TLC-Ag dressings: a prospective, multicentre study on 728 patients with wounds at risk of or with local infection

Objective: This study aimed to evaluate the management of an unselected cohort of patients with wounds at risk of or with clinical signs of local infection, treated with two antimicrobial contact layers impregnated with silver (TLC-Ag healing matrix), under real-life conditions during the COVID-19 pandemic.

Method: A large, prospective, multicentre, observational study with two TLC-Ag dressings (UrgoTul Ag/Silver and UrgoTul Ag Lite Border, Laboratoires Urgo, France) was conducted in Germany between May 2020 and May 2021. The main outcomes included a description of the treated patients and their wound management, the changes in wound infection and wound healing outcomes over a maximum period of four weeks of treatment, as well as the overall clinical assessment of the performance, local tolerance and acceptability of dressings.

Results: A total of 728 patients with wounds of various aetiologies and wound infection status were treated with the evaluated dressings in 39 centres for a mean duration of 26±19 days, with an intermediate visit conducted in 712 (97.8%) patients after a mean period of 12±9 days. At the initial visit, it was established that the majority of patients (60.4%) had a wound infection, while the remaining cohort presented first clinical signs of a local wound infection (25.1%) or were at risk of wound infection (13.2%) (unclear status in 1.2%). Throughout the study period, all the parameters of wound infection continuously decreased, resulting at the final visit in a reduction by 78.9% of the prevalence of local wound infections and by 72.0% of the clinical signs of wound infection, the most rapidly diminished clinical sign being wound deterioration. Concurrently, in terms of the healing process, 92.1% of the wounds healed or improved, 3.2% remained unchanged and 1.7% worsened (data missing for 3.0%), and an improvement of the periwound skin was reported in 65.7% of the patients. Overall, the two dressings were 'very well accepted' by the majority of patients, with no uncomfortable feeling at wearing and no pain at dressing removal, and were assessed by the physicians as 'very useful' in the majority of the cases with a 'very good' efficacy in terms of antimicrobial activity and promotion of the wound healing process. Similar results were reported regardless of the wound type treated or of the TLC-Ag dressing evaluated.

Conclusion: These results are consistent with previous clinical evidence on TLC-Ag dressings. They support the good efficacy, good tolerability and usefulness of these antimicrobial dressings in the management of patients with wounds at risk or with clinical signs of local infection, in association with appropriate standard of care.

Declaration of interest: This study was supported by a grant from Laboratoires Urgo. EB, UM, LT and SB are employees of Laboratoires Urgo. SL, AG, MD, CL and JD provide advisory and speaking services to pharmaceutical and other healthcare organisations including, but not limited to, Laboratoires Urgo. Data management and statistical analyses were conducted independently by INPADS GmbH, Bad Dürkheim, Germany.

clinical signs of infection • observational study • risks of infection • silver • TLC-Ag dressings • wound • wound care • wound healing • wound infection

Wound infection represents a high-risk medical situation with important challenges in wound care management. The additional human resource mobilisation and considerable costs associated with these complications are accounted for by the healthcare systems in terms of additional visits and care by health professionals, additional treatment costs, possible number of hospitalisations, readmission, surgical revisions or prolonged hospital stays.[1–6] For the patient, infected wounds can also be associated with delayed wound healing, malodour, increased pain and anxiety, and impaired quality of life.[1,2,7–11] Moreover, if diagnosed too late or inappropriately managed, they can lead to spreading infection, amputation, sepsis and death.[2,11–14]

Guidelines and consensus documents on best clinical practices for wound infection management include prevention, early diagnosis, prompt and appropriate infection control measures, and frequent re-assessment of the situation.[15–16] A comprehensive and holistic approach, considering the individual, their wound and their environment, is essential to accurately assess the risk, diagnose and treat an individual with a wound infection. As described by the International Wound Infection Institute (IWII) in their consensus document on wound infection in clinical practice, 'In most cases, development of wound infection is multifactorial and

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occurs when cumulative risk factors overwhelm the host's defence system.'[17] Clinical signs gradually emerge, and while the presence of a direct indicator such as purulent discharge leaves no doubt on the presence of a wound infection, the first signs of infection can be subtle, and sometimes mistakenly identified as common signs of the medical conditions associated with wound occurrence or even absent if the patient's immune system is deficient.[15,16] Most of the time, the diagnosis is made in the community by health professionals who have to initiate the appropriate treatment.[18]

As the fear of antibiotic resistance has led to more responsible antibiotic stewardship, with use restricted to deep and/or systemic infections and to a few high-risk medical conditions, alternatives such as antimicrobial dressings have been developed to manage wounds at risk of or with clinical signs of infection and prevent the extension of local infection to the surrounding tissue. Several systematic reviews have supported the antimicrobial efficacy of silver ions against many species of Gram-negative and Gram-positive bacteria and their biofilms, including *Staphylococcus aureus*, meticillin-resistant *Staphylococcus aureus* (MRSA), *Streptococcus pyogenes* and *Pseudomonas aeruginosa*, which are most frequently responsible for wound infections, as well as certain fungi, yeast and viruses.[15,19,20] These reviews also acknowledge the still very present utility of silver dressings in antimicrobial strategies, when used appropriately and in association with standard of care, such as wound cleansing, debridement and aetiological treatment.[15,16,20–26]

Dressings based on the Technology Lipido-Colloid with silver (Ag+) ions (TLC-Ag dressings) have been commonly used in the management of wounds at risk of or with clinical signs of local infection since 2006, and supported by both in vitro and clinical evidence.[27–43] In contact with wound exudate, the hydrocolloid particles of the TLC-Ag healing matrix gel form a lipido-colloid film that maintains a moist environment favourable to the promotion of wound healing.[27] Meanwhile the Ag+ ions confer to the dressing their anti-inflammatory properties and antimicrobial activity, leading to reduction of the bacterial load.[27–29] The superior efficacy of these dressings in reducing the clinical signs of local infection and promoting wound healing, in the absence of antibiotic therapy, has been demonstrated, compared to dressings without silver, in a randomised controlled trial (RCT) on chronic leg ulcers (LUs),[30,31] and their good performance in real-life conditions has been confirmed in several observational studies[34–36] and case series.[37–43] These dressings have also been proved to be well tolerated and accepted both by health professionals and patients, notably due to their atraumatic and painless removal at dressing changes in various clinical studies conducted in the management of acute and chronic wounds.[30–43] In order to meet the specific needs of each patient and wound, the TLC-Ag dressing range is available as absorbent dressings with foam or polyabsorbent fibres or contact layers, with or without adhesive border.

