MEPILEX® AG IN THE MANAGEMENT OF PARTIAL-THICKNESS BURNS:

A review of the clinical evidence

Wounds INTERNATIONAL

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BURNS AND THE ROLE OF DRESSINGS

OVERVIEW

Burn injuries are the result of direct contact with fire/flame, hot liquids/surfaces, and electrical sources that cause cellular damage to the skin, and chemical agents that damage skin structures (Toussaint and Singer, 2014).

Even as emergency management improves, burns continue to cause significant morbidity and mortality (Warby and Maani, 2019); globally, an estimated 180,000 deaths are caused annually by burns, which occur mainly in the home and workplace (World Health Organisation [WHO], 2018). In 2008, over 410,000 burn injuries were recorded in the United States of America, with approximately 40,000 of the victims requiring hospitalisation (WHO, 2018). In the United Kingdom, there are approximately 13,000 hospitalised burn casualties and 300 deaths annually, with a mortality rate of 2.31% (Page et al, 2017). Additionally, it is estimated that over 10 million individuals suffer from burns every year in China (Zheng et al, 2019).

CATEGORISATION OF BURNS

Burns represent a challenging wound type. They vary significantly in terms of severity, with a wide variety of clinical needs depending on a spectrum of factors such as anatomical location, degree of temperature, duration, surface area and depth (Evans et al, 2010). Burns are generally classified by depth, according to the following categories (Warby and Maani, 2019):

- **Superficial (first-degree):** involves only the epidermis of the skin; appears pink-red, dry but no blisters; typically heals without scarring within 5–10 days
- Partial-thickness
  - **Superficial partial-thickness (second-degree):** involves the superficial dermis; appears red, wet, and with blisters; erythema blanches with pressure; associated with severe pain; typically heals within 3 weeks with minimal scarring
  - **Deep partial-thickness (second-degree):** involves the deeper dermis; appears yellow-white and dry; does not blanch with pressure; associated with minimal pain due to decreased sensation; typically heals between 3–8 weeks with scarring.
- Full thickness (require skin grafting)
  - **Third-degree:** involves the full thickness of the skin and subcutaneous structures; appears white or black/brown, leathery and dry; does not blanch with pressure; associated with minimal to no pain due to decreased sensation; heals by contracture typically taking longer than 8 weeks; requires skin grafting
  - **Fourth-degree:** associated with charred skin with possible exposed bone
  - **Fifth-degree:** associated with charred, white skin and exposed bone
  - **Sixth-degree:** associated with loss of skin and exposed bone.

See **Figure 1** for a representation of the skin layers and how these are affected by burns by category.

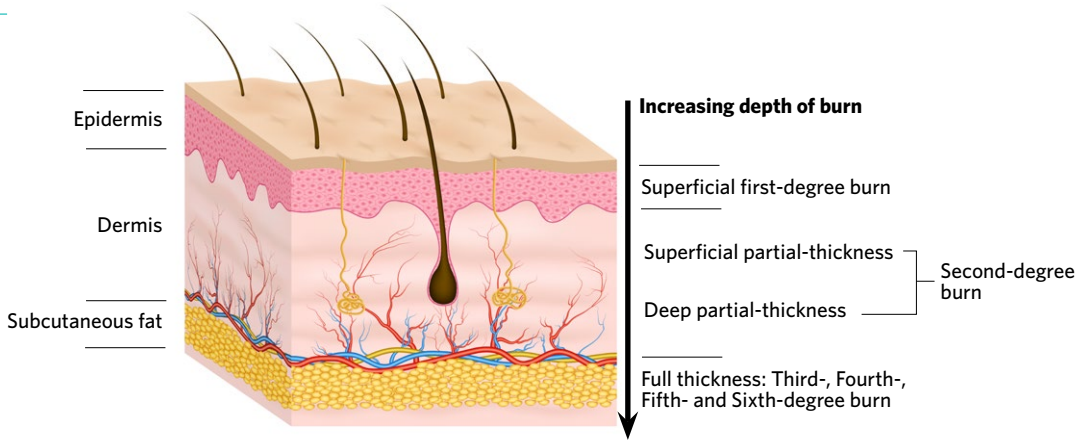

Figure 1 | Burn classifications and their degree of impact on the skin

Box 1 explains what happens when the skin is burned (adapted from Church et al, 2006).

Box 1. What happens when the skin is burned (adapted from Church et al, 2006)

The breached skin barrier is the hallmark of burn injury. The body tries to maintain homeostasis by initiating a process of contraction, retraction, and coagulation of blood vessels immediately after the burn injury.

Local inflammation following injury is essential for wound healing and host defence against infection. Therefore, following thermal injury, the innate immune system responds immediately by stimulating localised and systemic inflammatory reactions.

Significant thermal injury induces a state of immunosuppression that heightens the risk of infection.

When examining a burn, there are four components to consider when assessing depth (Toussaint and Singer, 2014):

- Appearance
- Blanching to pressure
- Pain
- Sensation.

It is important to note that burns may present differently in different skin types and skin tones – for example, much of the evidence in the literature rests largely on observations from individuals with light skin, whereas burns on individuals with dark skin may present differently (Boissin et al, 2015).

CHALLENGES IN BURN MANAGEMENT

While morbidity and mortality rates for severe burns remain high, early burn wound excision and skin grafting are now common clinical practices that have significantly improved the outcomes for people with severe burns. However, slow wound healing, infection, pain, and hypertrophic scarring continue to remain major challenges in burn management (Wang et al, 2018). Partial-thickness burns typically present a number of clinical challenges; these are discussed below.

Infection

Burn wound infections are one of the most important and potentially serious complications that occur in the acute period following injury (Church et al, 2006). Reducing the risk of infection is considered to be the highest priority in burn wound management (Wounds International, 2014).

Individuals with burns are susceptible to acquiring infections; therefore, sustained efforts to maintain infection control and attention to prevention of transmission of pathogenic microorganisms are vital, according to the International Society for Burn Injuries (ISBI) practice guidelines for burn care (ISBI, 2016). It is recognised that early excision of a burn in a specialised burn unit can improve survival and may reduce the risk of sepsis, which is the leading cause of death for people with burns (ISBI, 2016).

Burn wound surfaces are sterile immediately following thermal injury, but rapidly become colonised with microorganisms, as wounds provide an ideal environment for bacterial growth (Erol et al, 2004). Gram-positive bacteria that survive the initial burn (e.g. *staphylococci* located deep within sweat glands and hair follicles) recolonise the wound surface within the first 48 hours of the injury unless topical antimicrobial agents are used. Within 5 to 7 days, the wounds are subsequently colonised with other microorganisms, including other Gram-positive bacteria, Gram-negative bacteria, and yeasts derived from the host's normal gastrointestinal and upper respiratory flora and/or from the hospital environment or that are transferred via a health care worker's hands (Erol et al, 2004).

Studies have confirmed the importance of biofilms in the pathogenesis of burn wound infections; *in vitro* experiments with *Pseudomonas aeruginosa* strains recovered from human burn wounds have demonstrated that mature biofilms can form within approximately 10 hours of injury (Harrison-Balestra, 2003).

If infection develops, it can cause a delay in epidermal maturation and lead to additional scar tissue formation; the delay in healing also increases the risk of further complications developing and can cause increased pain and distress to the individual (Wounds International, 2014).

