Clinical evaluation of UrgoClean Ag (poly-absorbent dressing based on technology lipido-colloid with silver ions) in the management of infected wounds in Asia

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Wound infections, including biofilms play a significant role in delaying wound healing and are considered to be one of the major challenges in wound management. The presence of non-viable tissue, such as slough, is a prominent feature of chronic wounds and is considered as a barrier against successful wound healing. A key component in wound care is to integrate in our care evidence-based dressings that provides continuous cleaning, antimicrobial activity and which are also effective against biofilms. UrgoClean Ag is a dressing composed of cohesive poly-absorbent fibres impregnated with a silver lipido-colloid matrix (Technology Lipido-Coloid-Ag healing matrix [TLC-Ag]) that has shown very good results in clinical trials, including a prospective, multicentre, non-comparative clinical trial, but also large scale observational studies. In this article, we attempt to replicate the results obtained in Europe in patients from different countries in the Asian Continent by means of a case series.

One of the main functions of the skin is to provide an effective barrier to an organism from the environment and is the first line of defence to external influences (Vlahovic, 2020). When a wound is present, causing a break in the protective surface, a portal of entry to microorganisms is created, causing imminent vulnerability of the subcutaneous and deeper tissues which are now exposed to potential harm from these microorganisms and pathogenic organisms are able to invade the viable tissue surrounding the wound (Warriner and Burrell, 2005). Microorganisms that are found on the skin have an effect on wounds, they can become hard-to-heal and are mostly prevalent in elderly populations and diabetics. For example, the role of microorganisms has been well studied in diabetic foot ulcers (DFU), where it is estimated that over 50% of DFUs are infected (Byrd et al, 2018). After exposure of the subcutaneous tissue from wounding, the moist, warm and nutrient-rich environment exposed is conducive to microbial colonisation and proliferation (Gottrup et al, 2013).

It is important to detect wound infection at an early stage; moreover, it is important to treat it promptly as wound infections may lead to delayed healing, systemic infection with a higher risk of severe sepsis, which may lead to potentially life-threatening complications. Even more so, wound infection has a detrimental effect on the patients' health-related quality of life (HRQoL), as well as increases in the economic burden in relation to wound management (Dissemond et al, 2020a).

Wound infection

Generally, intervention is required to assist the host defences to fight the invading microorganisms that will cause tissue damage and impedance of wound healing (Eberlein and Assadian, 2010). In order to deliver effective wound infection management, the clinician's goal requires a holistic approach and continuous assessment to optimise the host's defence to fight potential pathogens and reduce the microbial load (Swanson et al, 2016).

Antibiotics, such as quinolones, tetracyclines,

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aminoglycosides and cephalosporins, have been used in wound management. However, it was found that about 70% of bacteria which cause wound infections are resistant to at least one of the most commonly used antibiotics (Friedman et al, 2016). Additionally, infectious strains have acquired resistance to most classes of antibiotic, which has led to the need of finding new methods of succeed in overcoming infections in wounds (Negut et al, 2018). Use of non-antibiotic antimicrobials has shown benefits in wound infection management as a small amount at the site of infection can achieve a good outcome, while avoiding systemic adverse effects and resistance (Lipsky et al, 2016). Moreover, antibiotics that require systemic administration, may have disadvantages such as minimal delivery due to poor circulation, while antimicrobials require lower amounts to be applied to have beneficial effects on the wound, and many antiseptics are much more effective with fewer side-effects than local antibiotics (Sarheed et al, 2016; Kramer et al, 2018). Furthermore, in a position paper from the British Society for Antimicrobial Chemotherapy (BSAC) and European Wound Management Association (EWMA), it was stated that:

> *"We advise avoiding using antibiotics (as opposed to antiseptics) topically for treating wound infections as there is limited evidence of their effectiveness and they often select for resistant colonising bacteria. Furthermore, topical treatment may cause periwound skin irritation, rash, eczema or impairment of wound healing"* (Lipsky et al, 2016).