In the past two years, the COVID-19 pandemic and its consequent restrictions, such as self-quarantine and public lockdowns, have deeply impacted healthcare organisations around the world, adding further complexity to the daily challenges faced by health professionals responsible for the care of patients.[44,45] Postponed diagnosis, follow-up, screening and treatment of acutely or chronically ill patients were reported in relation to reduction of non-essential medical services, temporary work absence of health professionals due to COVID-19 infection or quarantine, or some refusals of doctor visits for fear of potential exposure to the virus.[44,46] In Germany, surveys and observational studies have revealed a reduction in clinical wound management capacity, with the closure of outpatient wound clinics for several weeks, and dramatic reductions of the number of general practitioner consultations, of wound treatments and pain therapy.

In this context, and to complement the clinical evidence available on the TLC-Ag dressings, a new clinical study was conducted to document the characteristics of the patients and wounds treated with two TLC-Ag dressings (UrgoTul Ag/Silver and UrgoTul Ag Lite Border) and to assess the performance, tolerance and acceptability of both these dressings, under these difficult real-life conditions.

Method

Study design and patients

This study was conducted as a prospective, observational, multicentre clinical study with the participation of 39 active centres, including general practitioners, internists, surgeons, dermatologists and other specialists located throughout Germany.

Any patient with a wound at risk of or with clinical signs of a local infection, that the investigator had decided to treat with one of the two evaluated silver dressings (any size available) between May 2020 and May 2021, was eligible for inclusion. In the case of patients with multiple eligible wounds, it was recommended to select the wound considered most suitable for evaluation in the study.

Each patient was treated according to the local clinical routine and evaluated during a treatment period of a maximum of four weeks, or for a minimum of three documented visits (initial, intermediate and final). A re-evaluation visit, during which the physician can assess the wound progression, the changes in wound infection parameters, and review the efficacy and relevance of the wound management put in place, is usually scheduled two weeks after the treatment initiation, as recommended in guidance for appropriate use of silver dressings,[16] but in this real-life study, the timing of the visits was left to the discretion of the participating physicians. The application of best clinical practices was assumed and differences in care protocols

were expected between clinical settings, for example, the use of antibiotics according to institutional protocols. Within the scope of their responsibility, the participating physicians could discontinue the use of the evaluated dressing and the patient's participation in the study at any point.

Evaluated wound dressings

The two antimicrobial wound dressings evaluated (UrgoTul—written UrgoTül in Germany—Ag/Silver and UrgoTul Ag Lite Border, Laboratoires URGO, France, any size available) are sterile, lipido-colloid contact layers impregnated with silver salts, derived from Lipido-Colloid Technology (TLC). The silver healing matrix (TLC-Ag) of the dressings, in contact with the wound, is made of polyester mesh impregnated with hydrocolloid particles (carboxymethylcellulose), petroleum jelly, cohesion polymers and silver salts. The Lite Border dressing is also composed of a thin absorbent pad and a white protective polyurethane backing coated with a high skin tolerance adhesive mass.

The two dressings have been CE-marked since 2006 and 2010, respectively, and were expected to be used according to the manufacturer's instructions. Of note, the manufacturer's instructions, recommend changing the dressings every 1–3 days, depending on the wound treated and the course of its healing. The maximum duration of treatment with the dressings is one month, and their use is contraindicated in patients with known sensitisation to silver or hypersensitivity to any of the dressing components, and in patients undergoing magnetic resonance imaging (MRI) examination. UrgoTul Ag Lite Border ensures optimum drainage of low-exuding wounds thanks to its thin absorbent pad, while its adhesive border facilitates the application of the dressing on healthy periwound skin. Conversely, because of its non-adhesive nature, the contact layer UrgoTul Ag/Silver may be used on all types of wounds, including those with fragile or damaged periwound skin, in association with a secondary dressing suitable for the level of exudate, and secured in place with a fixing system.

Data collection, assessments and outcomes

At the initial visit, the following information was collected as well as the patient's sex, age, body mass index (BMI) and relevant medical history:

- Risk factors for wound infection such as conditions affecting the immune system (for example, diabetes, immune deficiency syndrome, renal insufficiency), health behaviour at risk of wound infection (for example, obesity, malnutrition, smoking), advanced age (for example, ≥80 years old) or young age at risk, wound area or depth at risk (for example, ≥10cm²), penetrating wounds (for example, bites or wounds caused by an intruding foreign object), heavily contaminated or dirty wounds, wound duration at risk (for example, ≥1 year), prolonged period of hospitalisation, haematological conditions or active cancer (or current chemotherapy)
- Presence of clinical signs of infection: increased local temperature; increased level or change in odour or colour of exudate; wound enlargement or worsening; wound healing delay or stagnation; spontaneous pain or tenderness; swelling, induration or oedema; erythema; suspicion of biofilm; others
- Presence of direct indicators of wound infection: purulent discharge, surgical septic wound, positive laboratory test for the presence of microorganisms such as MRSA, *Pseudomonas aeruginosa*, *Streptococcus* and others
- Evaluation if an established wound infection was present, diagnosed after the medical examination of the patient and the presence of clinical signs of wound infection, and/or in association with the presence of direct indicators of wound infection.

Wound characteristics were registered such as: aetiology, pressure ulcer (PU) stage according to the international National Pressure Injury Advisory Panel and the European Pressure Ulcer Advisory Panel classification, wound location for PUs and burns, percentage of total body surface area and location complications in burns, wound area in cm², wound duration in days, level of exudate ('none', 'low,' 'moderate', 'high'), periwound skin appearance score (on a scale of 1–5, where 1=healthy skin), the presence of macerated periwound skin.

