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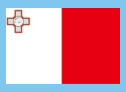

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Contents

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REVIEW

Contents

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REVIEW

Evidence based review of negative pressure wound therapy

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Abstract

Vacuum-assisted closure, sometimes referred to as microdeformational wound therapy or most commonly negative pressure wound therapy (NPWT), has significantly improved wound care over the past two decades. NPWT is known to affect wound healing through four primary mechanisms (macrodeformation, microdeformation, fluid removal, and alteration of the wound environment) and various secondary mechanisms (including neurogenesis, angiogenesis, modulation of inflammation, and alterations in bioburden) which are described in this review. In addition, the technique has many established uses, for example in wound healing of diabetic and pressure ulcers, as well as burn and blast wounds. This therapy also has many uses whose efficacy has yet to be confirmed, for example the use in digestive surgery. Modifications of the traditional NPWT have also been established and are described in detail. This therapy has various considerations and contraindications which are summarized in this review. Finally, future perspectives, such as the optimal cycling of the treatment and the most appropriate interface material, are touched upon in the final segment. Overall, despite the fact that questions remain to be answered about NPWT, this technology is a major breakthrough in wound healing with significant potential use both in the hospital but also in the community.

Key words: Negative pressure wound therapy; Chronic wounds; Microdeformational wound therapy; Vacuum assisted closure; Pressure ulcers

Core tip: Negative pressure wound therapy has been very beneficial in the wound care of many different kinds of wounds, from pressure ulcers to open fractures mostly

due to its mechanism of action which we explain in detail. We explain the original purpose of this technology and going into detail about the many different ways it is currently being used in a clinical setting. Our review also explains its advantages and disadvantages and how they could be overcome. The last part of this review discusses the future of this technology and how it will keep impacting the field of wound care.

Panayi AC, Leavitt T, Orgill DP. Evidence based review of negative pressure wound therapy. *World J Dermatol* 2017; 6(1): 1-16 Available from: URL: http://www.wjgnet.com/2218-6190/full/v6/i1/1.htm DOI: http://dx.doi.org/10.5314/wjd.v6.i1.1

INTRODUCTION

Since its introduction 19 years ago by Argenta and Morykwas, negative pressure wound therapy (NPWT) has emerged as a common treatment for acute and chronic wounds, including diabetic wounds, pressure ulcers, and burns[1]. In simple terms, NPWT refers to any device that tightly seals the wound creating a near airtight environment to which a vacuum can be applied resulting in a series of biological reactions that enhance wound healing.

The terms Vacuum Assisted Closure (VAC, KCI, San Antonio, TX) and microdeformational wound therapy (MDWT) are sometimes used interchangeably with NPWT. MDWT refers to devices (generally foam) that substantially deform the wound surface[2]. VAC now commonly refers to a family of devices using a highly porous foam based on the first commercially available NPWT device. Much of the clinical and basic science literature is based on these early devices (Figure 1). "Negative pressure" is somewhat of a misnomer as technically all pressure values should be positive.

Research on the application of NPWT in treating chronic non-healing wounds has largely taken the form of case studies, single-center studies, non-randomized controlled trials, with few randomized controlled trials (RCTs). This paper will analyze the available literature in order to summarize the current understanding of NPWT in terms of its mechanism of action, its applications, complications, contraindications and its future.

NPWT

In NPWT the wound is first filled with a porous material such as foam or gauze, that facilitates pressure transmission within the wound. A drainage port is then attached above the porous material and the wound is sealed with an adhesive film dressing. The drainage port is connected to a controlled vacuum pump which maintains negative pressure, usually ranging from -50 to -150 mmHg[2,3]. The pressure can be applied in a continuous, intermittent, or variable mode, with the continuous type being the most frequently used. In the variable mode, the suction level changes but is never turned off, whereas in the intermittent mode the pressure is switched on and off throughout the course of treatment.