However, clinicians have to be careful in choosing an appropriate topical antimicrobial as some may hinder the wound healing process (Gottrup et al, 2013; Lipsky et al, 2016). Certain antiseptic dressings, such as povidone iodine and chlorhexidine often show dose-dependent cytotoxicity to the host cells including keratinocytes, fibroblasts, and leukocytes (Mirhadi et al, 2014; Lipsky and Hoey, 2009; Drosou et al, 2003).

In a recent publication by Dissemond et al (2020b), the importance of early diagnosis of wound infection was highlighted, as "any delay in diagnosis would affect the healing process prognosis". In this paper, an interdisciplinary international group of experts developed the Therapeutic Index for Local Infections score (TILI) that enables a rapid and reliable diagnosis of local wound infections. The TILI score (*Table 1*) aims to help health professionals in early identification of patients with locally infected wounds and can provide clinicians, depending on the results, with the basis for early topical antimicrobial intervention. The authors highlight that wound infections must be detected and treated as early as possible. However, the authors also point out that local or systemic antibiotics are frequently used to manage local infection rather than considering local antiseptic options for treatment. Local antimicrobials have been shown to be more effective and do not pose the risk of developing resistance (Hessam et al, 2016).

Therefore, it was concluded that it is of importance to identify and diagnose early as delay affects the healing prognosis. The authors suggest that the tool would enable a rapid and reliable diagnosis of local wound infections (Dissemond et al, 2020b).

***Table 1.* Therapeutic Index for Local Infection Score (TILI) to diagnose local wound infection.**

TILI Score Criteria
Indicative Parameters
Erythema to surrounding skin
Heat
Oedema, induration or swelling
Spontaneous pain or pressure pain†
Stalled wound healing
Increase and/or change of colour or smell of exudate
Direct indication
Presence of wound pathogens‡
Surgical septic wound
Presence of free pus
† Caution in patients with polyneuropathy or when using painkillers; *‡ This can be very different. An example is the detection of multidrug-resistant organisms such as methicillin-resistant Staphylococcus aureus (MRSA)*
Diagnosis of local wound infection based on the presence of 6 indicative parameters OR *1 direct parameter (i.e. « direct indication »)*

UrgoClean Ag

UrgoClean Ag is an advanced wound care dressing made of cohesive poly-absorbent fibres impregnated with a silver lipido-colloid matrix (Technology Lipido-Coloid-Ag healing matrix [TLC-Ag]). The poly-absorbent fibres are effective with desloughing properties as shown in a randomised controlled trial (RCT) (Meaume et al, 2014) where the poly-absorbent fibres showed similar efficacy and safety when

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Case 1.

- 48-year-old diabetic male patient referred with right side infected great toe gangrene, a toe amputation was performed. This was followed by hyperbaric oxygen treatment and local application of papain based creams and cotton absorbent dressings for three weeks.
- On referral, the wound showed signs and symptoms of local infection with slough, hyper-granulation, malodorous discharge and periwound skin maceration(*Figure 1a*).
- After cleaning with normal saline, the wound was dressed by UrgoClean Ag dressing (*Figure 1b*), which was changed every three days.
- After the third dressing change, local signs of infection were reduced. Exudate levels and sloughy tissues had decreased; the wound bed appeared healthy and clean (*Figure 1c*).
- After six dressing changes (day 18) the wound appeared healthy with granulating tissue (*Figure 1d*).

Case provided by Dr Belehalli Pavan. Ankle & Foot surgeon, Karnataka Institute of Endocrinology And Research, Bangalore, India

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compared with Hydrofiber, but presented better desloughing properties in the management of ulcers. The value of TLC-Ag healing matrix has also been recognised in its effectiveness in the management of wounds presenting with a risk of infection as demonstrated in two RCTs (Harding et al, 2012; Lazareth et al, 2012).

