicians should withhold topical antimicrobials if wound infection is present or to prophylactically treat high-risk patients and wounds. This is a controversial subject that needs to weigh the pros and cons of use of antimicrobials for an individual patient against worldwide guidance for antimicrobial stewardship. The use of topical antimicrobials as prophylaxis is interesting because they can be applied *in situ*, thus circumventing potential systemic toxicities and the risk of systemic antibiotics not arriving through avascular tissue to the site of infection (Glasser et al, 2010). Infection control procedures and good hygiene practices are important to prevent

further contamination of the wound and cross-contamination (World Union of Wound Healing Societies, 2008).

Overt signs and symptoms of infection include erythema, local warmth, swelling, purulent discharge, delayed wound healing, new or increasing pain and increasing malodour, while covert signs and symptoms include hypergranulation, bleeding, friable granulation, epithelial bridging and pocketing in granulation tissue, wound breakdown and enlargement, delayed wound healing beyond expectations, new or increasing pain and increasing malodour (International Wound Infection Institute, 2016).

Burn infections

In India, around 7 million people suffer burn injuries each year, with 140,000 dying and 240,000 becoming permanently disabled (Rastogi, 2016). Gupta et al (2010) state that around 10% of burn wounds are life-threatening and require hospitalisation, and approximately half of those who are hospitalised will die as a result of their injuries.

Infection still accounts for approximately 75% of all deaths in burn injuries globally (Al-Aali, 2016). The burn trauma not only destroys the skin, which is the first line of defence, but also contributes to the suppression of the immune system, while the protein-rich eschar produced offers an ideal environment for microorganisms to grow. These factors make burn wounds more prone to infections (Valarmathi et al, 2013; Hasan et al, 2016; Dahag et al, 2018). The avascular zone of coagulation diminishes immunological defences, while the inflammation also impairs wound healing due to the release of proteases from macrophages. Other factors that might predispose the wound for infections are patient factors, such as age, obesity, malnutrition, and endocrine and metabolic disorders (Pujji et al, 2019).

Thermal injuries are suggested to be free from microorganisms during and just after the trauma, due to the high temperature. However, these wounds become colonised within 48 hours with the patient's endogenous bacteria (mostly Gram-positive bacteria, and some Gram-negative bacteria from the gastrointestinal and respiratory tract), and the nosocomial microorganisms present in the environment (Mundhada et al, 2015).

Apart from burn wound sepsis, burn wound infections also may lead to wound alteration, skin graft failure and prolonged hospitalisation (Cartotto, 2017). The virulence, quantity and antibiotic resistance of bacteria also play a part in escalating the problem of wound infection. There are a number of varieties of common bacteria found in burn wounds, and positive bacterial cultures are more frequent in wounds of more than 2 weeks' duration (Valarmathi et al, 2013; Singh et al, 2019).

Bhama et al (2013) found that monomicrobial infection was most common in the early stages of a wound, with the proportion of wounds with polymicrobial infection increasing over time.

Wound dressings and antimicrobials

In a survey, 121 participants from 39 countries, most of whom were surgeons (72.1%), suggested that attributes of the ideal burn wound dressing include non-adhesion, antimicrobial activity, atraumatic removal and requires less frequent dressing changes (Selig et al, 2012). Irrespective of burn depth, topical antimicrobials are indicated when there is clinical suspicion of risk of infection, or when a wound infection is evident (Cartotto, 2017). The choice is based on factors such as wound depth, anticipated time to healing, need for surgical intervention, known cytotoxicity of the agent pain or irritation, and the required frequency of application (Cartotto, 2017).

Modern dressings have been reported to achieve better results than traditional dressings, such as silver sulfadiazine (Ag-SD), which ihas been found to cause wounds to dry up and not support optimal healing (Jiang et al, 2017). It has been argued that the main drawbacks associated with Ag-SD topical creams are their tendency to form pseudo-eschar, which is difficult to distinguish from burn eschar and may impede the penetration of the antimicrobial into the wound. The fatty acids or lipid-soluble carrier are relatively insoluble in water, making it difficult to remove old or residual cream from the wound (Ghodekar et al, 2012). The yellow-gray pseudo-eschar may be several millimetres thick and results from interaction between the cream and the wound exudate (Bessey, 2007). It has also been suggested that Ag-SD cream is relatively short-acting and is time-consuming and messy to apply and remove (International Consensus, 2012). The lipid base may make removal of the product painful for the patient (Black and Drake, 2015). Clinicians show dissatisfaction regarding the necessary daily dressing when using Ag-SD cream (Jester et al, 2008).