Excess exudation

Burns are a wound type typically affected by high exudate production (WUWHS, 2019), mostly in the initial phase of wound healing. High exudate production can be associated with wound pain and discomfort, particularly at dressing change, and a predisposition to wound bed trauma and disruption (Dowsett et al, 2012; Wounds UK, 2013).

Other challenges

Wound desiccation, infection, poor patient management and inappropriate wound care can lead to complications (Wounds International, 2014), such as partial-thickness burns developing into full thickness skin loss, resulting in the need for costly surgical intervention and increased risk of morbidity and mortality. The goals of local wound management should therefore include the prevention of desiccation of viable tissue and control of microbial burden through moist wound healing (Wounds International, 2014).

Additionally, there are challenges associated with the role of topical antimicrobials, such as monitoring of antibiotic dosage and duration of therapy (Ray et al, 2019).

The overall aim of burn care is to minimise the adverse effects caused by the injury in terms of maintaining range of movement, minimising contracture development and impact of scarring, maximising functional ability, maximising psychological wellbeing, and maximising social integration (Procter, 2010). The objectives of topical treatment include promoting wound healing, preventing wound infection and graft loss, maintaining movement and function of the affected body part, and achieving timely closure (Wounds UK, 2013; Wounds International, 2014).

ROLE OF TOPICAL ANTIMICROBIALS

'Antimicrobial' is an umbrella term that is used to describe all agents that suppress microorganisms: encompassing disinfectants, antiseptics, and antibiotics (Vowden et al, 2011).

Antimicrobial treatment for burns is important, and most commonly antimicrobial therapy prescribed for people with burns is administered topically. Studies have demonstrated the role of topical antimicrobials in decreasing morbidity and mortality in individuals with burn injuries with partial- or full-thickness skin involvement. Application of an effective topical antimicrobial agent substantially reduces the microbial load on the open burn wound surface and reduces the risk of infection (Church et al, 2006).

Driven by an increase in microbial antibiotic resistance, topical antimicrobials are being increasingly used, as opposed to systemic antibiotics. Antimicrobial resistance (AMR) is a serious and growing problem, which occurs when microorganisms evolve over time and no longer respond to specific antimicrobials, groups of antimicrobials or even to any antimicrobial therapy (Fletcher et al, 2020). Antimicrobial stewardship (AMS) is an approach that uses clinical practices and products that attempt to minimise the possibility of microorganisms developing resistance. All infection management should consider AMS-based approaches to care (Fletcher et al, 2020).

Topical antimicrobials are also increasingly being used alongside systemic antibiotics to provide adjunctive, antimicrobial therapy to wounds that are clinically infected or at risk of infection (Davies et al, 2017).

Topical antimicrobial agents that have broad-spectrum efficacy combined with low potential for systemic absorption and toxicity, thus being suitable as part of an AMS approach, include iodine, zinc, honey, and silver-based preparations and dressings (Vermeulen et al, 2007; Lipsky and Hoey, 2009; Davies et al, 2017).

Silver as a topical antimicrobial

Silver has been used for its antimicrobial properties in many different forms for centuries. Ionised silver has broad-spectrum activity against microorganisms, while not causing toxicity or AMR, therefore is an appropriate topical antimicrobial for use to prevent acute infection in individuals at increased risk, to treat localised wound infection and, in conjunction with systemic antibiotics, to treat local spreading or systemic wound infection (Davies et al, 2017). Silver is recommended as a topical antimicrobial for burns by the International Wound Infection Institute (IWII; 2016). **Box 2** details how silver works.

Box 2. How silver works (adapted from Wounds International, 2012)

In its metallic (elemental) form, silver is unreactive and cannot kill microorganisms. To become active, silver atoms (denoted as Ag or Ag^0) must lose an electron and become positively charged silver ions (Ag+). Elemental silver ionises in air but ionises more readily when exposed to an aqueous environment, such as wound exudate. In contrast, silver compounds contain positive silver ions bound to negatively charged ions or molecules. When exposed to aqueous environments, some of the silver ions become detached from the compound.

Studies of the effects of silver dressings on experimental models of biofilms have suggested that silver may reduce bacterial adhesion and destabilise the biofilm matrix, as well as kill bacteria within the matrix and increase susceptibility of bacteria to antibiotics (if they must be used; Percival et al, 2008; Thorn et al, 2009; Kostenko et al, 2010).

Antimicrobial dressings

Antimicrobial dressings offer many benefits, including the following (Vowden et al, 2011):

- Easy to use
- Widely available
- Often more affordable than antibiotics
- Available without prescription
- Less associated with risk of AMR than antibiotics.

As well as managing bioburden, antimicrobial dressings – impregnated with an antimicrobial agent such as silver – can help to provide an environment that supports wound healing tailored to the individual wound type.

Silver-containing dressings are used on wounds at increased risk of infection, to treat localised wound infection and, in conjunction with systemic antibiotics, to treat local spreading or systemic wound infection (IWII, 2016).

Additionally, in terms of cost-effectiveness, studies have shown that silver-containing dressings are associated with (Wounds International, 2012):

- Reduced healing times
- Shorter hospital stays
- Reduced dressing change frequency
- Reduced need for analgesia during dressing change
- Lower incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria resulting from MRSA-infected wounds.

When selecting an antimicrobial dressing for burns, it is important to ensure that a dressing is selected that does not cause additional trauma to the burn wound and surrounding skin and pain to the patient, as well as reducing the risk of infection. **Box 3** provides characteristics of an ideal dressing for burn management (ISBI, 2016).

Box 3. Characteristics of an ideal dressing for burn management (ISBI, 2016)

- Provides an optimum environment for moist wound healing
- Allows gaseous exchange of oxygen, carbon dioxide and water vapour
- Provides thermal insulation
- Impermeable to microorganisms
- Free from particulate contaminants
- Non-adherent
- Safe to use
- Acceptable to the individual
- High absorption properties
- Cost-effective
- Allows monitoring of the wound
- Provides mechanical protection
- Non-flammable
- Sterile
- Available in all care settings
- Requires infrequent changes
- Ready for use to reduce dressing time.

INTRODUCTION TO MEPILEX® AG

Mepilex® Ag (Mölnlycke) is indicated for use on a variety of different wound types including partial-thickness burns, with low-to-medium exudate levels, where management of infection risk is required. It is a foam dressing impregnated with silver, with a strong evidence base supporting its effectiveness, both in terms of healing and associated cost benefits.

Mepilex® Ag consists of the following components:

- Safetac® (soft silicone) wound contact layer
- Flexible absorbent pad of grey polyurethane foam containing a silver compound and activated carbon
- Outer film, which is vapour-permeable and water-, bacteria- and virus-proof.

Case 1 and 2 show examples of the typical burn wounds on which Mepilex® Ag is used.

CASE 1

A 38-year-old female was admitted to hospital with a second-degree scald burn injury (10% total body surface area [TBSA]) within 17 hours after the injury (**Figure 2**). Surgical debridement was performed at the hospital (**Figure 3**) and Mepilex® Ag was applied as part of the burn treatment regimen. Complete healing was recorded on Day 8 (visit 2; **Figure 4**).