In most commercially available silver-containing dressings, the silver is impregnated into the dressing's absorbent component (e.g. fibrous material such as hydrofibres, or polyurethane foam). UrgoClean Ag differs as the silver sulphate is incorporated in lipidocolloid layer that is in contact with the wound (Desroche et al, 2016). Furthermore, UrgoClean Ag not only addresses the high microbial burden that can delay or prevent wound healing (Dalac et al, 2016), but is also effective against biofilms that prolong and prevent healing, cause chronic inflammation, increase the risk of infection and are often tolerant to antimicrobials (Desroche et al, 2016; Percival, 2017). Additionally, sloughy tissue slows re-epithelialisation and creates an environment that encourages microbial proliferation (Dalac et al, 2016; Percival and Suleman, 2015). UrgoClean Ag exhibits a broad spectrum antimicrobial activity, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, vancomycin resistant *Enterococci* and methicillin-resistant *Staphylococcus aureus* (MRSA) (Desroche et al, 2016). After 24 hours, UrgoClean Ag reduced the biofilm population by more than 99.99% (4.6 log reduction), which was maintained for seven days (up to 4 log reductions). The *in vitro* evidence is supplemented by a prospective, multicentre, non-comparative clinical trial involving patients that were considered at high-risk of infection (Dalac et al, 2016). They were treated for a maximum period of four weeks (UrgoClean Ag), and followed by the physician on a weekly basis. The primary efficacy criterion of the trial was the relative wound surface area reduction at the end of the four weeks of treatment. Wound

Case 2.

- A 43-year-old diabetic male patient presented with a three month old wound over right lateral malleolus following excision of infected lateral malleolus bursitis (*Figure 2a*).
- The wound had signs of local infection with moderate exudate, unhealthy granulation and slough. The wound was previously managed with papain-based cream and cotton absorbent dressings.
- After cleaning with normal saline, UrgoClean Ag was applied (*Figure 2b*) and the dressing was changed every three to four days.
- After two dressing changes (*Figure 2c*) signs of local infection had subsided, slough and exudate levels reduced, the wound bed appeared healthy and granulating. The wound size had also gradually reduced.
- By the third week the wound bed is completely clean and healthy granulating tissue appeared and wound size considerable reduced (*Figure 2d*).

Case provided Dr Belehalli Pavan. Ankle & Foot surgeon, Karnataka Institute of Endocrinology And Research, Bangalore, India

surface area, mostly covered by sloughy tissue, was reduced by 32.5%. A total of 54.1% were considered debrided (as defined by >30% of sloughy tissue covering the wound bed). The relative reduction of sloughy tissue was of 62.5% (median value) versus baseline with only 20% of the wound surface area still covered by sloughy tissue (median value) versus 70% at baseline. The promotion of the wound healing process was shown through the wound surface area reduction, the rapid decrease of the inflammatory signs and of the sloughy tissue, a good safety profile and a high acceptability. The authors concluded that these clinical data support the concept that UrgoClean Ag is a credible therapeutic alternative for the management of wounds at risk of infection with inflammatory signs suggesting heavy bacterial load.

Therefore, it can be concluded that UrgoClean Ag provides a combined antimicrobial and complete cleaning action to fight against local infection. The antimicrobial and antibiofilm action has been shown by the clinical efficacy of TLC-Ag in reducing signs of local infection and in promoting healing (Lazareth et al, 2012), the fast and broad-spectrum antimicrobial efficacy, including on strains resistant to antibiotics (Desroche, 2016) as well as the superior antibiofilm efficacy compared with Hydrofibre Ag+Extra and dialkylcarbamoylchloride (DACC) (Desroche et al, 2016; Percival, 2017). The complete cleaning action with the mechanical action of the poly-absorbent fibres targets the source of chronic inflammation and exudate by trapping and binding to slough, microbial and biofilm residues, while maintaining a clean wound, optimising silver efficacy in the wound (Percival and Suleman, 2015).