It has also been suggested that Ag-SD cream prolongs healing time and inactivates natural enzyme debriding agents, and some have cytotoxic effects (Martindale, 2002; Muller

et al, 2003; Duc et al, 2007). Some topical antimicrobial preparations are cytotoxic to keratinocytes and fibroblasts, and therefore have the potential to delay wound healing (Cartotto, 2017). In a systematic review and meta-analysis, other materials showed better results than Ag-SD (Nimia et al, 2018).

Evidence shows that some topical antiseptics are non-selective and may be cytotoxic if not delivered to the wound in a sustained manner (Siddiqui and Bernstein, 2010; Leaper et al, 2012). Fraser et al (2004) found that there was almost no keratinocyte survival and a reduction in cell survival after 72-hour exposure to Ag-SD and chlorhexidine, and topical Ag-SD was associated with a reduction in cell numbers compared to control. Cytotoxicity may be dependent on concentration (Siddiqui and Bernstein, 2010; Leaper et al, 2012).

Technology Lipido-Colloid with silver

Technology Lipido-Colloid (TLC) comprises a matrix containing hydrocolloid and lipophilic substances, which have been shown *in vitro* to enable proliferation of fibroblasts, stimulate extracellular matrix production and contribute to the formation of new tissue through the creation of a moist environment (Bernard et al, 2005; McGrath et al, 2014). The healing matrix dressing is designed to reduce adhesion to the wound surface, whether the wound is acute or chronic (Meaume et al, 2002).

The atraumatic properties of the healing matrix were demonstrated in an observational study involving 5,850 patients (2,914 with acute wounds, 2,396 with chronic wounds) who were being treated with traditional dressings, such as gauze, paraffin-impregnated gauze, as well as foam and hydrocolloids. When the patients switched to TLC, pain reduction was reported in 88% of patients with chronic wound and in 95% of patients with acute wounds.

Two non-comparative multicentre prospective clinical studies were conducted using the same protocol in France and Germany and involved 100 paediatric patients aged 1–12 years, including 77 with burns (Letouze et al, 2004). At the end of the trial, the dressing acceptability parameters showed that TLC is easy to apply and remove, and is conformable and non-adherent. No pain (including minor pain) was reported using various age-suitable pain scales, confirming the atraumatic removal. Clinicians also noted that the dressing could be left in place for several days. The authors concluded that the product's pain-free removal could result in significant time savings and decrease the need for analgesia. The two studies confirmed the efficacy and safety of TLC.

TLC-Ag incorporates silver into the TLC healing matrix. Silver sulphate (3.5%) has been combined with TLC to produce TLC-Ag, which is indicated for the treatment of non- to low-exuding acute wounds (burns, skin abrasions, traumatic injuries and second-degree burns) and chronic wounds showing signs of infection. It can also be used on more heavily exuding wounds when used in combination with an absorbent dressing

TLC-Ag contains 0.35 mg/cm^2 of silver ions, delivered by silver sulphate (0.50 mg/cm^2). In contact with the wound exudate, the silver sulphate breaks down and releases the silver ion, while the carboxymethylcellulose particles swell to form a surface hydrocolloidal film. It is suggested that this controlled supply of silver at the surface into the lipido-colloid gel guarantees a constant antibacterial activity, when the dressing is in contact with the wound.

An *in vitro* analysis was carried out to determine the antibacterial properties of TLC-Ag on the survival of a range of bacteria, including strains resistant to antibiotics (White et al, 2015). The samples of dressings were inoculated with a bacterial suspension of 108 colony-forming units (CFUs) and then incubated. The number of surviving bacteria was calculated daily up until day 7. From day 1 and throughout the duration of the study, the reduction in the number of CFUs for all the bacterial strains studied was >105, making it possible to conclude that the TLC-Ag contact layer demonstrates antibacterial efficacy on the microorganisms tested.

