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LABORATOIRE DERMATOLOGIQUE

A new approach to
wound healing!

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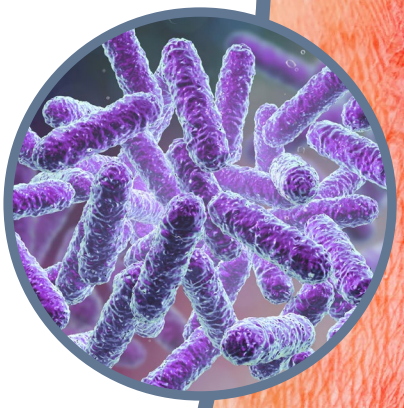

- **PERI-LESIONAL SKIN IN CHRONIC WOUNDS**
  Dr Sylvie MEAUME, *France (Paris)*
- **THE SKIN MICROBIOME: A FORGOTTEN PLAYER IN WOUND HEALING**
  Prof Brigitte DRÉNO, *France (Nantes)*
- **CICABIO+: AN ECOBIOLOGICAL APPROACH**
  Dr Stéphane FAUVERGHE, *France (Lyon)*

ECOBIOLOGY AT THE SERVICE OF DERMATOLOGY

Learn more about NAOS, a French ecobiological company and founder of Bioderma, at www.naos.com

EDITORIAL

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A new approach to wound healing
This was the title of the symposium organised by the Laboratoire BIODERMA for the Journée Dermatologique de Paris 2023.

PERI-LESIONAL SKIN IN CHRONIC WOUNDS

Dr Sylvie MEAUME, *Dermatologist - Geriatrics, France (Paris).*

Let's look at a few clinical case studies:

- Around **leg ulcers,** the skin is often covered in oily or dry scales, which are a source of concern for the patient and/or nurse. They must be removed mechanically with tweezers after each dressing and can be prevented by using suitable emollients.

- **Stasis dermatitis** is not uncommon; it can be dry or oozing and is sometimes difficult to distinguish from allergic contact eczema, or even erysipelas.
  This type of dermatitis is essentially treated with compression therapy, as well as with 1% aqueous silver nitrate for oozing and with short courses of topical corticosteroids.

- **Changes related to venous insufficiency** can manifest themselves as ochre dermatitis, asteatotic eczema or white atrophy.
  - For ***ochre dermatitis,*** which is often scaly, emollients should be recommended. Management of the venous disease will be entrusted to the vascular physician.
  - ***Asteatotic eczema*** will not benefit from topical corticosteroids – the opposite is actually true – but it can be treated with emollients and reinforced compression therapy.
  - As for ***white atrophy,*** which is fragile and difficult to treat, it requires reinforced compression therapy and the application of emollients.

- Large amounts of **exudate**, a source of skin maceration, are likely to form around a **colonised wound or in the absence of compression therapy,** despite absorbent dressings.
  The wound must then be investigated for possible infection, which in some cases will require general antibiotic therapy or debridement if the infection is local, but the use of local antibiotics or antiseptics in general should be avoided. In the presence of oedema, look for a general cause: cardiac, hepatic, renal, nutritional, etc.

- The question often arises of how to **distinguish between allergic contact dermatitis and irritant dermatitis.**
  In the event of irritation, there is no prior sensitisation, the patient feels pain and burning rather than pruritus, and the lesions have sharp contours, limited to the contours of the dressing. The onset is rapid, occurring within a few minutes to a few hours. There is no spread of the lesions. ***Contact eczema,*** on the other hand, is due to an immune mechanism, is more pruritic than painful, is not always vesicular, has jagged borders, and may extend beyond the limits of the area to which the responsible product was applied. It is likely to become more widespread.

  The treatment of ***contact dermatitis,*** whether allergic or not, involves identifying the product responsible, asking the patient about any self-medication with essential oils or other products, and carrying out use tests or allergy testing, after taking the precaution of giving the patient the list of products not to be used.

  The doctor will suggest "barrier" creams, which are emollients with ceramides; in the event of allergy or discomfort, Class 2 topical corticosteroids are indicated, in a reasoned manner.