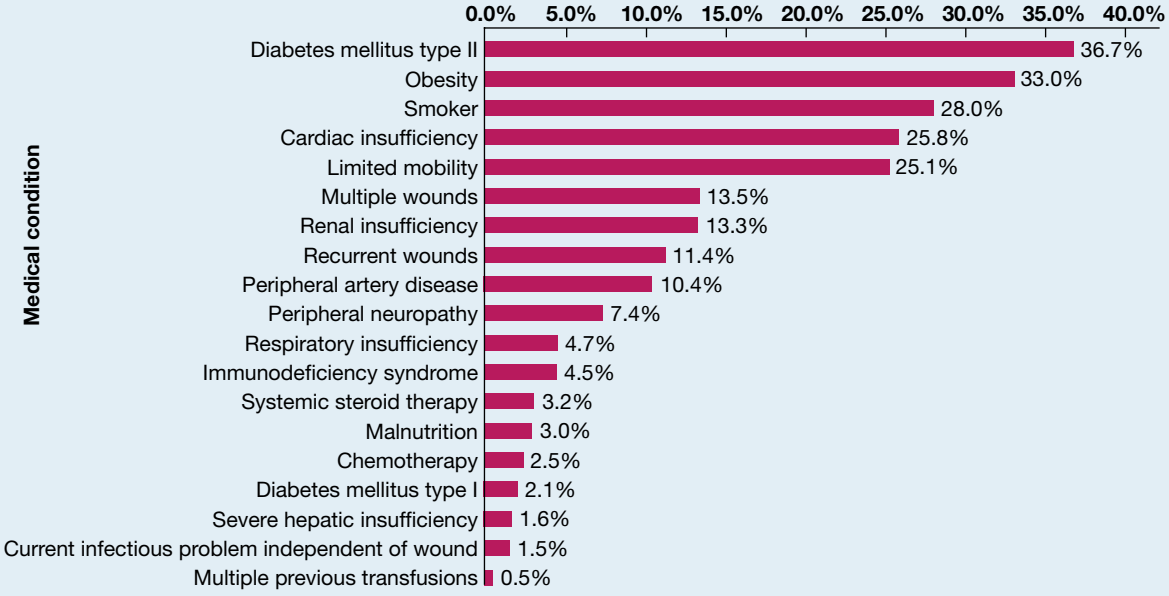
Local care (cleansing, debridement, periwound care), the main reasons for having prescribed the evaluated dressing to treat the patient, the primary and secondary dressings applied, the aetiological treatments provided (compression for LUs, pressure relief for diabetic foot ulcers (DFUs) and PUs) and the use of antibiotics were also recorded. A first evaluation of the handling, conformability and acceptability of the dressing was also performed according to a 4-point Likert scale ('very easy/good', 'easy/good', 'average', 'difficult/poor/').

At the subsequent visits (intermediate and final), a wound assessment was undertaken, recording the presence of clinical signs and direct indicators of local infection, the diagnosis of local infection, the characteristics of the wounds (wound area, level of exudate, periwound skin appearance score and macerated periwound skin), the primary and secondary dressings applied, the dressing change frequency since the last visit, the aetiological treatment worn (compression and pressure relief) and the use of antibiotics.

At the final visit, a global evaluation of the wound healing progression since the initial visit ('healed', 'greatly improved', 'slightly improved', 'unchanged', 'slightly worsened' or greatly worsened'), and the overall evaluation of the performances of the dressings, from both clinician and patient perspectives, were performed in terms of:

- Ease of handling, antimicrobial efficacy, efficacy in promoting wound healing, and usefulness (according to 4-point Likert scales 'very easy/good/extremely

Fig 1. Medical condition of the treated patients in the total cohort (n=728)



useful', 'easy/good/useful', 'average/hardly useful', 'difficult/poor/not useful')

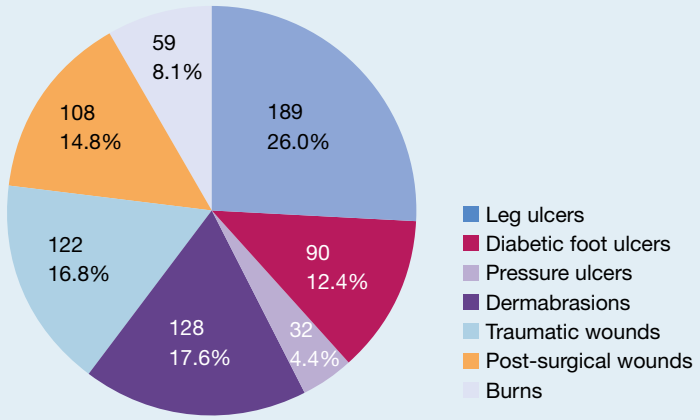
- Pain at dressing change ('painless', 'with slight, brief pain', 'with slight, persistent pain', 'painful' or 'very painful') and patient acceptance ('very good: the patient feels the dressing but does not have an uncomfortable feeling', 'good: the dressing sometimes bothers the patient but does not interfere with everyday activities', 'moderate: the dressing is often uncomfortable during the day, interferes with the patient's activities', or 'poor: the dressing is often or even always uncomfortable during the day, interferes with the patient's activities and sleep').

The participating physicians were also asked if they intended to continue to use these dressings in the treated indications ('yes even more', 'yes', 'rather not', 'no, the clinical results of the treatment did not convince me').

Throughout the study period, the occurrence of adverse events was documented and the local tolerance of the dressings was assessed by the physicians at the final visit.

The endpoints of the study included: the treatment and evaluation duration (in days), the changes in wound infection status, presence of clinical signs or direct indicators of local wound infection, the changes in wound area and wound healing progression, the dressing change frequency and the overall evaluation performance, tolerance and acceptability of the dressings.

Fig 2. Distribution of the type of wounds in the total cohort (n=728)



Data management and statistical analysis

The data management and quality assurance of the study was carried out by an independent contract research organisation (INPADS) in accordance with the recommendations on planning, conducting and analysing post-marketing surveillance studies of the Federal Institute for Drugs and Medical Devices, Paul Ehrlich Institute. An electronic data entry system (eCRF) was used to collect the anonymous data, with automatic checks for data completeness and inconsistent data.

The estimation of the cohort size required for this study was based on the published clinical evidence of antimicrobial dressings in the local management of wounds at risk of or with signs of local infection, the clinical evidence available on TLC-Ag dressings, and the current benefit–risk profile of the evaluated dressings.[30,32–36] Considering a 5% probability of occurrence of local adverse events, as commonly

Fig 3. Risk factors of wound infection (multiple answers possible; total cohort n=728)