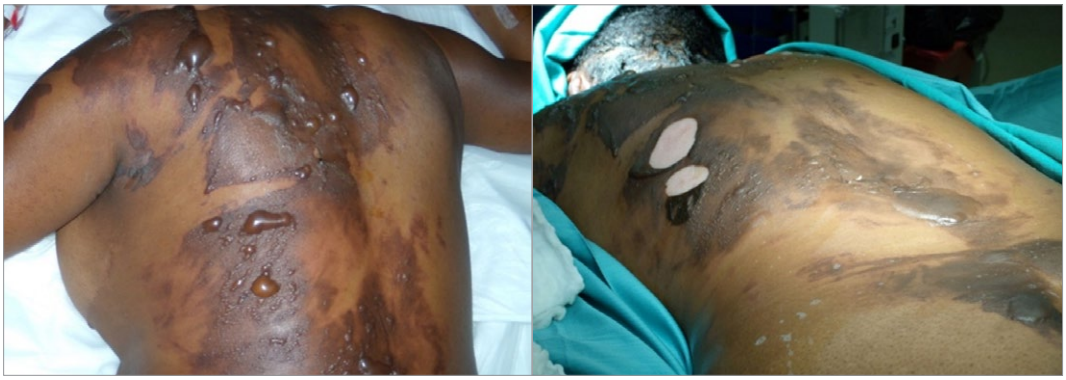

Figure 2 | Baseline visit before surgery

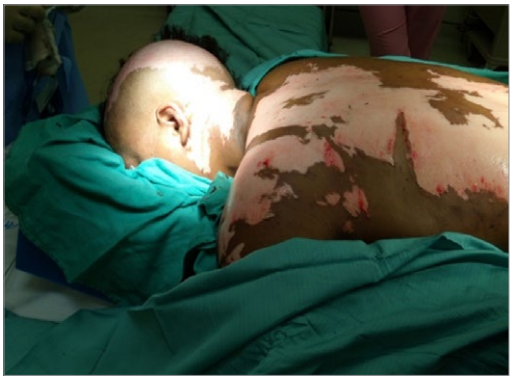

Figure 3 | Baseline visit after surgery

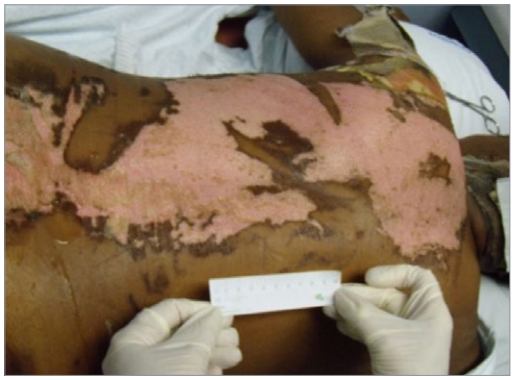

Figure 4 | End of treatment (Day 8)

Acknowledgement: This case study report has been prepared by Mölnlycke, based on information and photographs taken from a Mölnlycke-sponsored clinical investigation (ClinicalTrials.gov identifier: NCT00742183)

CASE 2

A 12-year-old male was admitted to hospital with a second-degree flash burn injury (11.75% TBSA) within 15 hours after the injury (**Figure 5**). Mepilex® Ag was applied as part of the burn treatment regimen. Complete healing was recorded on Day 7 (final visit; **Figure 6**).

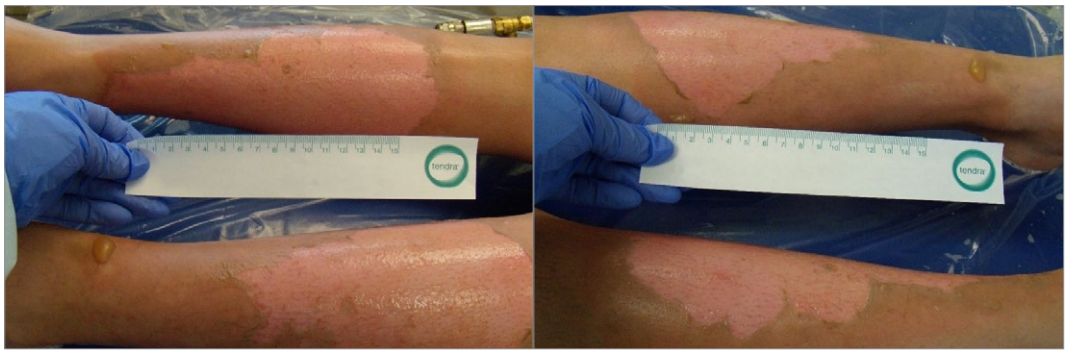

Figure 5 | Baseline visit

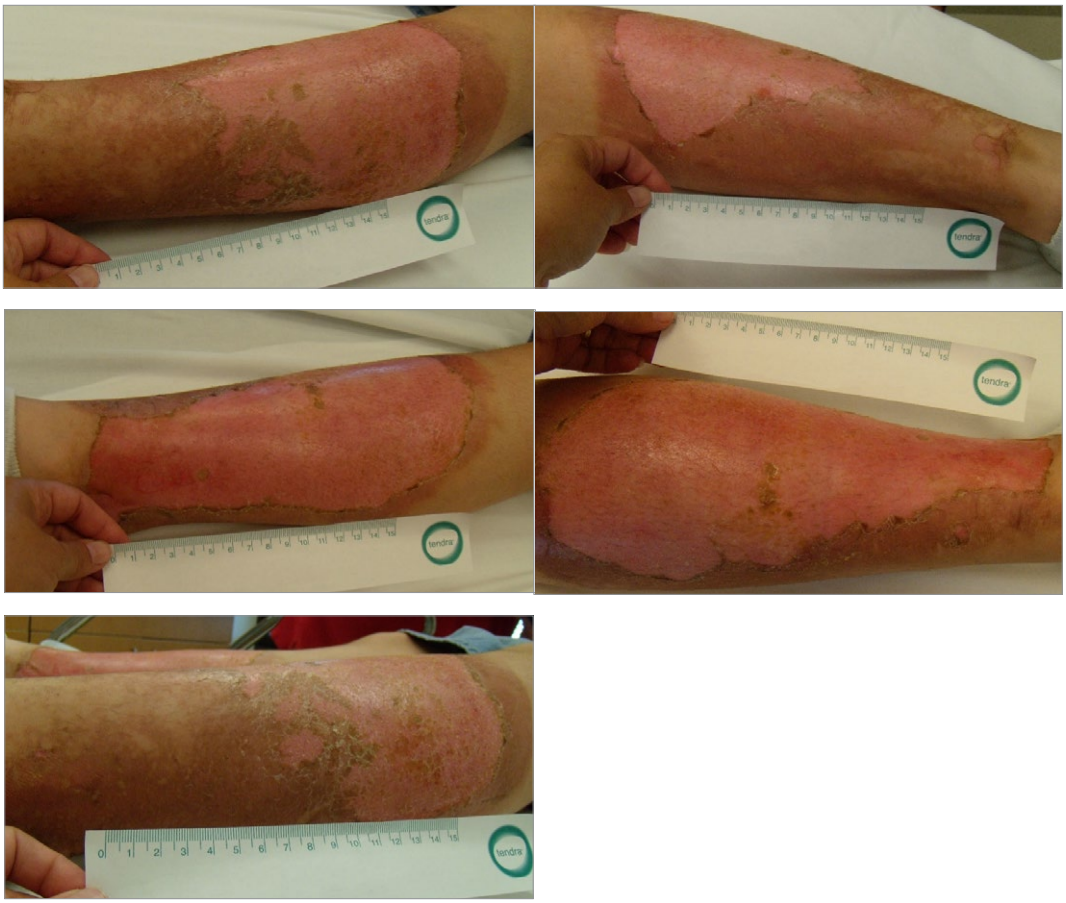

Figure 6 | Complete healing (final visit at Day 7)

Acknowledgement: This case study report has been prepared by Mölnlycke, based on information and photographs taken from a Mölnlycke-sponsored clinical investigation (ClinicalTrials.gov identifier: NCT00742183)

EVIDENCE SUPPORTING USE OF MEPILEX® AG IN BURN MANAGEMENT

Mepilex® Ag has been shown to inactivate a broad range of wound-relevant pathogens (bacteria and fungi) within 30 minutes and to deliver sustained activity for up to 7 days during *in vitro* testing (Chadwick et al, 2009).