In vivo evidence was provided through a multicentre, phase III, controlled, randomised trial. One cohort was treated with the TLC-Ag dressing for 4 weeks, followed by the silver-free TLC dressing for 4 weeks, while the control group was treated with a silver-free TLC dressing for the 8-week period (Lazareth et al, 2008). The primary study endpoint was reduction in the surface area of the wounds at weeks 4 and 8 of treatment. At the end of the first 4 weeks, the median surface area of the ulcers had decreased by 4.2 cm^2 in the group treated with silver versus 1.1 cm^2 in the control group (P=0.0223). In the next 4 weeks, the reduction in surface area continued in the group first treated with the silver dressing, in contrast with the control group. At the end of follow-up, the median ulcer surface area had decreased by 5.9 cm^2 in the silver group versus 0.8 cm^2 in the control group (P=0.002). At the end of 8 weeks of treatment, the relative median surface area reduction of

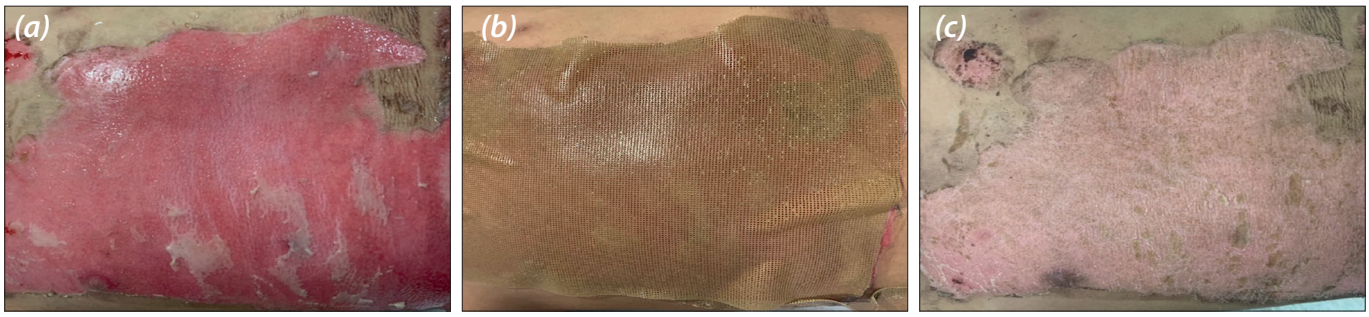

Figure 1. Case 1 at (a) presentation 4 days after the hot water burn; (b) with TLC-Ag dressing in place; and (c) wound closure after 11 days.

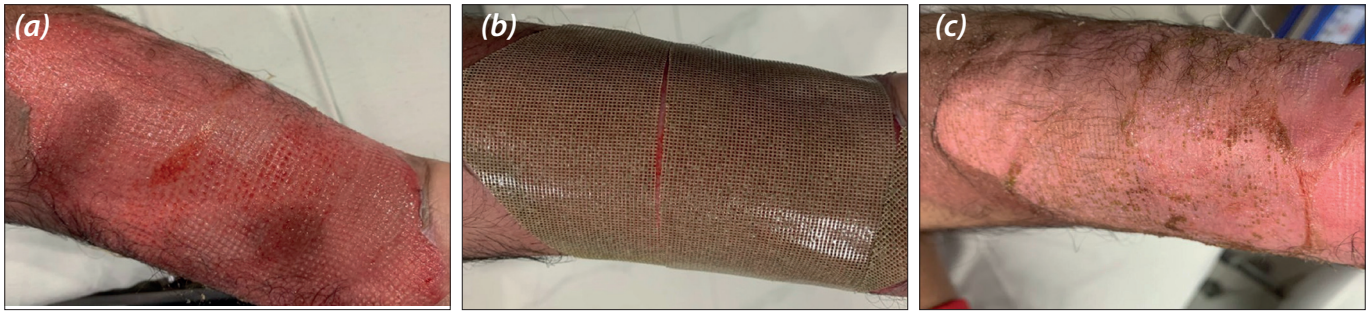

Figure 2. Case 2 at (a) presentation; (b) with TLC-Ag dressing in place; and (c) wound healing after two dressings.

the ulcers was significantly greater in the silver group at 47.9%, versus 5.6% in the control group (P=0.036).