Are you familiar with MARSI?

This is the acronym for ***medical adhesive-related skin injuries,*** which are lesions caused by adhesive products applied to the skin surrounding a leg ulcer, a stoma opening or a surgical suture. These can take the form of dermabrasion-type wounds, bullae, skin tears, folliculitis, maceration, or allergic or irritant contact dermatitis.

There are several ways to prevent them:

- ***Look after your skin,*** but without excessive bathing and showering. Always use non-detergent products, syndet or oil (with a pH close to that of the skin), as well as emollients;
- Remove adhesives using ***silicone solvents*** – do not use alcohol or ether;
- ***Use skin protectors*** containing polymers, organic solvents or silicone;
- ***Choose the right adhesive*** depending on the desired result and whether or not there is a compression bandage;
- ***Train nurses in adhesive application and removal techniques,*** noting that adhesives should not be pulled vertically, as this could tear fragile skin, particularly the skin of the elderly.

Compression therapy can also cause **skin lesions** such as purpura or oedema. Shearing or friction bullae require protection of the underlying skin. Eczema and irritant dermatitis are also possible, due to the compression devices that are nonetheless necessary for the healing of venous ulcers.

Occlusion can be responsible for **erosive and pustular dermatitis** of the leg:

- This ***particular condition,*** of inflammatory origin, occurs in the elderly and may or may not accompany a leg ulcer.
- It is characterised by ***non-follicular, amicrobial pustules in addition to scabs and erosions,*** on one or both legs, with some forms being purely erosive.
- Patients are ***often treated unsuccessfully*** for months or even years with various antiseptics, antibiotics and antifungal agents.
- ***Strong local corticosteroid therapy*** (Dermoval®, Clarelux®), continued for several weeks, is consistently effective.

THE SKIN MICROBIOME: A FORGOTTEN PLAYER IN WOUND HEALING

Prof Brigitte DRÉNO, *Dermatologist-oncologist, France (Nantes).*

Among our organs, the skin stands out for its visibility and size. It is on its surface and in its appendices that a second organ develops, i.e. the skin microbiome, made up of a myriad of micro-organisms, bacteria, viruses and eukaryotes. The skin of foetuses is sterile, so the microbiome appears at birth, taking advantage of the environment to characterise itself and therefore differing depending on whether childbirth took place by vaginal delivery or by caesarean section. Bacterial density is higher on the surface of the epidermis: the composition of the microbiome sampled by scratch testing differs from that collected via biopsy.

Four categories (phyla) of bacteria colonise the skin:

• **Actinobacteria, Firmicutes, Bacteroidetes and Proteobacteria.**
• **Cutibacterium and Staphylococcus** are of particular interest to dermatologists.

The composition of the microbiome changes over time:

On the face, Firmicutes predominate in children, while Proteobacteria are more numerous in adults. Biodiversity also changes over time, leading to chronic inflammation in the elderly. Diversity is a crucial element of the normal skin microbiome, which must be successfully maintained. The microbiome profile is obtained using traditional cultures, 16S RNA gene sequencing and, more recently, shotgun metagenomic sequencing.

The microbiome is involved in all the key phases of wound healing.

A rupture in the skin barrier destroys the microbiome that exists on the skin and creates an area rich in skin nutrients that favours the growth of opportunistic commensal or pathogenic microbes that compete with one another. This leads to an increase in skin pH and water loss, promoting the development of pathogens.

Dysbiosis in a wound varies according to its origin and the terrain in which it occurs (leg ulcer, burn, diabetic foot ulcer, etc.). For example, diabetic ulcers are mainly colonised by Streptococcus, burns by Gram-negative bacteria, and pressure ulcers by anaerobic bacteria: these different microbiomes require different treatments.

What happens when there is a wound?