The wound contact layer of Mepilex® Ag is based on Safetac® (soft silicone) technology, a material that readily adheres to intact dry skin but remains *in situ* on the surface of a moist wound or damaged surrounding skin without adhering to fragile tissue (Silverstein et al, 2011) – an important consideration when selecting a dressing for burns. Consequently, dressings utilising Safetac technology can be applied and reapplied without damaging the wound or stripping the epidermis of the periwound region (even in critical situations where exudate starts to dry out) and, in doing so, will also minimise pain and psychological stress at dressing change (Zillmer et al, 2006; Woo et al, 2009). The gentle but effective seal that forms between the intact skin and a dressing with Safetac inhibits the movement of exudate from the wound onto the periwound skin, helping to prevent moisture-related damage, such as maceration in this region (Meaume et al, 2003).

Mepilex® Ag is intended for short-term use for up to 4 weeks (for long-term use, a clinical assessment by a physician is recommended). The dressing may be left in place for up to 7 days depending on the condition of the wound and surrounding skin, or as indicated by accepted clinical practice.

RANDOMISED CONTROLLED TRIALS OF MEPILEX® AG IN THE MANAGEMENT OF PARTIAL-THICKNESS BURN WOUNDS

This section reviews the findings of numerous randomised controlled trials (RCTs), the so-called 'gold standard' approach for judging the efficacy of interventions, that have been undertaken to investigate the efficacy of Mepilex® Ag in the management of burn wounds, **Table 1** presents a summary of each RCT. Details of the non-randomised clinical studies that have been carried out to evaluate the performance of Mepilex® Ag in the management of burn wounds are summarised in the Appendix (page 20).

Table 1. RCTs of Mepilex® Ag

Reference	Patient population	Interventions	Key findings
Aggarwala et al (2020)	Partial-thickness burns (*n*=131) of adult patients (*n*=119)	TA1: Biobrane (biosynthetic dressing) TA2: Acticoat TA3: Mepilex Ag TA4: Aquacel Ag	• Shorter re-epithelialisation time (average) with Mepilex Ag (8.9±2.4 days) compared to Biobrane (10.8±2.4 days), Acticoat (9.6±3.2 days), Aquacel Ag (9.6±3.3 days) (ns) • A 26% increase in days to re-epithelialisation with Biobrane compared to Mepilex Ag ($p<0.01$)[1] • A 99%, 71% and 53% probability that Mepilex Ag dominated (cheaper and more effective) Biobrane, Acticoat and Aquacel Ag, respectively.
Karlsson et al (2019)	Partial-thickness scalds of paediatric patients (*n*=58)	TA1: EZ Derm TA2: Mepilex Ag	• Patients treated with Mepilex Ag had a significantly shorter healing time (median time to 97% healing was 9 (7–23) days compared to 15 (9–29) days in the EZ Derm group ($p=0.004$). Median time to complete healing for the Mepilex Ag group was 15 (9–29) days and for the EZ Derm group 20.5 (11–42) days ($p=0.010$) • Pain, wound infection, duration of hospital stay, and the proportion of operations were similar between the groups. Number of dressing changes and time for dressing changes were lower in the Mepilex Ag group ($p=0.03$ for both variables).
Hundeshagen et al (2018)	Partial-thickness burns of paediatric and adult patients (*n*=62)	TA1: Mepilex Ag TA2: Suprathel	• Time to re-epithelialisation was no different between the groups (12 days; $p=0.75$) • Viscoelasticity of burned skin was elevated compared with unburned skin in the Mepilex Ag group at 1-month post burn • The cost of treatment per cm^2 for Mepilex Ag was considerably lower than Suprathel.
Gee Kee et al (2017)	≤10% TBSA partial-thickness burns (*n*=96) of children (0–15 years)	TA1: Acticoat TA2: Acticoat with Mepitel TA3: Mepilex Ag	• Costs (dressing, labour, analgesics, scar management) were considerably lower in the Mepilex Ag group (median AUD$94.45) compared to the Acticoat (median $244.90) and Acticoat with Mepitel (median $196.66) interventions • A 99% and 97% probability that Mepilex Ag dominated (cheaper and more effective than) Acticoat and Acticoat with Mepitel, respectively.
Gee Kee et al (2015)	≤10% TBSA partial-thickness burns (*n*=103) of children (0–15 years)	TA1: Acticoat TA2: Acticoat with Mepitel TA3: Mepilex Ag	• Accelerated wound re-epithelialisation time with Mepilex Ag compared to Acticoat and Acticoat with Mepitel • Decreased pain during dressing changes with Mepilex Ag, compared to Acticoat, for clean, <10% TBSA partial-thickness burns in children.
Tang et al (2015)	Deep partial-thickness thermal burn injuries (2.5–25% TBSA) of patients aged between 5–65 years (*n*=153)	TA1: Mepilex Ag TA2: SSD cream	• No difference in healing rates between the Mepilex Ag group (56 [79%] of 71 patients, median follow-up time of 15 days) and the SSD group (65 [79%] of 82 patients, median follow-up time of 16 days), with both products well tolerated • Patients in the Mepilex Ag group had 87.1% of their study burn healed (out of the total burn area) compared with 85.2% of patients in the SSD group • Mean total number of dressings used was significantly more in the SSD group (14.0) compared with the Mepilex Ag group (3.06, $p<0.0001$).
Silverstein et al (2011)	Partial-thickness thermal burns (2.5–20% TBSA) of patients (*n*=100)	TA1: Mepilex Ag TA2: SSD cream	• The Mepilex Ag group (*n*=49) had shortened mean times to healing ($p=0.097$), reduced hospital stay ($p=0.0346$) and required fewer dressing changes, compared to the SSD group (*n*=51) • Differences in pain intensity, in favour of Mepilex Ag, were noted at application ($p=0.001$), during wear-time ($p=0.003$) and on removal during the initial post-burn period • Mean total cost of therapy/patient was US$296.80 and US$503.89 for the Mepilex Ag and SSD groups, respectively.

[1]. When adjusted for gender, age, smoking status, burn mechanism, TBSA, first aid frequency
TA = treatment arm; ns = not statistically significant; TBSA = total body surface area; SSD = silver sulfadiazine

METHODOLOGIES USED IN RCTS

Table 2 provides a detailed overview of the RCTs that have been undertaken to investigate the efficacy of Mepilex® Ag in the management of burn wounds, in terms of settings, study subjects, methods of randomisation, interventions and outcome measures.