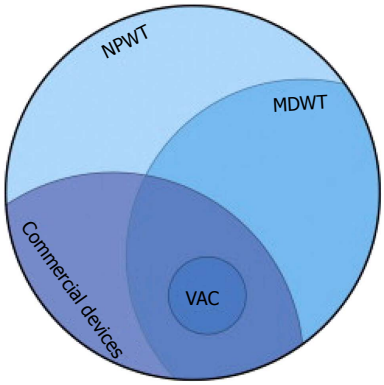

Figure 1 Visual representation of the definitions used in this article[2]. Negative pressure wound therapy (NPWT) defines the entire field of wound therapy that applies differential suction to the wound. Microdeformational wound therapy (MDWT) refers specifically to the field as applied to the science of the foam wound interface that causes deformation. The Vacuum-assisted closure (VAC) therapy system is the most commonly used commercially available device. Reproduced from, Huang C, Leavitt T, Bayer LR, Orgill DP. Effect of negative pressure wound therapy on wound healing. *Curr Probl Surg* 2014; 51: 301-331. Copyright 2016 by Elsevier.

The specific interface material that contacts the wound surface affects the biological response of the system. The most commonly used material is a reticulated open-pore polyurethane (PU) foam that forms a structure resembling a three-dimensional net. This lattice formation allows the vacuum to be evenly distributed throughout the foam and improves fluid drainage.

VAC

Three foam types are used in the VAC systems. Black polyurethane ether (VAC GranuFoam, KCI) is the most commonly used foam, and black polyurethane ester (VAC VeraFlow, KCI) is used in instillation systems. The white polyvinyl alcohol (VAC WhiteFoam, KCI) foam has very small pore sizes and is used to protect critical structures without inducing microdeformations, which will be discussed in the following section.

Gauze-based system

Usage of gauze in NPWT is based on the Chariker-Jeter method of application, which uses a moistened antimicrobial gauze (AMD; Covidien, Hampshire, United Kingdom) as a wound interface, along with 80 mmHg of negative pressure and a silicone drain[4]. In one retrospective study with a mixed group of patients with challenging wounds, gauze used as a wound filler material was found to achieve reductions in wound size and volume comparable with published data from polyurethane foam-based systems[5].

MECHANISMS OF ACTION

Primary mechanisms

NPWT is thought to promote wound healing *via* four

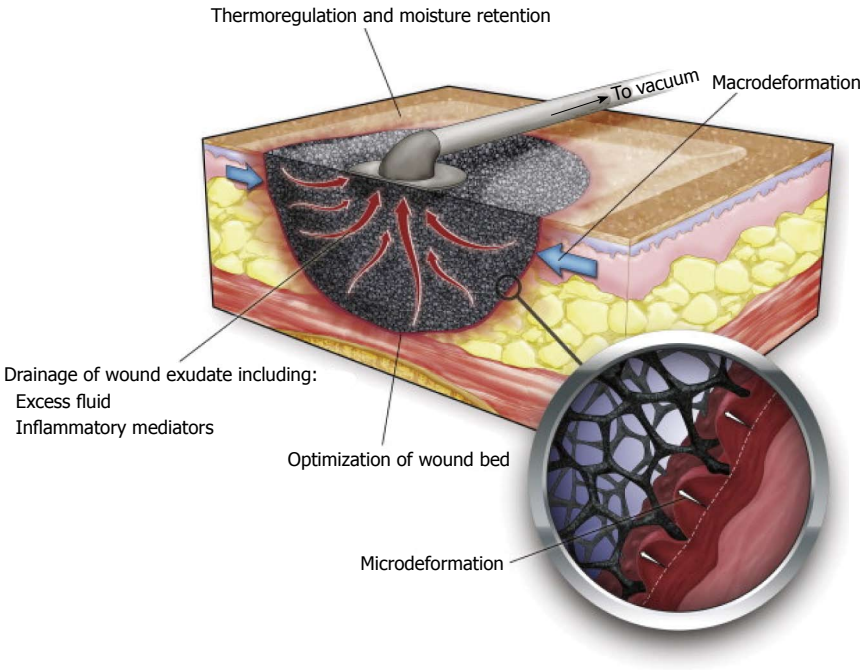

Figure 2 The 4 primary mechanisms of microdeformational wound therapy: (1) macrodeformation; (2) microdeformation (3) fluid removal; and (4) alteration of the wound environment[2]. Reproduced from, Huang C, Leavitt T, Bayer LR, Orgill DP. Effect of negative pressure wound therapy on wound healing. *Curr Probl Surg* 2014; 51: 301-331. Copyright 2016 by Elsevier.