UrgoClean Ag is indicated for the local treatment of chronic wounds (leg ulcers, pressure ulcers, diabetic foot ulcers) and acute

wounds (burns, traumatic wounds, postoperative wounds) at risk or with signs of local infection, from the debridement stage. Benefits of fighting local infection with a combined antimicrobial and complete cleaning action include:

- **For patients**
  - Fights the local infection and avoids complications
  - Is atraumatic and pain-free at removal but also well-tolerated and comfortable.
- **For clinicians**
  - Reduces the microbial load within the wound and keeps the wound clean from exudate, slough, bacterial residue and biofilm
  - Effectively fights against local infection with the combined antimicrobial and complete cleaning, thus avoiding complications.
- **For the healthcare system**
  - Avoids complications (amputation, hospitalisation).

German observational study

Joachim Dissemond from the Department of Dermatology, Venereology, and Allergology, University Hospital Essen, Essen, Germany, and his colleagues, conducted a large, prospective, multicentre, observational study in 81 centres in Germany where the authors evaluated UrgoClean Ag in 2270 patients (Dissemond et al, 2020a). Their main objective was to determine, under real-life conditions, the short-term clinical impact of the dressing on the wound healing process, including reduction in number of wound infections diagnosed and clinical signs of local infection, wound healing rate, clinical assessment of wound healing progression, relative wound area reduction (RWAR), local tolerability, handling and acceptance of the dressing. The patients included in the study had both acute and chronic wounds of various aetiologies that were treated with the UrgoClean Ag for a mean duration of 22±13 days.

Case 3.

- A 65-year-old female patient with a known history of diabetes mellitus, hypertension and rheumatoid arthritis, presented with an abscess on the plantar region left foot
- The wound was present for 10 days and appeared with signs of local infection including an unhealthy wound bed with purulent discharge (***Figure 3a***). The periwound was macerated and the pain score was described as severe (not measured).
- After cleaning, the wound was dressed with UrgoClean Ag (***Figure 3b***). Initially for the dressing was changed for every three to four days and thereafter the dressing change frequency was decreased to every seven days
- After four dressing changes, pain and exudate levels had decreased and the wound bed appeared healthier and cleaner (***Figure 3c***). The wound size gradually reduced and after 7 dressing changes (day 21), the wound appeared healthy with granulating tissue (***Figure 3d***).

Case provided by Dr Sanjay Sharma. Founder and Medical Director FootSecure, Bangalore, India

Case 4.

- A male patient with a known history of diabetes mellitus presented with two week old multiple ulcers in all the digits of the left lower limb with exposed bones and tendons (Fig 4a).
- After cleaning, the wound was dressed by UrgoClean Ag. The position of the wounds was challenging to dress but application was facilitated by the conformability of the UrgoClean Ag (Fig 4b).
- Initially for the first three dressing changes, UrgoClean Ag was replaced for every third day. Thereafter, dressing frequency decreased to once every seven days.
- After two dressing changes (Fig 4c), the exudate levels and viscosity was improved and the wound bed was covered with healthy tissue. The wound size gradually reduced.
- After the wound was completely healed after seven dressing changes (38 days) (Fig 4d).

Case provided by Dr Sanjay Sharma. Founder and Medical Director FootSecure, Bangalore, India

The authors stated that all clinical signs of local infection and the diagnosed wound infections were substantially reduced by two weeks after the treatment initiation, while all wound infection parameters continued to reduce until the last visit. Additionally, clinical improvement in wound healing was reported in 98.9% of acute wounds, with a wound closure rate of 68.5%, and, in chronic wounds, a median RWAR of 57.4% was achieved. An improvement in healing process was noted by clinicians in 90.6% of cases and stabilisation in 6.1%, regardless of exudate level and proportion of slough and granulation tissues in the wound bed at baseline.