Table 2. Settings, study subjects, randomisation methods, interventions, and outcome measures of RCTs

Reference	Setting/subjects/ randomisation	Interventions	Outcome measures
Aggarwala et al (2020)	**Setting:** Outpatients (specialist burns unit) **Subjects:** Adults aged 18–65 years with partial-thickness burns, presenting within 72 hours of injury **Randomisation method:** Sealed envelopes	• Subjects randomised to one of four treatment arms: biosynthetic dressing (Biobrane, Smith & Nephew); multi-layered dressing containing nanocrystalline silver (Acticoat, Smith & Nephew; silver-containing gelling fibre dressing (Aquacel Ag, ConvaTec); Mepilex Ag. Analgesia was administered prior to management of the wounds. • In the Biobrane, Aquacel Ag and Mepilex Ag arms, blisters were deroofed and the wounds cleansed prior to dressing application. In the Acticoat arm, fluid was removed from the blisters. Dressings were applied according to the manufacturers' instructions. In the Biobrane arms, the dressing was inspected until re-epithelialisation but not changed. In the other arms, dressings were replaced every 3 days until healing had occurred.	• Primary: Time to wound healing (>95% re-epithelialisation) from date of injury • Secondary: Number of outpatient clinic visits, pain, nursing experiences, scar quality and cost-effectiveness.
Karlsson et al (2019)	**Setting:** Specialist burns centre **Subjects:** Children with partial-thickness scalds, presenting within 72 hours of injury **Randomisation method:** Sealed envelopes	• Subjects randomised to either treatment with a porcine xenograft (EZ Derm) or Mepilex Ag. All burn wounds washed with saline before taking swabs on 1cm^2 of the burned skin to assess microbial growth according to the Levine method, at all dressing changes. Mepilex Ag was cut to fit the wound and held in place with a crepe bandage, and an elasticated tubular bandage or age-adapted elasticated cotton garments, or both. The porcine xenograft was cut to fit and applied to the wound, fixed outside the wound edges with a liquid topical skin adhesive and covered with a layer of nylon sheets and several layers of AMD gauze. It was held in place in the same way as Mepilex Ag.	• Primary: Time to wound healing from the date of injury to the date when the wound bed was assessed as 97% re-epithelialised and completely (100%) re-epithelialised • Secondary: Pain, need for operation, wound infection, duration of hospital stay, changes of dressings, and time taken.
Hundeshagen et al (2018)	**Setting:** Outpatients (specialist burns centre) **Subjects:** Paediatric and adults who sustained partial-thickness flame, scald, or contact burn, presenting within 48 hours of injury **Randomisation method:** Computerised algorithm	• Subjects randomised to either Mepilex Ag or a synthetic dressing (Suprathel). Mepilex Ag was cut to size and held in place with woven gauze and secured with elastic bandage. Suprathel was cut to size and applied to the wound as a monolayer, covered with a monolayer of petrolatum gauze, held in place with woven gauze, and wrapped with elastic bandage. • All patients were discharged into the outpatient setting within 24 hours of their admission and scheduled for regular follow-up visits every 3 to 7 days according to the standard protocol of care.	• Time to re-epithelialisation, wound pain, discomfort during dressing changes, and treatment cost.

TBSA = total body surface area; QALY = quality-adjusted life year; SSD = silver sulfadiazine

Table 2. Settings, study subjects, randomisation methods, interventions, and outcome measures of RCTs *(continued)*

Reference	Setting/subjects/ randomisation	Interventions	Outcome measures
Gee Kee et al (2017)	**Setting:** Emergency department; paediatric burns centre **Subjects:** Children aged 0–15 years with an acute partial-thickness (superficial partial to deep partial-thickness inclusive) burn and a burn TBSA of 10%, presenting within the first 72 hours of injury **Randomisation method:** Not stated	• Costs directly related to the management of the burn wounds were collected during the trial and for 1 year after re-epithelialisation. Incremental cost effectiveness ratios were estimated; dominance probabilities were calculated from bootstrap resampling trial data. Sensitivity analyses were conducted to examine the potential effect of accounting for infrequent but high-cost skin grafting surgical procedures.	• Cost-effectiveness.
Gee Kee et al (2015)		• Subjects randomised to one of three treatment arms: Acticoat; Acticoat with Mepitel; or Mepilex Ag dressings. All participants in the study had their dressings changed every 3–5 days until full re-epithelialisation of the wound occurred or grafting of the wound was undertaken. • At each dressing change appointment, measures of re-epithelialisation, pain and distress were taken (i) before and after dressing removal and (ii) before and after application of the new dressing.	• Primary: Time to re-epithelialisation and measures of pain • Secondary: Nursing staff's views of the dressings, patients' physical function while wearing the dressing, ease of application and removal, nursing time taken, amount and size of dressings used, and other resources utilised.
Tang et al (2015)	**Setting:** Specialist burns centres **Subjects:** Individuals aged between 5–65 years with deep partial-thickness thermal burn injuries (2.5–25% TBSA) **Randomisation method:** Block design	• Subjects randomised to either the SSD group or the Mepilex Ag group. Burns were debrided and/or cleansed according to standard practice, and the periwound skin dried thoroughly. SSD 1% cream was applied from 40g tubes in accordance with the manufacturer's instructions. Mepilex Ag was applied in accordance with the manufacturer's instructions and where necessary was cut to enable conformity to body contours. Gauze pad and wrap was used as a secondary dressing to ensure fixation. Dressing changes were performed every 5 days to 7 days, depending on the status of the wound. • Erythema, oedema, warmth, odour, presence of blistering, exudate level, nature of exudate, condition of surrounding skin, and clinical signs of local secondary infection were monitored at all assessments.	• Primary: Time to wound healing (defined as 95% epithelialisation by visual inspection) • Secondary: Percentage of burns epithelialised/healed, numbers of burns healed or not at each visit (not at baseline), number of study burns requiring a skin graft, number of dressing changes, tolerability and performance of the dressings on wound and periwound status, including pain and experience of use of the dressings.
Silverstein et al (2011)	**Setting:** Specialist burns centres **Subjects:** Individuals aged 5 years and older with partial-thickness thermal burns (2.5–20% TBSA) **Randomisation method:** Sealed envelopes	• Subjects randomised to either Mepilex Ag or an SSD cream (control) for 21 days or until healed, whichever occurred first. • Data collection took place at initiation (<36 hours post-burn) and at assessment days 7, 14, 21, with follow-up at day 35, when wound assessment and pain measurements were undertaken. The CBO questionnaire, SF-36 health survey and EQ-5D health utilities measurement were used to assess consequences of burns, quality of life and QALY analysis.	• Cost (direct and indirect), healing rates, pain, comfort, ease of product use, and adverse events.

TBSA = total body surface area; QALY = quality-adjusted life year; SSD = silver sulfadiazine

OUTCOMES REPORTED IN RCTS

Healing/time to healing

The ideal treatment outcome for burn wounds includes faster healing/re-epithelialisation. Wound healing is a complex biological process that results in the restoration of tissue integrity (Young and McNaught, 2011). To fully restore epidermal barrier function, a wound requires regeneration of the epidermis through wound re-epithelialisation (Sivamani et al, 2007); this is the final stage of wound healing.

In a number of the RCTs described above, healing time was found to be significantly shorter in groups receiving Mepilex® Ag, compared to those receiving other interventions. For example, Aggarwala et al (2020) demonstrated that Mepilex® Ag seemed the most effective dressing in terms of re-epithelialisation time. The average time to re-epithelialisation for Mepilex® Ag was 8.9±2.4 days, compared to 9.6±3.3, 9.6±3.2 and 10.8±2.4 days for a silver-containing hydrofiber dressing (Aquacel Ag), a nanocrystalline silver-containing absorbent dressing (Acticoat) and a biosynthetic dressing (Biobrane), respectively (difference not significant). Similarly, Gee Kee et al (2015) observed that burns treated with Mepilex® Ag were found to have the quickest time to re-epithelialisation (median 7.0 days), with the comparator dressing regimens (both including Acticoat) associated with significantly increased expected days to full re-epithelialisation by up to 40% (95% confidence interval [CI]: 1.14–1.73, $p<0.01$).