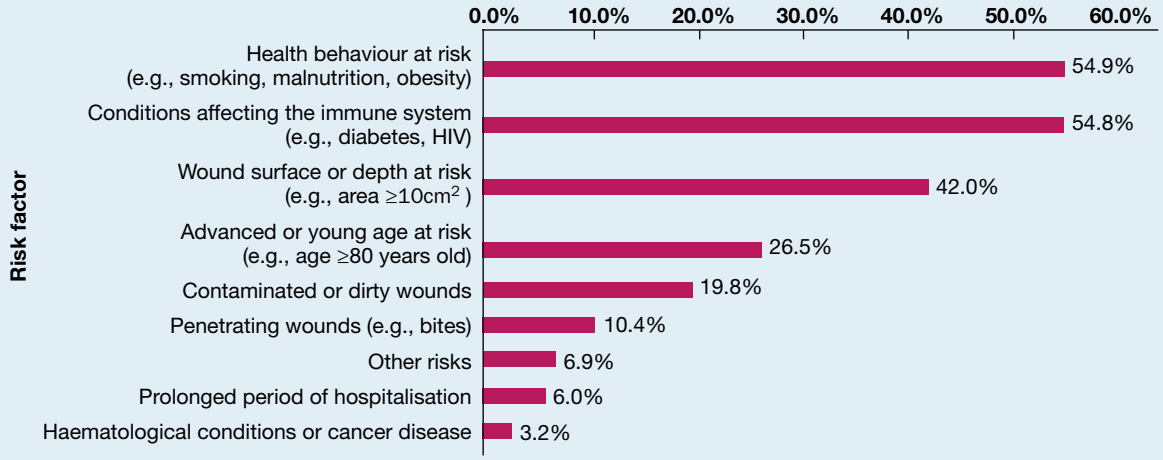
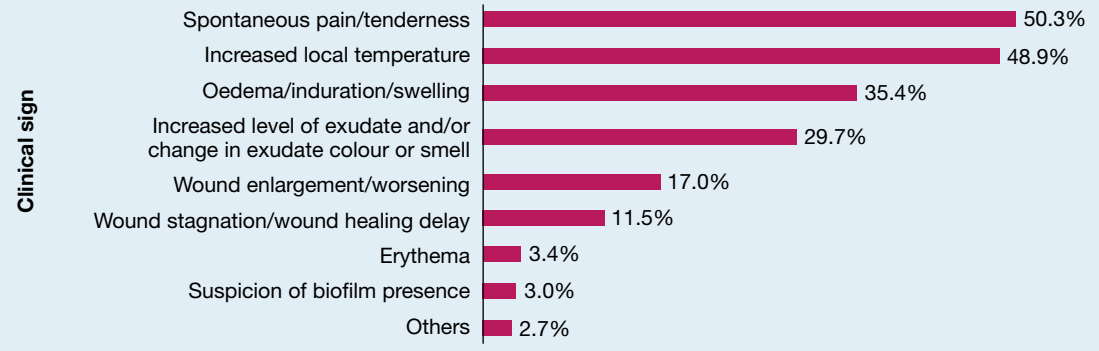


Fig 4. Clinical signs of wound infection reported at the initial visit (multiple answers possible; total cohort n=728)



reported in the literature with any dressings in the context of clinical investigations,[47] and a reasonable probability (80%) of observing at least one local event of an undesirable side-effect, a minimum sample size of 32 patients per wound type was calculated.[48]

Statistical analyses were performed according to the statistical analysis plan, by an independent contract research organisation (INPADS), using SAS 9.4 for windows (Statistical Analysis System, SAS Institute, US). The analyses were merely descriptive, and no statistical tests were used. Efficacy and safety analyses included all patients for whom the initial and final visits were documented. Values were reported as mean±standard deviation (SD); median and interquartile range (IQR), or count and percentage, per wound type, for the total cohort as well as for each evaluated dressing. Missing values were not replaced and listed in all evaluations. Post hoc analyses were conducted to assess the efficacy of the dressings depending on the wound infection status at baseline, in the absence of antibiotic use.

Ethical approval

The clinical study was performed in accordance with the European and national regulation (German Medical Devices Act, German Federal data Protection Law and General data protection regulation). The study protocol and required documentation were submitted to the International Medical and Dental Ethics Commission GmbH (IMDEC, Freiburg) and approved in March 2020.

All patients were informed about the objectives and methods of the study and the processing of their personal data, and their explicit and written consent were collected before they were included. In the case of minors (under 18 years of age), written consent was given by the parents or guardians.

No authority approval was required because of the non-interventional design of this clinical study performed on a CE-marked device used according to the manufacturer's instructions, with no additional diagnostic or therapeutic measures beyond those routinely performed.

Results

Baseline characteristics of included patients

The clinical data of the 728 patients treated with the evaluated dressings were collected by 39 active centres and analysed in this real-life study. An intermediate visit was completed for 712 (97.8%) patients after a

mean period of 12±9 days and a final visit was completed for 706 (97.0%) patients after a mean period of 26±19 days. By the final visit, 18 patients were lost to follow-up and four had discontinued their participation in the clinical study as a result of serious adverse events unrelated to the evaluated dressings.

The cohort comprised 381 (52.3%) male patients, 345 (47.4%) female patients and two (0.3%) people with diverse gender, with a mean age of 62.8±20.2 years (ranging from 5–99 years, and including 13 minors—seven boys and six girls). The mean BMI of adult patients was 28.2±6.4 kg/m².

A relevant medical history was documented for 623 (85.6%) patients. Type II diabetes, obesity, smoking, cardiac insufficiency, limited mobility, the presence of multiple wounds, renal insufficiency and peripheral arterial disease were the most frequently reported conditions (Fig 1).

Baseline characteristics of the treated wounds

The patients presented a large variety of wound aetiology, location, area and severity. The most represented wound types were LUs, dermabrasions and traumatic wounds (Fig 2).

The LU group included 109 venous LUs (VLUs), 36 arterial LUs, 27 mixed LUs (MLUs), nine lymphatic ulcers and eight atypical ulcers. The traumatic wounds included 47 wounds caused by an intruding foreign object, 29 bites, 26 contusions and 20 iatrogenic wounds. The group of PUs (n=32) included a majority of stage II (partial thickness skin loss, n=18, 56.3% of the PUs), ten stage III (full thickness loss, without bone, tendon or muscle exposed, 31.3% of the PUs), two stage IV (full thickness loss, with bone, tendon or muscle exposed, 6.3% of the PUs) and two unstageable PUs (depth unknown, 6.3% of the PUs). The majority of the PUs were located on the sacrum region (n=20, 62.5% of the PUs), seven (21.9%) were on the heel and five (15.6%) at other locations. Burns (n=59) were located on the lower or upper limbs in 30 patients (50.8% of the patients with a burn); on the hand, fingers, foot or toes in 20 patients (33.9% of the burn group), on the abdomen or thorax in seven patients (11.9% of the burn group) and at other locations in two patients (3.4% of the burn group). The mean total body surface area of the burn patients was 3.8±4.3% (ranging from 1–18%). A burn complication was reported in 25 patients (42.4% of the burns): with 12 cases involving large joints, nine cases circumferential extension and four cases peri-orifice location.