primary mechanisms: (1) macrodeformation; (2) microdeformation; (3) fluid removal; and (4) alteration of the wound environment (Figure 2).

Macrodeformation: Macrodeformation, or simply induced wound shrinkage, occurs when suction is applied to the foam causing pore collapse. This results in deformational forces being exerted on the wound edges, which draws them together. Macrodeformation can also induce compressive forces such as when these devices are used circumferentially on extremities[6,7].

Studies in a porcine model showed that suction of 125 mmHg can decrease the volume of a PU foam by approximately 80% resulting in a substantial shrinkage of the wound[8,9]. The extent of contraction is largely dependent on the deformability of the wound[2].

The inherent tension in the dermis, which can cause wound margins to pull apart, and the attachment of the dermis to underlying structures vary in different parts of the body. Consequently different wounds contract to different degrees. For example, scalp skin is constrained by attachments to the underlying skull resulting in minimal deformation of the surrounding tissue when a foam based NPWT device is applied. In contrast, when a large open abdominal wound in an obese patient is treated with a similar device, the wound edges can be brought together in close approximation.

Microdeformation: Microdeformation describes the mechanical changes that occur on the microscopic scale when suction is applied to the porous material resulting in an undulated wound surface. For PU foam interfaces, treating wounds for several days results in a cobblestone appearance of the wound surface. Models that mimic the strain applied to a wound by the opposing forces of the suction and the sponge have been designed to investigate these mechanical changes. Using finite element analysis (FEA), these models have shown that at 110 mmHg, MDWT results in a 5%-20% strain across the wound surface. This strain directly corresponds to the percentage change in length of the material exposed to the external forces[10].

Mechanical forces, which include compression and tension from the foam, shear and hydrostatic forces from the extracellular fluid, and the effect of gravity, are transmitted throughout the tissue *via* the extracellular cell matrix (ECM). These forces vary greatly across the wound surface. For example, the tissue just underneath the foam struts is exposed to focal high compression, whereas the wound surface centrally in the pore is focally exposed to high tension[10]. Microdeformation is the morphology that occurs due to the interplay between these forces.

Shear forces affect the cytoskeleton and activate a signaling cascade that upregulates granulation tissue formation and, hence, enhances wound healing[11-13]. Furthermore, microdeformation is believed to stimulate vessel sprouting towards the wound[2]. This is described in further detail in the secondary effects of NPWT. Microdeformation causes localized hypoxia that causes an increase in local vascularity. Factors known to affect the efficiency of microdeformation include the level of suction, the pore size and the consistency of the foam, the tissue being treated and the deformability of the surrounding tissues.

Fluid removal: Fluid accumulation in the extracellular space or edema, which often occurs in chronic wounds, inhibits healing by compressing local cells and tissues. For example, during wound healing in peripheral diabetic ulcers, cell proliferation occurs due to the intrinsic tension generated in the cells by the interaction of their

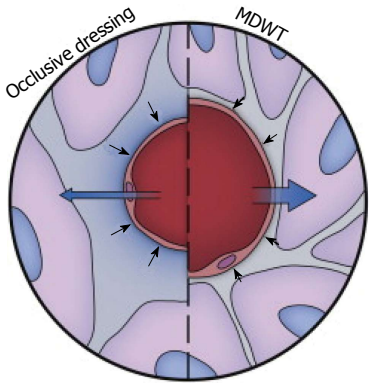

Figure 3 Removal of edema results in decreased hydrostatic compression of the capillaries and, hence, reduction of the required diffusion distance[2]. The overall increase in tissue perfusion optimises wound healing. MDWT: Microdeformational wound therapy. Reproduced from, Huang C, Leavitt T, Bayer LR, Orgill DP. Effect of negative pressure wound therapy on wound healing. *Curr Probl Surg* 2014; 51: 301-331. Copyright 2016 by Elsevier.