Individuals treated with Mepilex® Ag had a significantly shorter healing time in the RCT described by Karlsson et al (2019). The median time to 97% healing for this group was 9 (7–23) days compared to 15 (9–29) days in the porcine xenograft group ($p=0.004$). Furthermore, the median time to complete healing in the Mepilex® Ag group was 15 (9–29) days, compared to 20.5 (11–42) days in the porcine xenograft group ($p=0.010$) (Karlsson et al, 2019).

Silverstein et al (2011) reported that the Mepilex® Ag group ($n=49$) had shortened mean times to healing compared to the silver sulfadiazine (SSD) group ($p=0.097$) (i.e. an average healing time of 13.44 days for the Mepilex® Ag group versus 17.11 days for the SSD group), plus reduced hospital stay ($p=0.0346$) and required fewer dressing changes, compared to the SSD group ($n=51$) (Silverstein et al, 2011). In another RCT, the number of healed burns was significantly greater in the Mepilex® Ag group ($n=13$, 18%) compared with the SSD group ($n=4$, 5%; $p=0.016$) at week 1, as was the mean percentage of healed burns: Mepilex® Ag group, 44.3% versus SSD group, 27.0% ($p=0.0092$).

However, by week 4, patients in the Mepilex® Ag group had 87.1% of their burns healed (out of the total burn area) compared with 85.2% in the SSD group (difference not significant) (Tang et al, 2015). Hundeshagen et al (2018) detected no statistically significant differences in healing time between treatment arms. In the Mepilex® Ag group, viscoelasticity (e.g. stiffness) of burned skin was elevated compared with baseline (unburned skin) at 1-month post-burn ($p=0.004$).

Pain assessment

Managing the pain of burn wounds is a significant factor as failure to control direct pain can cause individuals immediate suffering following a burn; they may take longer to recover, and chronic pain is more likely to develop (Judkins and Clark, 2010). Several RCTs have observed significantly lower pain severity scores in individuals receiving Mepilex® Ag, relative to the comparator dressing regimens.

Differences in pain intensity, in favour of Mepilex® Ag compared to the SSD group, were noted by Silverstein et al (2011) at application, ($p=0.001$) during wear-time ($p=0.003$) and on removal during the initial post-burn period. The trend in pain reduction at dressing change was supported by a significant difference in average weekly costs of pain medication ($p=0.031$). Background pain analgesia was significantly lower ($p=0.078$) in the Mepilex® Ag group compared to the SSD group (Silverstein et al, 2011).

Tang et al (2015) found that, by week 1, there was a significant difference in the mean visual analogue scale (VAS) score in terms of pain before dressing removal in the Mepilex® Ag group (11.7) compared with the SSD group (23.9, $p=0.0001$). There were also significant differences in mean pain scores during dressing removal (Mepilex® Ag at 19.4 compared with SSD at 40.1) and for mean pain scores after dressing removal (Mepilex® Ag at 17.3 compared with SSD at 44.3, $p=0.0001$). At the final follow-up assessment, patients

in the Mepilex® Ag group had a significantly lower mean VAS pain score of 6.8 before dressing removal compared with a mean of 11.0 in the SSD group (p=0.0081; Tang et al, 2015). Similarly, Gee Kee et al (2015) observed lower pain scores in patients receiving Mepilex® Ag compared to those receiving the comparator dressing regimens.

Karlsson et al (2019) discovered that pain was similar across both treatment groups. Consistently low pain scores were given on the Face, Legs, Activity, Cry, Consolability (FLACC) scale before, during, and after dressing changes, which indicated that both dressings were capable of minimising pain. Aggarwala et al (2020) also found no statistically significant differences in pain scores between treatment groups.

Receiving the Mepilex® Ag dressing significantly decreased the expected Visual Analog Scale-Pain (VAS-P) score after dressing removal by up to 25% (p=0.04) in the RCT described by Gee Kee et al (2015). Expected FLACC scores in the Mepilex® Ag group were 32% lower at dressing removal (p=0.01) and 37% lower at new dressing application (p=0.04; Gee Kee et al, 2015).

Infection

Infection rates were zero to low across most of the reported studies and groups. Hundeshagen et al (2018) confirmed wound infection in 2 patients (8%) in the Suprathel group, with none observed in the Mepilex® Ag group (p=0.5). In the study described by Tang et al (2015), 4 patients (6%) in the Mepilex® Ag group experienced five adverse events compared with 7 patients (9%) in the SSD group experiencing seven adverse events. The adverse events in the Mepilex® Ag group included two cases of *P. aeruginosa* infection and one case of MRSA infection (the other reported events were one case of fever and one case of insomnia). In the SSD group, there were three cases of hypoproteinaemia, one case of upper respiratory tract infection, one case of neurogenic shock, one case of fever, and one case of irritability (Tang et al, 2015).

Karlsson et al (2019) diagnosed infection in 9 children in the porcine xenograft group and 10 in the Mepilex® Ag group. The most common bacteria found in the wound swabs within the first week after injury was *Staphylococcus aureus*, which was found in 86% of all swabs (50/58). Antibiotics were prescribed for 11 children in the porcine xenograft group and 12 in the Mepilex® Ag group. The reasons for antibiotic treatment, other than wound infection, were upper airway infection (n=1), pneumonia (n=1), prophylaxis (n=1), and group A *streptococcus* (n=1) (clinical routine to treat).

Scar outcome

Scar outcomes can range in size, colour, contour, and visibility. The quality of a scar can affect patients both physically and psychologically; patients may avoid engagement in daily activities and develop feelings of self-consciousness or embarrassment. The choice of burn dressing should therefore help to reduce the possibility of scarring.

In a follow-up study, Gee Kee et al (2016) monitored patients who had participated in their RCT (Gee Kee et al, 2015) at 3 and 6 months to investigate outcomes regarding scarring. The study found:

- Dressing type was identified as having a significant effect on the Patient and Observer Scar Assessment Scale (POSAS) scores
- Days to re-epithelialisation was a significant predictor of skin/scar quality at 3 and 6 months (p<0.01)
- Patient-rated colour and observer-rated vascularity and pigmentation POSAS scores were comparable at 3 months (colour versus vascularity 0.88, p<0.001; colour versus pigmentation 0.64, p<0.001), but patients scored higher than the observer at 6 months (colour versus vascularity 0.57, p<0.05; colour versus pigmentation 0.15, p=0.60)
- Burn depth was significantly correlated with skin thickness (r=0.51, p<0.01)
- Hypopigmentation of the burn site was present in 25.8% of children who re-epithelialised in ≤2 weeks.

Scar quality was determined by Aggarwala et al (2020) through a telephone follow-up call with every patient who was successfully enrolled and had complete data until >95% epithelialisation. In patients where 3- and 6-month follow-up was possible, Mepilex® Ag showed the second-lowest mean Vancouver Scar Scale (VSS) scores at 3 months (1.10 [1.20]) and lowest at 6 months (0.63[0.74]), thus showing the best overall outcomes for scarring (Aggarwala et al, 2020).