In the total cohort, the median wound area was 6.7cm² (IQR: 2.4–15.7cm²), ranging from 3.1cm² for both DFUs (IQR: 1.3–5.5cm²) and traumatic wounds (IQR: 0.8–9.4cm²) to 16.5cm² for burns (IQR: 6.3–28.3cm²). The wounds had more frequently high and moderate levels of exudate (n=405, 55.6%) than low and no exudate (n=323, 44.4%). A healthy periwound skin was documented in 106 (14.6%) patients.

Globally, the included wounds were recent, with a median duration of 6 days (IQR: 2–20 days), and the majority of them were previously covered with gauze and dry dressings (n=447, 61.4%) or absorbent dressings (n=138, 19.0%), but 63 (8.7%) had an antimicrobial dressing and the remaining wounds were covered by other types of dressing (n=76, 10.4%) or the data were missing (n=4, 0.5%).

Wound infection status at baseline

At the initial visit, the patients presented with different wound infection statuses. A wound infection was established in 440 (60.4%) patients, based on direct indicators and/or clinical signs of wound infection; 183 (25.1%) patients presented first clinical signs of a wound infection (but not yet an established wound infection); 96 (13.2%) patients were at risk of wound infection (but with no clinical signs of wound infection); and nine (1.2%) patients had an unclearly documented wound infection status.

From a global perspective, risk factors of wound infection were very prevalent in the total cohort (93.3%, n=679 patients), the most frequent risks being a health at-risk behaviour (for example, smoking, malnutrition, obesity, etc., n=400, 54.9%), a medical condition affecting the immune system (for example, diabetes, HIV, n=399, 54.8%), a wound area or depth at risk (for example, ≥10cm², n=306, 42.0%), and an advanced or young age (for example ≥80 years old, n=193, 26.5%) (Fig 3).

Clinical signs of wound infection were also reported in the large majority of the treated patients (n=600, 82.4%). The most frequently reported sign was spontaneous pain or tenderness (n=366, 50.3%) in the total cohort (Fig 4), but depended on wound type, and in patients with a DFU, increased local of temperature (71.1%, 64/90) was more common.

Finally, direct indicators of wound infection were present in 304 (41.8%) patients: a purulent discharge was reported in 199 (27.3%) patients and a surgical septic wound in 97 (13.3%). A laboratory test of wound swab was available for 178 (24.5%) wounds, with a positive result for the presence of wound pathogens for 101 (13.9%). *Streptococcus* spp. was identified in 43 cases (most often in patients with VLUs, DFUs and post-surgical wounds), *Pseudomonas aeruginosa* in nine cases (in patients with LUs, DFUs and post-surgical wounds) and MRSA in three cases (in patients with arterial LUs, DFUs and PUs), respectively. The 46 remaining positive tests involved other species.

Local care, primary and secondary dressings and antibiotic therapy

Most frequently, the wounds were cleaned with an antiseptic solution (n=333, 45.7%) or a saline solution (n=316, 43.4%). Wound debridement (mechanical or surgical) was documented for 389 (53.4%) wounds and periwound skin care for 40 (5.5%) patients.

At the initial visit, 539 (74.0%) patients were treated with UrgoTul Ag/Silver and 189 (26.0%) with UrgoTul

Table 1. Change in wound infection, direct indicators and clinical signs of wound infection over the treatment period

	Initial visit (n=728)		Intermediate visit (n=728; 16 missing visits)		Final visit (n=728; 22 missing visits)		Reduction versus initial visit	
	n	%	n	%	n	%	Intermedate visit (%)	Final visit (%)
Wound infection	**440**	**60.4**	**247**	**33.9**	**93**	**12.8**	**43.9**	**78.9**
Direct indicators of wound infection	**304**	**41.8**	**155**	**21.3**	**72**	**9.9**	**49.0**	**76.3**
Purulent discharge	199	27.3	67	9.2	13	1.8	66.3	93.5
Surgical septic wound	97	13.3	47	6.5	30	4.1	51.5	69.1
Positive laboratory test*	101	13.9	58	8.0	35	4.8	42.6	65.3
Clinical signs of wound infection	**600**	**82.4**	**382**	**52.5**	**168**	**23.1**	**36.3**	**72.0**
Spontaneous pain/tenderness	366	50.3	197	27.1	71	9.8	46.2	80.6
Increased local temperature	356	48.9	158	21.7	33	4.5	55.6	90.7
Induration/swelling/oedema	258	35.4	137	18.8	74	10.2	46.9	71.3
Increased in level of exudate and/or change of exudate colour or smell	216	29.7	73	10.0	19	2.6	66.2	91.2
Wound enlargement/worsening	124	17.0	8	1.1	5	0.7	93.5	96.0
Wound stagnation/wound healing delay	84	11.5	35	4.8	15	2.1	58.3	82.1
Erythema	25	3.4	16	2.2	1	0.1	36.0	96.0
Suspicion of biofilm presence	22	3.0	8	1.1	3	0.4	63.6	86.4
Others	20	2.7	19	2.6	10	1.4	5.0	50.0

*Laboratory tests were performed in 178, 118 and 94 patients at the initial, intermediate and final visits, respectively.

Ag Lite Border. Both dressings were used on each type of wound, except no UrgoTul Ag Lite Border was applied in lymphatic ulcers and a higher proportion of UrgoTul Ag Lite Border was applied in PUs (53.1%). The main reasons for specifically prescribing the evaluated dressings among other choices of wound dressings indicated in the management of the included wounds were: the good tolerance of these antimicrobial dressings (n=622, 85.4%), the promotion of wound healing due to control of local infection (n=553, 76.0%), the antimicrobial efficacy of the TLC-Ag healing matrix (n=531, 72.9%) and the convenience of an all-in-one antimicrobial dressing with adhesive edges for the Lite Border (n=121/189, 64.0%). During the treatment period, dressings were changed on average 2.7±1.1 times per week. A switch between the two dressings was reported in 29 (4.1%) and 41 patients (5.6%) at the intermediate and final visits, respectively. A secondary dressing (dry gauze or superabsorbent in the majority of cases) was used with UrgoTul Ag/Silver in 94.6% (n=510/539), 94.5% (n=497/526) and 80.2% (n=418/521) of cases at the initial, intermediate and final visits, respectively.

An antibiotic therapy was prescribed to 175 (24.0%) patients at the initial visit, to 102 (14.0%) patients at the intermediate visit and to 26 (3.6%) at the final visit.

Aetiological treatments

At the initial visit, compression therapy was applied in 77.8%, 75.2% and 59.3% of patients with a lymphatic ulcer, a VLU and an MLU, respectively. During the treatment period, a good level of adherence to compression therapy was documented in these patients, with 93.3% of them wearing their compression system at each visit.