A neo-microbiome appears two weeks after a wound forms, resembling that of the dermis and the deep layers of the epidermis. A healed lesion therefore does not have the same microbiome as the normal surrounding skin. The stratum corneum is covered in antimicrobial peptides (AMPs) called "antibiotic-like peptides" and thus forms an antimicrobial barrier. **If a pathogenic microbe penetrates the stratum corneum, the epidermis develops a new defence strategy:** during the healing process, there are constant interactions between commensal bacteria, their antimicrobial peptides and keratinocytes: therapeutically, the aim is to restore this balance.

To summarise, there are three targets in the skin microbiome for wound healing:

- Commensal bacteria prevent pathogenic invasions by producing antimicrobial peptides;
- Accelerate healing by limiting the duration of inflammation via the innate immune system;
- Induce the production of T-cells specific to the commensal microbes, which promote tissue repair.

Each commensal bacterium has a skin barrier protection function: it protects the skin from invasion by other pathogenic microbes.

- Cutibacterium acnes interacts with Staphylococcus epidermidis, with both bacteria having self-regulating capacities.
- C. acnes maintains the skin pH at 5.
- Streptococcus thermophilus and Staphylococcus epidermidis are involved in ceramide production.

Lastly, many commensal bacteria act to inhibit the development of S. aureus.

Activation of the innate immune system by the skin microbiome can have a negative impact:

- Excessive production of proteases, reactive oxygen species and other bio-active substances that delay healing;
- Certain external factors can alter the activity of the skin microbiome: age, nutrition, comorbidities, genetic factors, etc.
- Induction of chronic inflammation when acute inflammation has not been controlled;
- Formation of biofilms by certain bacteria.

This means efforts need to be made to strike a balance. In 60% of wounds, chronic activation of the innate immune system is accompanied by the development of a biofilm by the bacteria in the wound bed, which maintains chronic inflammation and delays wound healing.

Stress, whether physiological or psychological, modifies the profile of the skin microbiome, alters the innate immune system and stimulates the formation of a biofilm, resulting in the development of chronic neurogenic inflammation. Discovery of an injury causes the brain to send signals to the nerve endings around the sebaceous glands to produce substance P. Substance P receptors in these glands cause sebum to be produced; this in turn leads to changes in the microbiome, particularly as regards Staphylococcus aureus and epidermidis.

Therapeutic approaches take account of the fact that a healed wound does not regain the microbiome of normal skin. **The aim of treatment is to restore a skin microbiome as close as possible to the normal microbiome.**

- ***Thanks to bacteriophages***, which are intra-bacterial viruses capable of targeting resistant bacteria, Anglo-Saxons have developed topical and oral bacteriotherapy using bacterial transplants, probiotics (live bacteria), prebiotics (bacterial extracts), a combination of pro- and prebiotics, and postbiotics (antimicrobial peptides). Bacterial resistance, particularly that of C. acnes, can thus be reduced by phages, which should reduce the need for antibiotics.
- ***Probiotics from lactic acid bacteria****: induce the migration and differentiation of keratinocytes and fibroblasts, stimulate the formation of collagen, reduce the inflammatory phase and accelerate wound healing in rats.*

Key messages:

• Human skin has a complex and symbiotic relationship with the microbiome.
• The skin microbiome is involved at every stage of healing.
• By altering the skin microbiome, stress increases the risk of impaired healing.
• The microbiome of healed skin is not the same as that of normal skin.
• Bacteriotherapy to stimulate wound healing is a new, essential target for therapy.

CICABIO: AN ECOBIOLOGICAL APPROACH TO WOUND HEALING

Dr Stéphane FAUVERGHE, *BIODERMA/NAOS Medical Director.*

The concept of Ecobiology underpins the development of all Laboratoire BIODERMA products, as part of an integrative approach to skin health.

The microbiome plays a key role in each of the 4 stages of wound healing: haemostasis, inflammation, proliferation and remodelling. Diversified, it reduces colonisation by and infection with pathogenic bacteria, helps resolve the inflammatory phase, and promotes reconstruction of the epidermis.

Bioderma's ecobiological approach takes account of the need for a balanced microbiome for optimal healing. Ecobiology involves considering the skin as a living ecosystem, in constant interaction with other ecosystems.