Cost-effectiveness

An economic analysis of the study that compared four dressing types on partial-thickness burn wounds of adult patients demonstrated that there was a 99%, 71% and 53% probability that Mepilex® Ag dominated Biobrane, Acticoat and Aquacel Ag, respectively (i.e. Mepilex® Ag was found to be the overall most cost-effective dressing; Aggarwala et al, 2020).

Gee Kee et al (2017) conducted a cost-effectiveness analysis of the data generated from their RCT (Gee Kee et al, 2015). They identified that costs (dressing, labour, analgesics, scar management) were considerably lower in the Mepilex® Ag group (median AUD$94.45) compared to the Acticoat (median AUD$244.90) and Acticoat with Mepitel® (median AUD$196.66) dressing regimens. There was a 99% and 97% probability that Mepilex® Ag dominated (cheaper and more effective than) Acticoat and Acticoat with Mepitel®, respectively. This pattern was consistent across raw cost and effects, after a priori adjustments, and sensitivity analyses. Similarly, Hundeshagen et al (2018) reported the cost of treatment per cm^2 for Mepilex® Ag was considerably lower than that of the comparator dressing.

The mean total cost of wound management per patient was calculated by Silverstein et al (2011) at US$309.31 for the Mepilex® Ag group and US$513.57 for the SSD group (p=0.000). Within this study, the average cost-effectiveness in each group was calculated by determining total cost of in-clinic treatment and then dividing this by the rate of full re-epithelialisation at 20 days. For the Mepilex® Ag group, the average cost-effectiveness per burn healed was US$395.03 and US$775.79 for the SSD group. Therefore, the net savings per burn healed was US$380.76, with a protocol of care using Mepilex® Ag instead of SSD. The incremental cost-effectiveness ratio was calculated to be -$1,688; 10 in favour of the Mepilex® Ag protocol (Silverstein et al, 2011).

Patient and clinician perspectives

In their RCT, Aggarwala et al (2020) observed that Mepilex® Ag was one of the two dressings reporting by nursing staff as being significantly easier to apply and remove, and easier to use overall (Aggarwala et al, 2020).

Cumulative dressing removal and application time at the first dressing change observed by Gee Kee et al (2015) was significantly faster in the Mepilex® Ag group (5:03 min, IQR 2:48–7:53 min) compared to both comparator dressing regimens. Nursing staff generally rated Mepilex® Ag as 'extremely easy' to 'very easy' to apply and remove. Mepilex® Ag dressings were also reported to be the easiest to remove from both hands or feet and flat surfaces. However, Mepilex® Ag was observed to be the hardest to apply to the hands or feet of very young children (under the age of 3 years) due to it being the thickest of the three dressings evaluated in the study and difficult to conform to very small fingers and toes (Gee Kee et al, 2015). There was no significant difference between the treatment groups regarding physical function when wearing the dressings (Gee Kee et al, 2015).

In another RCT, clinicians considered the ease of use of Mepilex® Ag to be superior (rated 95.6% extremely well or very well) compared to SSD (78.4% [p=0.028]) and flexibility (rated 97.8% extremely well or very well, compared to 74.6% [p=0.038]). The mean number of dressing applications undertaken in the first week following injury was 1.54 in the Mepilex® Ag group and 6.82 in the SSD group (Silverstein et al, 2011). The number of dressing changes and time spent by staff on dressing changes were reported to be significantly less in children who received Mepilex® Ag dressings, compared to those who received a porcine xenograft (p=0.03 for both variables; Karlsson et al, 2019).

Similarly, Tang et al (2015) observed that significantly fewer dressings were required for patients in the Mepilex® Ag group (p=0.0001). The mean total number of dressing changes for Mepilex® Ag was 3.06 compared with 14.0 for the SSD group. The mean number of dressing changes per week was 1.36 for the Mepilex® Ag group compared with 5.67 for the SSD group (Tang et al, 2015).

Tang et al (2015) also noted that the responses for 'ease of application of the dressing' significantly favoured Mepilex® Ag at the first dressing application (96% compared with SSD at 76%, p=0.0001) and at every subsequent application. Responses for 'adherence of the dressing' also significantly favoured

Mepilex® Ag by the second dressing application (85% compared with SSD at 68%, p=0.0003) and at all subsequent dressing changes. 'Ease of removal of the dressing' significantly favoured Mepilex® Ag from the first dressing removal (93% compared with 59%, p=0.0001) and at all subsequent dressing removals. Responses for 'overall experience of use of the dressing' were also significantly in favour of Mepilex® Ag, from the first dressing removal (96% compared with SSD at 49%, p=0.0001) until the final dressing removal at the end of week 4 (Mepilex® Ag at 99% compared with SSD at 59%, p=0.0001; Tang et al, 2015).

Additionally, patient evaluations of the dressings were all significantly in favour of Mepilex® Ag compared with SSD in terms of 'good' or 'very good' responses (p=0.0001 for all responses). These included parameters such as anxiety during dressing change, ease of movement, dressing remaining in place, and stinging and burning while wearing the dressing (Tang et al, 2015).

Karlsson et al (2019) discussed that it was possible that the fast healing seen in the Mepilex® Ag group could be related to properties of the dressing, other than that associated with its silver component, such as the control of exudate, and the avoidance of minor disturbances of the wound bed due to its Safetac® wound contact surface.

CONCLUSION

It is well recognised that burns represent a challenging wound type, and as estimated by the WHO (2018), the burden is continuing to rise with an estimated total of 180,000 deaths per year globally. As previously mentioned, the objectives of topical treatment include promoting wound healing, preventing wound infection and graft loss, maintaining movement and function of the affected body part, and achieving timely closure (Wounds UK, 2013; Wounds International, 2014).

Silver-containing wound dressings have been designed to treat a variety of different wound types, including partial-thickness burns with low-to-medium exudate levels. These dressings prevent additional trauma to the burn wound and surrounding skin and pain to the patient and help to reduce the risk of infection. The clinical evidence summarised in this document highlights the efficacy and performance of Mepilex® Ag in helping clinicians to achieve the goals of care. In the majority of these studies, Mepilex® Ag was associated with faster times to healing/re-epithelialisation, reduced pain, fewer dressing changes and faster dressing change time, significant and measurable cost-savings, savings of other resources (e.g. analgesics due to reduced pain and reduced staff time), overall ease of use, and patient and clinician satisfaction, compared to the comparator dressing regimens utilised in the studies.

Mepilex® Ag has been widely studied and results demonstrate the dressing's consistent ability to perform well versus a variety of other wound care products, such as silver-containing topical preparations, silver-containing dressings, and semi-biological dressings, when used for the management of partial-thickness burns, in both adults and children.