Acceptability and tolerability was well reported by both patients and health professionals. The authors' conclusion was that the results support and complete the clinical evidence on the healing properties and safety profile of the UrgoClean Ag previously discussed in the management of wounds at risk or with clinical signs of local infection, regardless of wound and patient characteristics.

'*Repeatability*' in Asia

'Repeatability' and other similar terms have been used to define the general concept of one experiment or study confirming the results of another (NASEM, 2019). Reproducibility can be explained as obtaining consistent results using the same methods, while replicability is obtaining consistent results across studies aimed at answering the same scientific question (NASEM, 2019).

Regarding the management of patients with wounds, one of the dilemmas we are faced with is if the results of studies conducted in Europe can be reproduced in Asia, where climate and culture and way of life are so different. Moreover, different regions and countries in Asia itself can be very diverse.

The gold standard for confirming results and reducing error, omission, and fraud is

Case 5.

- A 49-year-old female presented with non-healing chronic ulceration of 8 months, which started from blister formation. Patient has been previously being treated with cadexomer iodine dressing and compression bandage with no improvement. Regular sharp debridement has been limited due to pain.
- Her medical history includes type 2 diabetes mellitus, hypertension, hyperlipidemia and chronic venous insufficiency. Wound bed is observed to have central area of adherent slough (60%) and circumferential area hypergranulation tissue (40%) (*Figure 5a*). Decision was made to switch to Urgoclean Ag and 2-layered compression bandage (Urgo K2®) after little improvement was made with the previous treatment regimen.
- By the second week, the wound bed had progressed to granulation there was epithelialisation from the edges (*Figure 5b*) with no slough or hypergranulation.
- By the 4 weeks, the wound size has reduced to just one-tenth of the original size (*Figure 5c*). Full wound closure has achieved in 8 weeks (*Figure 5d*).

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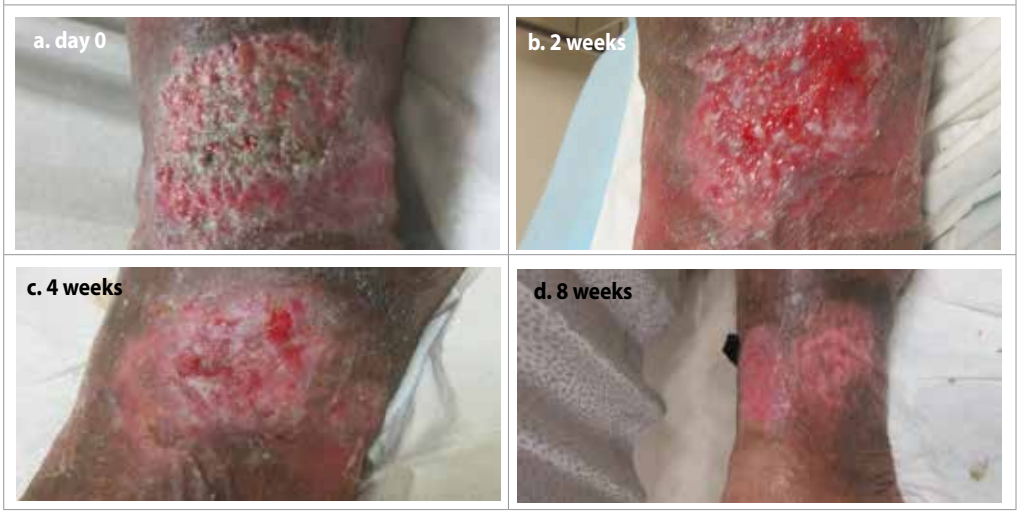

Case 6.