It means acting on the biology of the skin to protect it and help it to defend itself:
- by favouring biomimetic components;
- by acting on the skin's own mechanisms;
- by acting on the causes and not just the consequences.
In this way, lasting positive effects can be achieved and recurrences limited.

This was the approach we used when designing our new innovation, Cicabio Crème+.

- **The patented Optimal Repair complex** features polyglutamic acid for surface hydration, medium-molecular-weight hyaluronic acid, which hydrates the epidermis, and xylose, a restructuring agent that penetrates deep down to contribute to healing by boosting collagen synthesis.
- These **biomimetic and biosimilar** active ingredients act on the skin's repair mechanisms, as proven by several studies:
  - K14/Involucrin immunostaining study:
  Improved proliferation and differentiation of keratinocytes from day 4 with the active complex compared to those not treated, contributing to better epidermal closure on day 7.
  - Study on a bilayer human skin model:
  As early as four days after applying the Optimal Repair complex to a wound, there was a 58% increase in keratinocyte proliferation, and the epidermis already appeared dense and stratified, with a stratum corneum.
  In comparison, 14 days after the formation of a wound not treated with Cicabio Crème+, histology showed only a slight start of healing.

Using the same human skin model, the action of Cicabio Crème+ was demonstrated from day 4, for several types of collagen: type III collagen, which improves the volume of the dermis, and types VII and XVII collagen, which are involved in the regeneration of the epidermis and cohesion between the dermis and epidermis. **The result was newly formed skin of better quality.**

In order to **restore the diversity of the microbiome**, it is important to consider the skin as an ecosystem and therefore seek to recreate a favourable environment. Tests using the Shannon index demonstrated restoration of the microbiome thanks to Cicabio Crème+: after disinfecting the skin of 20 women with 70% ethanol, which greatly degraded the diversity of the microbiome, this diversity was restored just three hours after applying Cicabio Crème+.

- **Antalgicine** is another important ingredient in Cicabio Crème+. This biomimetic active ingredient stimulates pro-opiomelanocortin, a precursor of ß-endorphin in descending nerve endings, inhibiting nociceptive messages: neuronal hyperactivity after stimulation is reduced by 85% with antalgicine. This anti-itching and pain-relieving action helps to soothe the skin and prevent scratching.

In short, Cicabio Crème+ respects the skin and its natural healing cycle by rapidly restoring the diversity of its microbiome. It nourishes, protects and soothes, while at the same time optimising the natural healing process thanks to the Optimal Repair complex.

This is reflected in the results of two clinical studies:

- 34 subjects with a post-surgical scar on the palm of the hand that had been progressing for more than three months took part in the first of these studies. **After just 14 days of applying Cicabio Crème+, there was a clear improvement in redness (-46%), thickness (-32%) and suppleness (+45%).**
- The second study, which involved women with caesarean scars, demonstrated, even in the long term, **the efficacy of Cicabio Crème+ within 14 days, particularly for the important parameter of suppleness**.

In parallel, the sun protection version of Cicabio Crème+ was launched under the name of **Cicabio Crème 50+**: in addition to the components already listed and **UVA + UVB** filters, it contains **lipoamino acids** to combat oxidative stress and help repair the dermal-epidermal junction, as well as **glabridin** to reduce hyperpigmentation marks.

- A clinical study of 31 subjects treated with laser therapy showed significant improvement within 14 days: **19% reduction in immediate erythema** observed by dermatologists, **17% reduction in hyperpigmentation** from day 3, **69% reduction in immediate burning sensations** reported by patients, as well as a feeling of comfort and protection against external stresses.

Lastly, **Cicabio Baume lavant** cleanses, purifies, soothes, protects and limits friction, to respect the integrity of damaged skin.

Therefore, with biomimetic active ingredients, a microbiome with restored diversity, and moisturised, soothed, protected and repaired skin without marks, BIODERMA is perfectly in line with the ecobiological approach.

INSPIRED BY NAOS

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Learn more about NAOS, a French ecobiological company and founder of BIODERMA, at www.naos.com

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