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APPENDIX

Appendix: Additional clinical studies of Mepilex® Ag for burn wounds			
Reference	**Design and methodology**	**Main outcome measures**	**Main results**
Zens et al (2018)	Interventional (historical control) Specialist burns centre Paediatric (≤10 years) patients (*n*=219) with burn injuries (TBSA ≤15%) **TA1:** Mepilex Ag (*n*=142) **TA2:** Bacitracin with petroleum-impregnated gauze (historical control) (*n*=77)	• Length of hospital stay • Dressing usage • Complications.	• TA1 associated with shorter inpatient length of stay than TA2: 2.93 days vs 5.21 days ($p<0.001$) • TA1 associated with fewer dressing changes than TA2: 2.32 vs 4.71 ($p<0.001$) • No significant differences between TAs regarding readmission rates ($p=0.375$) and number of burns requiring grafting ($p=0.155$) • Fewer patients in TA1 had infectious complications ($p=0.054$) or required reoperation in 2-year follow-up period ($p=0.081$), but differences not statistically significant.
Gee Kee et al (2016)	Observational; prospective Specialist burns centre Sub-group (*n*=43) of paediatric patients (median age = 1 year (IQR 1-6 years) (*n*=43) with partial thickness injuries (< 72 hours post burn; TBSA < 10%) who participated in RCT[a] and were randomised to 1 of 3 TAs (up to 14 days) **TA1:** Acticoat **TA2:** Acticoat with Mepitel **TA3:** Mepilex Ag	• Assessment at 3 and 6 months after re-epithelialisation: • Scar quality (vascularity/ pigmentation; POSAS) • Skin thickness (ultrasonography).	• Sample size too small to compare TAs • Days to re-epithelialisation was significant predictor of skin/scar quality at 3 and 6 months ($p<0.01$) • Patient- and observer-related vascularity / pigmentation POSAS scores comparable at 3 months (colour vs vascularity 0.88, $p<0.001$; colour vs pigmentation 0.64, $p<0.001$); patients scored higher than observer at 6 months (colour vs vascularity 0.57, $p<0.05$; colour vs pigmentation 0.15, $p=0.60$) • Burn depth significantly correlated with skin thickness ($r=0.51$; $p<0.01$) • Hypopigmentation of burn site present in 25.8% of patients who re-epithelialised in ≤2 weeks.
Glat et al (2015; also reports observational, retrospective study – see below)	Observational, prospective Specialist burns centre Paediatric (1–4 years) patients (*n*=22) with partial-thickness injuries **Treatment:** Mepilex Ag **Treatment duration:** Not stated	• Length of hospital stay • Time to healing (complete epithelialisation) • Dressing usage • Pain severity (Wong-Baker faces scale).	• Mean time to discharge: 3.77 days • 11 (50%) completely healed at first visit (7 days after baseline). Complete healing by visit 4 for all 20 patients completing investigation (partial healing for 2 patients not completing investigation) • Mean number of dressing changes: 1.64 • Occurrence of 'stinging' or 'burning' reported as 'never', 'rarely' and 'sometimes' in 13 (65%), 8 (40%) and 1 (5%) of patients, respectively.
Glat et al (2015; also reports observational, prospective study – see above)	Observational, retrospective Specialist burns centre Paediatric (< 18 years) patients (inpatients, *n*=60; outpatients, *n*=43) with partial thickness injuries (< 24 hours post burn; TBSA 1-40%) **Treatment:** Mepilex Ag **Treatment duration:** Not stated	• Length of hospital stay • Analgesia usage • Time to healing (complete epithelialisation.	• Mean length of inpatient stay (days): 1.9±2.2 (range: 0-11; median: 1) post-burn, and 0.5±0.9 (range: 0-5; median: 0) post-dressing application [Shorter length of stay than historical control] • Mean number of IV narcotic administrations in inpatient group: 2.6±3.6 [less analgesia required than historical control] • Mean healing time (days): • Inpatient group; 9.3±4.9 (median: 7.5) post burn, 7.9±4.9 (median: 6) post dressing application • Outpatient group: 9.8±3.0 (median: 9) post burn, 7.1±2.4 (median: 7) post-dressing application.

DBSA = deep burn surface area; IQR = interquartile range; IV = intravenous; POSAS = Patient and Observer Scar Assessment Scale; RCT = randomised controlled trial; TA = treatment arm; TBSA = total body surface area; VAS = visual analogue scale)

Reference: a) Gee Kee EL, Kimble RM, Cuttle L et al (2015) Randomized controlled trial of three burns dressings for partial thickness burns in children. *Burns* 41(5): 946-55

Appendix: Additional clinical studies of Mepilex® Ag for burn wounds *(continued)*			
Reference	**Design and methodology**	**Main outcome measures**	**Main results**
Trouchetet et al (2012)	Observational, prospective Community care Patients (mean age: 69.0±15.4 years) (*n*=794) with variety of chronic/ acute wounds, including 60 partial-thickness burns **Treatment:** Mepilex Ag **Treatment duration:** until follow-up (median: 19 days; range 7–97 days)	• Wound condition • Clinical signs of localised infection (10 signs) • Periwound condition • Pain severity (VAS).	• At follow-up, wound had healed in 17% of patients (35% of acute wounds), improved in 73% of patients (61% of acute wounds) • Compared with baseline, number of signs of localised infection decreased by 2.3±1.5 (p<0.001) and by 2.6±1.5 (p<0.001) for acute wounds • Wound malodour noted in only 1% of patients • Compared to baseline, peri-wound skin was less frequently erythematous (52% vs 74%) • Mean VAS pain score at follow-up visit (on a scale from 0-100): 24.6±20.9.
Budkevich et al (2010)	Observational; prospective Acute care (burns department) Paediatric (8 months–3 years) patients (*n*=20) with thermal burns (grade I-II-IIIA-IIIAB); TBSA 2-30% (DBSA ≤1%) **Treatment:** Mepilex Ag **Treatment duration:** Not stated	• Time to healing • Pain at dressing change • Dressing change frequency.	• Complete healing achieved by day 8-9 for burn wounds grade I-II-IIIA (TBSA up to 8%), and by day 11 for burn wounds grade III AB (TBSA 1-2%) • Minimal pain at dressing changes (no additional analgesia required) • Mepilex Ag could be left on burn wounds grade I-II-IIIA without dressing changes for up to 48 hours, resulting in 2-fold decrease in dressing change frequency.
Meites et al (2008)	Observational, prospective Specialist burns centre Patients (aged not specified) (*n*=18) with partial-thickness injuries; mean TBSA 7.2% (range: 1–18%) **Treatment:** Mepilex Ag **Treatment duration:** Not stated	• Burn condition • In-use characteristics • Patient mobility.	• Mepilex Ag provided antimicrobial protection, leaving burns with clean appearance • No dressing adherence: an opportunity for clinicians to examine burns or leave dressings *in situ* for up to 7 days • All patients able to perform range of motion exercises throughout treatment period.
Meuleneire (2008)	Observational, prospective Specialist wound care centre Patients (median age: 74 years; range 29–91 years (*n*=30 with variety of different acute/chronic wounds with signs of localised infection (not requiring antibiotics), including 4 burn injuries (TBSA: not stated) **Treatment:** Mepilex Ag **Treatment duration:** Up to 28 days	• Clinical signs of localised infection • Healing response (visual assessment) • Pain severity (VAS) • In-use characteristics.	• Clinical signs of localised infection eradicated in 90% of wounds • Proportion of wounds healed or almost healed at end of treatment period was 53% and 27%, respectively • Pain severity (ongoing and at dressing change) was lower at the first and final dressing changes, relative to baseline (p<0.0001) • Mepilex Ag rated as 'excellent'/'very good' in 77% of investigator's evaluations and 82% of patients' evaluations.

DBSA = deep burn surface area; IQR = interquartile range; IV = intravenous; POSAS = Patient and Observer Scar Assessment Scale; RCT = randomised controlled trial; TA = treatment arm; TBSA = total body surface area; VAS = visual analogue scale)

Reference: a) Gee Kee EL, Kimble RM, Cuttle L et al (2015) Randomized controlled trial of three burns dressings for partial thickness burns in children. *Burns* 41(5): 946-55

Appendix references

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