The clinical score for wound colonisation (defined by the presence of clinical signs among five pre-specified signs at baseline) was significantly lower in the TLC-Ag group than in the control group (1.43 versus 2.31, respectively, P=0.0001), while the number of patients with a surface area reduction ≥40% of the initial surface area was higher in the TLC-Ag group: 54.9% of ulcers versus 35.4% in the control group (P=0.051), with an odds ratio 2.7 (95% CI 1.1–6.7, P=0.038) in favour of the silver group. Laboratory tolerance assay of blood silver levels was conducted to analyse if silver passes into the bloodstream (argyremia) at day 0, week 4 and week 8. It was shown that the TLC-Ag dressing did not induce any increase in blood silver levels.

Case studies

The following cases were conducted in view of the robust evidence in favour of the TLC-Ag, discussed above. The authors sought to test if the modality that had been proven effective in Europe would have the same results in patients managed in India using TLC-Ag.

Case 1

An 8-year-old girl presented with a 4-day-old thermal burn from hot water (17 × 20 cm) on the anterior chest wall and abdomen (*Figure 1a*). Initially, the burn had been managed at a local hospital with gauze saline dressing. Her pain score was severe and the wound had moderate exudate with an erythematous periwound area.

The wound was irrigated with normal saline and TLC-Ag was applied (*Figure 1b*). Thereafter, the dressing was reapplied every 3–4 days. After two dressing changes, pain and exudate levels had subsided and the wound bed appeared healthy and granulating. By day 11, after three dressing changes, there was no exudate present and the wound had closed (*Figure 1c*).

Case 2

A 27-year-old man presented with a 5-day-old thermal burn on the right forearm (10 × 7 cm). Pain score was moderate and the wound had mild exudate, along with inflammation and exposed dermis layer (*Figure 2a*). The wound had been initially managed with povidone iodine as the cleansing agent and topically with petroleum jelly gauze dressings.

Management changed to cleaning with normal saline and application of TLC-Ag (*Figure 2b*). The dressing was changed on day 4. The wound was granulating with no exudate and pain was decreased. After two dressings, the wound had completely healed (*Figure 2c*).

Case 3

A 35-year-old man presented with a scald burn on his left forearm (15 × 7 cm). Pain was moderate to severe with no exudate and an erythematous periwound area (*Figure 3a*). TLC-

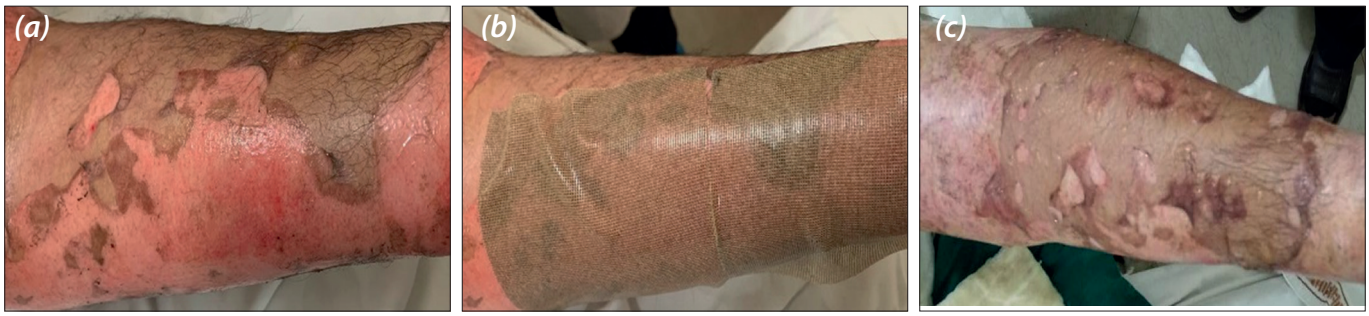

Figure 3. Case 3 at (a) presentation; (b) with TLC-Ag dressing in place; and (c) wound on day 4 at first dressing change.