- A 75-year-old female presented with a traumatic wound sustained during a motorcycle accident, previously treated in a provincial local hospital. The wound was cleansed with povidone iodine and then sutured.
- After one month, the wound deteriorated and was showing signs of local infection and the patient was re-hospitalised to Viet Duc Hospital in Hanoi.
- On admission (*Figure 6a*), the wound measured 20cm x 10cm and was covered entirely by necrotic tissue and slough. Systemic antibiotics were initiated, wound cleansed with betaine/polyhexanide solution, and UrgoClean Ag was applied as a primary dressing.
- The dressing was changed alternate days and by the second dressing change (*Figure 6b*) the wound was already showing progress with a relevant reduction in necrotic tissue and slough. On the next dressing change (*Figure 6c*), the wound showed further improvement noted and by day 19 (*Figure 6d*), the wound was clear of slough tissue and signs of any infection.
- A skin graft was then applied by day 31 (*Figure 6e*)

Dr. Dao Van Hieu: Traumatic wound. Viet Duc Hospital, Hanoi, Vietnam

Case 7.

- A 20-year-old male refereed to Da Nang General Hospital with a three day old electrical burn wound on the wrist. The wound was self-treated but the patient self-referred to Da Nang Hospital as the wound started showing sign of local infection (*Figure 7a*) including hypergranulation, slough and malodour.
- The patient was started on systemic antibiotics and the wound was irrigated by physiological solution of saline. UrgoClean Ag applied and the dressing was changed daily. By the sixth day (*Figure 7b*), all signs of local infection were eliminated and healthy granulation tissue appeared.

Do Van Hung: Traumatic wound Da Nang Hospital, Hospital, Da Nang, Vietnam

Case 8.

- A 32-year-old female was admitted after a motor vehicle accident. The patient sustained both tibia and fibula fractures and an open wound on the lateral aspect of the left lower limb, malleolus area.
- External fixation of the fracture was operated and the wound was cleaned with saline solution and UrgoClean Ag applied (*Figure 8a*).
- The dressing was changed daily, and by day four (*Figure 8b*), the wound showed very good progress with healthy granulation tissue covering most of the wound bed.
- By day eight (*Figure 8c*), further improvement was noted and the wound bed appeared healthy. After that, the split-thickness skin graft was performed to cover the defect.

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replication, or conducting an entire study a second time to verify its results (Asendorpf et al 2013). However, as replication is not always practicle due to cost, reproducing a study, or analysing an existing data source to produce the same study results, has been proposed as a minimum standard increasing the reliability of reported research findings (Peng et al, 2006; Peng, 2015).

In view of these arguments, the authors sought to assess UrgoClean Ag in their different countries in Asia, along the same lines of the German Observational Study previously discussed. The countries where the authors manage patients have different climates and cultures that were earlier discussed. The wounds included also have different aetiologies to be able to emulate as much as possible the different type of wounds included in the German Observational study.

Discussion

Wound infection has always been a challenge for clinicians and patients. In our modern society, wound management is based on evidence to ensure that our patients are receiving safe, effective care to increase their HRQoL and close their wounds at the earliest possible.

The cases reviewed in this paper represent a cohort of patients suffering from chronic wounds, managed under real-life conditions. The results, after the application of UrgoClean Ag, show a rapid decrease of the inflammatory signs and of the slough tissue as well as improvement of the wound healing process through wound surface area reduction. The results of these clinical cases are in line with the findings of the German Observational Study (Dissemond et al, 2020a), corroborating that UrgoClean Ag provides a real clinical benefit for the management of chronic wounds presenting

inflammatory clinical signs and should be considered as a viable option for the management of such chronic wounds when used as part of evidence based standard of wound care.

Conclusion

UrgoClean Ag can be considered as one of the important introductions to the wound care clinicians' toolbox. With its polyacrylate fibres, silver sulphate and technology lipido colloid, UrgoClean Ag has provided clinicians with the much needed evidence based dressing that they now have to provide a continuous cleaning action, antimicrobial efficacy and biofilm removal. By means of these cases (among others), clinicians in the continent of Asia have clear indications that results obtained in studies in Europe can be replicated in their countries, no matter the climate and ways of life. WAS

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Declaration of interest

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