Pressure relief was provided, at the initial visit, to 54.4% and 53.1% of patients with a DFU and a PU, respectively, and these pressure relief measures were also well maintained during the treatment period (reported at each visit for 72.7% of them).

Wound infection status over the treatment period

At the intermediate visit, after a mean period of 12 days of treatment with the evaluated silver dressings, a reduction of all the parameters of wound infection was reported (Fig 5).

The number of wound infections decreased by 43.9%, in relation with a decrease of the direct indicators by 49.0% and of the clinical signs by 36.3% (Table 1). In regard to the direct indicators, the most marked effect was reported for purulent discharge, the presence of which decreased by 66.3%. In regard to the clinical signs, the most marked effects were reported for wound enlargement or worsening, which was stopped in 93.5% of the affected wounds, followed by the effect on wound exudate, which returned to normal in 66.2% of the cases where an increase in level, change in odour or colour was detected at the initial visit.

Until the final visit, the presence of each direct indicator and clinical sign of wound infection continued to decrease, leading to a decrease of the prevalence of wound infection from 60.4% at the initial visit to 12.8% at the final visit.

In particular, in the subgroup of patients who had a

Fig 5. Change in wound infection, direct indicators and clinical signs of wound infection over the treatment period

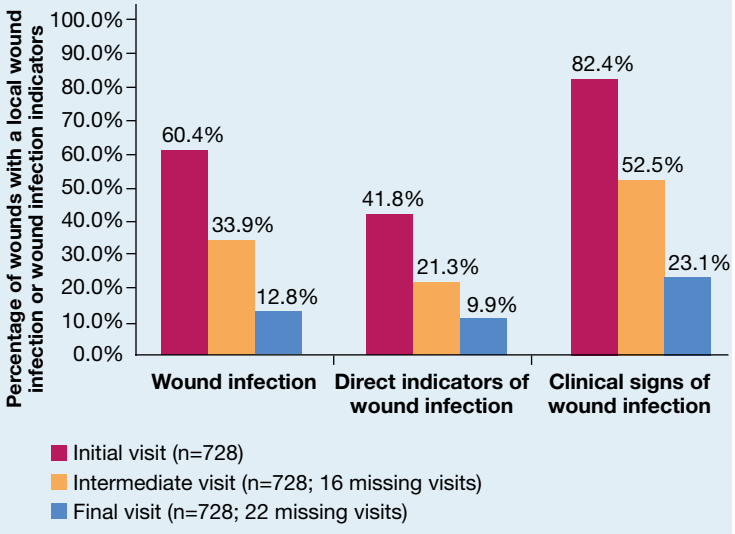
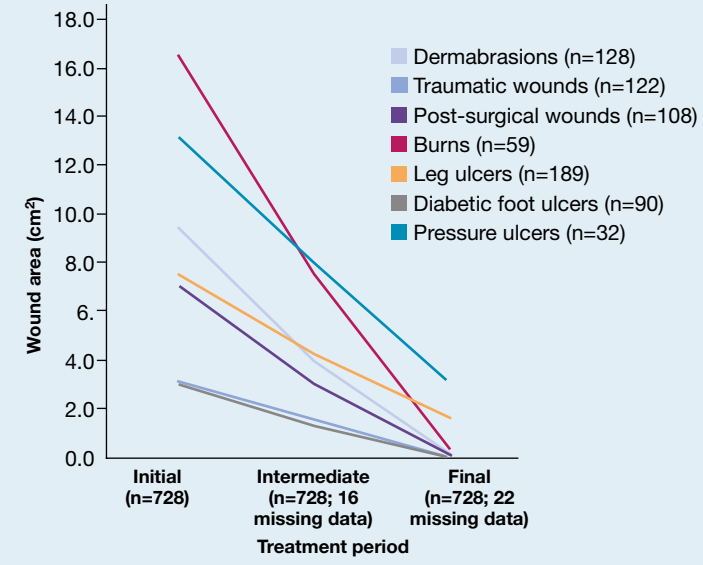


Fig 6. Change in wound area over the treatment period (median values)



wound infection and were treated with antibiotics at the initial visit (n=153), 122 (79.7%) wound infections were resolved, 27 (17.6%) were still present and data for four patients (2.6%) were missing at the final visit. In the subgroup of patients who had a wound infection but didn't received antibiotics at the initial visit (n=287), 219 (76.3%) wound infections were resolved, 62 (21.6%) were still present, and data for six patients (2.1%) were missing at the final visit. Finally, in the sub-group of patients who did not yet have an established wound infection at the initial visit (n=288), 272 (94.4%) patients finished their treatment with no wound infection, four (1.4%) had a wound infection at the final visit, and the data were missing for 12 (4.2%) patients.

Wound healing progression with the TLC-Ag dressing treatment

During the treatment period with the TLC-Ag dressings, a clear improvement of the wound healing process was recorded. The wound areas progressively decreased, regardless of the wound type (Fig 6), and by the final visit, 307 (42.2%) wounds had healed, 293 (40.2%) had greatly improved, 71 (9.8%) had slightly improved, 23 (3.2%) were unchanged, 10 (1.4%) had slightly worsened, two (0.3%) had greatly deteriorated and the data were missing for 22 (3.0%) patients.

In conjunction with the reduction of the clinical signs of infection and the promotion of the wound healing process, the proportion of wounds with macerated periwound skin decreased, from 32.0% (n=233) at the initial visit to 14.4% (n=105) at the intermediate visit, and then to 5.6% (n=41) at the final visit; and in the total cohort, the appearance of the periwound skin improved in 65.7% (n=478) of the patients, was unchanged in 29.5% (n=215) and worsened in 1.8% (n=13) (data were missing for 22 (3.0%) patients).

Pain at dressing change, local tolerance of the evaluated dressings and adverse events

At the final visit, the pain at dressing change during the study was reported 'painless' for 66.6% (n=485) of the patients, 'associated with a brief, mild pain' for 28.3% (n=206), 'with a slight, persistent pain' for 1.2% (n=9), 'painful' for 0.7% (n=5) and 'very painful' for 0.1% (n=1) (22 missing data, 3.0%). Both dressings were judged by the investigators as 'very well tolerated' by 85.2% (n=620) of the patients and 'well tolerated' by 11.8% (n=86), without difference between the two dressings (22 missing data, 3.0%).

During the course of the study, four serious adverse events occurred in four patients who had a DFU, a PU, a post-surgical wound and an atypical ulcer, respectively. The investigators judged that none of these events were related to the evaluated dressings.