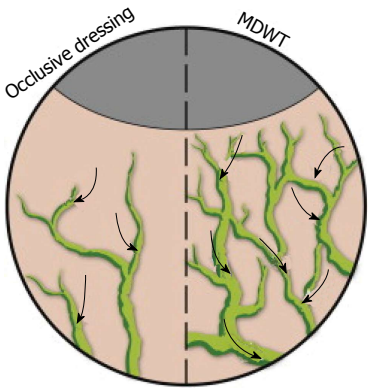

Figure 4 Lymphatic drainage is promoted though gradual increase in the density of the lymphatics at the wound edges[2]. MDWT: Microdeformational wound therapy. Reproduced from, Huang C, Leavitt T, Bayer LR, Orgill DP. Effect of negative pressure wound therapy on wound healing. *Curr Probl Surg* 2014; 51: 301-331. Copyright 2016 by Elsevier.

cytoskeleton and the ECM[14]. Fluid accumulation in the extracellular space elevates pressure in the interstitium and inhibits proliferation by decreasing the buildup of intrinsic tension. Since the fluids in the extracellular space communicate with the surface of the wound, vacuum application can remove fluid from the wound. Depending on the type of wound, significant amounts of fluid can be removed, as is the case with open abdominal and fasciotomy wounds. By removing fluid, the compression forces acting on the microvasculature allow increased blood flow and perfusion of the tissue (Figure 3)[1]. The adhesive film dressing covering the wound is semipermeable and hence allows some air to enter the system preventing a fluid lock and enabling continuous fluid removal. Other devices have been designed to let a small amount of air into the system through a remote port.

NPWT is believed to affect the lymphatic system *via* two mechanisms. First, since edema is cleared *via* the lymphatic system, by removing fluid, NPWT concurrently reduces the burden on the lymphatic system. Second, NPWT promotes lymphatic drainage by inducing a gradual increase in the density of the lymphatics at the wound edges (Figure 4)[15].

Alteration of the wound environment: When fluid is evacuated, electrolytes and proteins are removed that may stabilize osmotic and oncotic gradients at the wound surface[14]. The foam and drape act as insulators maintaining a warm wound environment[2]. The drape is semipermeable and helps maintain a sterile, moist environment by reducing wound contamination with microorganisms and minimizes water evaporation from the wound. In addition, NPWT can be more comfortable to patients by reducing the number of dressing changes. Special types of NPWT have been designed that serve to address specific issues in healing. For example, foam can be bound with antimicrobial silver or bioactive factors.

Secondary effects

The four primary mechanisms of NPWT affect various wound healing processes including neurogenesis, hemostasis, angiogenesis, modulation of inflammation, cellular proliferation, differentiation, and migration, granulation formation, and alterations in bioburden.

Neurogenesis: MDWT has been linked to enhanced neural growth and neuropeptide expression through upregulation of neurotrophin nerve growth factor, substance P, and calcitonin gene-related peptide[16]. Epinephrine and nonepinephrine show a transient elevation, which is followed by a slower but more long-lasting elevation of substance P and neuropeptide Y (Figure 5). Neuropeptides are believed to be key homeostatic factors in the skin which play a role in the secondary effects of NPWT. The extent of neurogenesis has been directly linked to the level of microdeformation. In addition, intermittent suction results in greater neurogenesis than continuous MDWT[16].