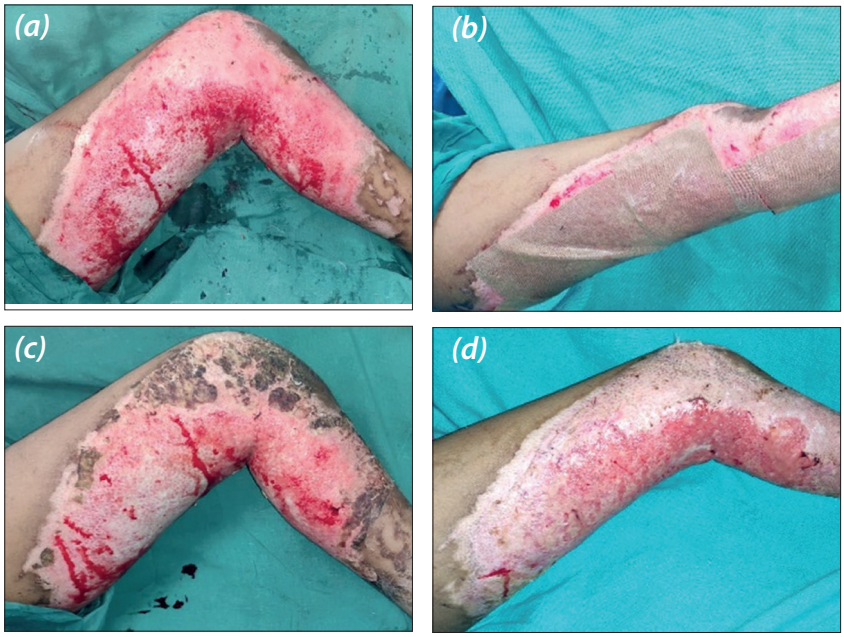

Figure 4. Case 4 at (a) presentation; (b) with TLC-Ag dressing in place; (c) wound on day 4 at first dressing change; and (d) wound on day 5.

Ag was applied after cleaning with normal saline (*Figure 3b*). The dressing was changed on day 4, and the pain and exudate levels had already subsided and the wound bed appeared healthy (*Figure 3c*).

Case 4

A 9-year-old girl presented with a 10-day-old flame burn on the right lower leg (*Figure 4a*), which was initially treated in a local hospital with silver sulphadiazine cream. Pain was moderate to severe, and the wound had minimal exudate with a visibly unhealthy wound bed. TLC-Ag was applied after cleaning with normal saline (*Figure 4b*). The dressing was changed on day 4 (*Figure 4c*). After two dressing changes (day 5), the pain and exudate levels had subsided and the wound bed appeared healthy and granulating (*Figure 4d*).

Case 5

A 30-year-old man presented with an electrical burn on the right forearm (*Figure 5a*). This was initially treated at his local hospital with topical ointments and paraffin gauze dressings for 2 days. Pain was severe and the wound had mild exudate, with sloughy tissue and unhealthy wound bed.

TLC-Ag was applied after cleaning with normal saline (*Figure 5b*). The dressing was changed on day 5. Pain and exudate levels had subsided and the wound bed appeared healthy and granulating. (*Figure 5c*).

Conclusion

The authors have presented five cases of burn wounds in India that were managed by TLC-Ag. These cases showed promising results. However, it is suggested that further cases need to be conducted to suggest policy change to include TLC-Ag in the standard of care in the facilities concerned.

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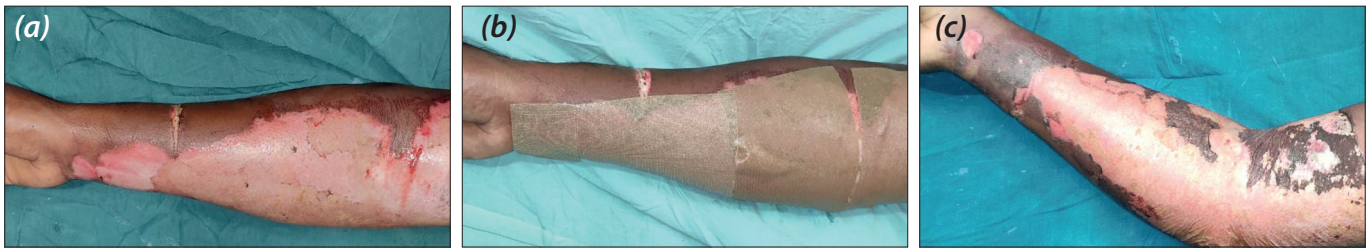

Figure 5. Case 5 at (a) presentation; (b) with TLC-Ag dressing in place; and (c) wound at first dressing change on day 5.

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