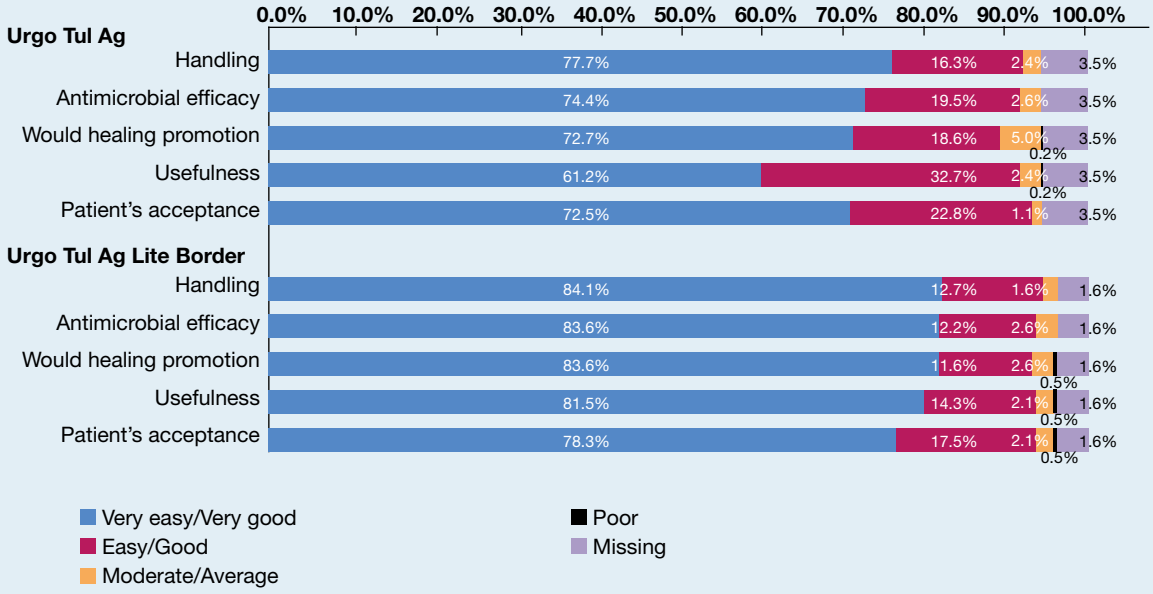
Acceptability and overall assessment of the dressing performances compared to other dressings

At the initial visit, the investigators assessed:

- The handling of the evaluated dressing as 'very easy' in 84.1% (n=612) of the cases, 'easy' in 13.7% (n=100) and 'average' in 2.2% (n=16)
- The conformability of the dressings to the wound as 'very good' in 76.2% (n=555) of the cases, 'good' in 21.4% (n=156), 'average' in 2.2% (n=16) and 'poor' in 0.1% (n=1)
- The patient's acceptance of the dressings as 'very good' in 77.2% (n=562) of the cases, 'good' in 19.0% (n=138), 'average' in 3.7% (n=27) and 'poor' in 0.1% (n=1).

As illustrated in Fig 7, at the final visit, based on their

Fig 7. Final assessment of the evaluated dressings (n=728)



global experience during this clinical study, the investigators assessed the evaluated dressings in the majority of the cases:

- 'Very easy' or 'easy' to handle (n=690, 94.8%)
- With a 'very good' or 'good' antimicrobial efficacy (n=687, 94.4%)
- With a 'very good' or 'good' efficacy to promote wound healing (n=672, 92.3%)
- 'Very well' or 'well' accepted by the patients (n=695, 95.5%)
- 'Very useful' or 'useful' for the wound management of the patients (n=687, 94.4%).

Similar results were reported, regardless of the dressing evaluated, the wound type treated or the wound infection status at baseline when the dressings were used in the absence of antibiotics (data not shown).

Regarding possible future use in this indication, in most cases (94.1%, n=685), the investigators specified that they will continue to use these dressings. In 15 cases (2.1%) the physicians expressed their preference to use other dressings in the future, and in one case (0.1%), a physician estimated that the clinical outcomes achieved during the study were not convincing enough for future use (missing data for 27 cases, 3.7%).

Discussion

The results of this clinical study, documented in a large cohort of 728 patients treated in real-life conditions, during the COVID-19 pandemic, support the good performance and safety profile of the two TLC-Ag dressings evaluated in the management of wounds at risk of or with clinical signs of local infection. The use of the TLC-Ag dressing was beneficial in reducing clinical signs of local infection and resolving local infection episodes, while promoting wound healing, supporting the management of wound exudate, reducing maceration, improving the periwound skin appearance and alleviating the patients' pain.

The dressings were prescribed to treat wounds of various types, locations and degrees of severity, in patients who most often had clinical signs of or direct indicators of wound infection (85.6%), or who were at risk of wound infection (13.2%). With only nine patients (1.2%) with an unclear documentation of their wound infection status and therefore of their need for an antimicrobial dressing, these data confirm use of these dressings in daily practice in line with their indication.

The most common wound infection parameters present at baseline included, as often reported in the literature, pain, local warmth, induration, changes in level or nature of exudate, wound deterioration and the presence of pus.[15,16,20,34,35,49] The presence of a purulent discharge is unanimously accepted as conclusive of wound infection.[15,16,20,50,51] This direct indicator, as well as the two others used in this study (a surgical septic wound or the detection of wound pathogens such as MRSA), are actually also included in several other consensus documents addressing wound infection diagnosis and treatment.[15,16,20,50,51]

In our study, and despite the pandemic context, the participating physicians succeeded in providing a prompt follow-up visit with 97.8% of their patients, on average 12 days after the start of silver treatment. This re-evaluation visit is particularly important to assess the wound progression and review the efficacy and relevance of the wound management strategy put in place, and recommended in guidelines and best practice consensus on the appropriate use of antimicrobial

dressings.[15,20,24,25] At this visit, improvements of all the parameters of wound infection as well as of the healing process were observed in the treated cohort. The parameters that improved most rapidly were related to wound deterioration, wound exudate and the presence of pus, and provided good visual indicators for a confident and reliable assessment of the progression of the wound and its infection status.

At the final visit, the improvement initiated during the first two weeks resulted in an even greater reduction in all wound infection parameters and a steady progression of the wound healing progress, with median relative wound area reductions depending on wound types but ranging between 65.0% for LUs and 99.3% for traumatic wounds. This finding was consistent with the results of the 'UTAG' RCT which demonstrated the superior efficacy of the TLC-Ag contact layer compared to a non-silver contact layer in promoting wound healing and reducing clinical signs of VLUs with clinical signs of infection, in the absence of systemic antibiotic therapy.[31]

Similar substantial improvements of the wound healing process were also reported in previous observational studies conducted on wounds at risk of or with clinical signs of infection treated with TLC-Ag dressings.[34,35] In the 'IMAg' clinical study, 1027 physicians in Germany and France assessed the performances of TLC-Ag dressings (contact layer and foam) in 4960 patients.[34] At the final visit, the average wound reduction in the largest wound axis reached 53.6% in Germany and 49.9% in France. In another clinical study, conducted on 2270 patients treated with a TLC-Ag dressing with polyabsorbent fibres, complete wound healing was reported in 43.9% of the patients and an improvement of the wound healing in 51.0% (with median relative wound area reductions of 100.0% and 57.4% in acute and chronic wounds, respectively) after a mean duration of 22 days of treatment.[35] In this latter study, as in our study, all clinical signs of wound infection, as well as the presence of infected wounds, were substantially reduced at the final visit. The intensity of the effect on the wound infection parameters reported in our study was also consistent with those reported in the IMAg study, where all 16 wound infection parameters documented at baseline were reduced by 70% to 91% at the final visit.[34]

In our study, as in the previous studies, effective results were reported in all wounds types, regardless of the wound infection status at baseline, while the use of systemic antibiotics was restricted to a limited number of patients.[34,35] The high rate of infection resolution achieved in the present study in the absence of systemic antibiotics, as well as the low number of new wound infections established at the final visit, were associated with a positive evaluation of the usefulness of the dressing by the majority of the participating physicians. The evidence reviewed showed that using the evaluated dressings can support the antibiotic stewardship initiative, such as suggested by previous documentary consensus.[15,23–25] However, these results should not be interpreted as evidence that the use of systemic antibiotics could be replaced in all circumstances, and while the reasons for antibiotic prescription was not collected in this study, it may be assumed that the physicians globally followed the current related guidelines.[15,16,24,25] Adjuvant prescription of systemic antibiotics is usually restricted to strict medical indications such as systemic or spreading infections but, since transition from local to systemic infection can happen seamlessly, it may also, in certain cases, be considered at an early stage for patients at high level of risk, for instance with multimorbid, immunocompromised patients or patients with a similar wound condition.[15,16]

Unsurprisingly, risk factors for wound infection were very prevalent (93.3%) in the treated cohort of this study, whether they were systemic, local, behavioural or environmental in nature. In Europe, use of antimicrobial dressings, in the presence of risks but in the absence of clinical signs of local infection remains much rarer than in the presence of clinical signs, as was the case in this real-life study or in the previous real-life studies conducted with TLC-Ag dressings.[24,34,35] Nonetheless, in relation to the few isolated cases of new wound infection established at the final visit in this sub-group of patients, the efficacy and usefulness of the TLC-Ag dressings in this indication was also strongly appreciated by the large majority of the physicians.

Investigating and identifying all these risk factors at the first wound consultation is essential to better identify those patients most likely to develop infectious episodes during the wound healing process, adapt the wound care strategy and be more alert to the potential onset of clinical signs of local infection. Involving the patient in this process could also help them understand the sensitive nature of their wound, when they should ask for an emergency consultation, and support their adherence to their treatment.

Analysis of the results by dressing revealed that the Lite Border dressing was assessed to be at least as effective as UrgoTul Ag/Silver in promoting the healing process and reducing local infection parameters, and both dressings were also similarly 'very well' or 'well' tolerated and accepted, and 'very useful' or 'useful' in the management of wounds at risk of or with clinical signs of local infection, consistent with previous evidence on TLC-Ag dressings.[30–43] The painless change of these comfortable dressings, which did not interfere with the patient's daily activities, as well as the reduction of the wound-related pain and the good management of exudate, may have contributed to the patients' acceptance of the treatment and improved their quality of life. The ease of application, conformability and acceptability of the border dressings was notably appreciated in cases of burns, bites, iatrogenic wounds or DFUs, where the location of the wounds can present additional challenges and a border dressing can facilitate wound care.

According to the consensus document on best practice recommendations for silver wound dressings, the appropriateness of a silver dressing does not depend on the aetiology of the wound but is mainly determined by the wound characteristics (level of exudate, wound depth, wound bed tissue) and the condition of the surrounding skin.[25] The range of TLC-Ag dressings, including contact layers, with 'Lite Border' versions, foams or poly-absorbent fibres, provides therefore a wide choice of effective dressings, all including the silver healing matrix and supported by clinical evidence,[30–43] but each with specific secondary properties to best meet the specific needs of each patient and their wound. A patient-centred approach is considered a key element of success in the management of wounds in general, and in the management of wounds at risk of or with clinical signs of infection in particular.

Comprehensive identification of the risks and clinical signs of wound infection, as well as the diagnosis of wound infection, requires clinical skills, especially when the host system presents some inability to mount a robust immune response. A thorough documentation of the patient's risk factors and clinical signs or direct indicators of wound infection should always be encouraged in routine practice in order to support the most appropriate wound care strategy.

Limitations of the study

The limitations of this clinical study are associated with its non-comparative design but are offset by the consistency of the results with pre-existing evidence, notably the UTAG RCT.[31] The diversity of patient characteristics and care protocols considered here and the conduct of subgroup analysis also provide a more realistic representation of what happens in real life and therefore complement the results of the previous clinical trials.

Reflective questions

- What are the elements that lead to the diagnosis of a local wound infection and a change in the management strategy in wound care practice?
- Do you consider wound infection risk factors and clinical signs of local infection in your wound care practice? Is this in a formal or informal manner?
- When selecting an antimicrobial dressing, do you consider the effects of the dressing not only on local infection parameters but also on the healing process?
- Do you consider the patient's perspectives when choosing a wound dressing?

Conclusion

The data from this clinical study support the use of UrgoTul Ag/Silver and UrgoTul Ag Lite Border dressings for their intended use in the treatment of wounds at risk of or with clinical signs of wound infection, in association with good standard of care. A unique aspect of this study was the documentation of the typical use of these dressings during the COVID-19 pandemic and the confirmation of their usefulness in the management of the treated patients. These dressings have been shown in this study to control wound infection and promote wound healing. Well tolerated and well accepted by both patients and health professionals, they remain therefore an asset in the therapeutic arsenal for the management of the intended wounds, in real-life practice. **JWC**

Acknowledgements

The authors would like to thank all the physicians who participated in this study.

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