Hemostasis: NPWT is postulated to promote haemostasis *via* two mechanisms. First, the negative pressure is believed to constrict and occlude small blood vessels mechanically reducing hemorrhage. It should be noted that this constrictive effect persists even after negative pressure is discontinued. Second, compression due to negative pressure strongly apposes the dressings to the wound surface favoring clot formation by the gauze[17]. In terms of the appropriate usage of the device, suction is applied when hemostasis is nearly complete, taking special care in patients with coagulopathies. In addition to the filler material, dressing, connecting tube and the vacuum pump, most systems also have a fluid collection canister which sounds an alarm when full, alerting clinicians of excessive blood loss[18].

Angiogenesis and blood flow: MDWT treatment of chronic wounds results in increased microvessel density[19]. Microdeformation causes temporary hypoperfusion to the

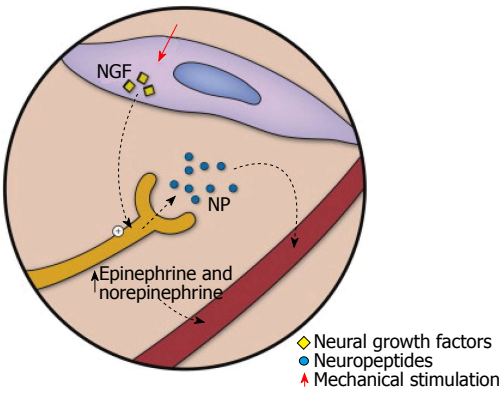

Figure 5 Microdeformational wound therapy promotes neurogenesis *via* upregulation of substance P, neurotrophin nerve growth factor, and calcitonin gene-related peptide[2]. Plasma epinephrine and norepinephrine are also transiently elevated. Reproduced from, Huang C, Leavitt T, Bayer LR, Orgill DP. Effect of negative pressure wound therapy on wound healing. *Curr Probl Surg* 2014; 51: 301-331. Copyright 2016 by Elsevier.

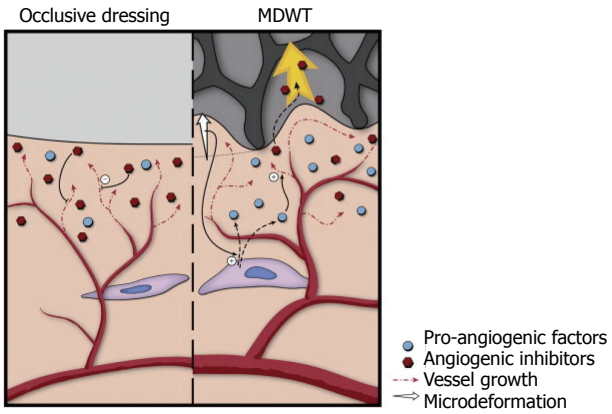

Figure 6 Angiogenesis is stimulated *via* several mechanisms, including microdeformation, upregulation of proangiogenic factors and removal of inhibitory factors[2]. MDWT: Microdeformational wound therapy. Reproduced from, Huang C, Leavitt T, Bayer LR, Orgill DP. Effect of negative pressure wound therapy on wound healing. *Curr Probl Surg* 2014; 51: 301-331. Copyright 2016 by Elsevier.

wound edge resulting in localized hypoxia of the tissues, subsequent upregulation of hypoxia-inducible factor-1α and in turn increased VEGF expression[20]. Ultimately this leads to increased angiogenesis (Figure 6). Similar results to angiogenic response stimulation have been replicated in *in vitro* studies using intermittent MDWT[21]. Furthermore, *in vivo* studies in patients have shown a difference between the initial and final stages of wound healing. Initially MDWT results in upregulation of angiogenin-2 (Ang-2) expression and downregulation of angiogenin-1 (Ang-1) expression, hence leading to decreased ratios of Ang-1/Ang-2. This favors destabilization and regression of microvessels leading to increased angiogenesis. In contrast, in the latter stages, Ang-1 is increased and the ratio of Ang-1/Ang-2 also increases. Phosphorylation of tyrosine kinase receptor-2 is activated, enhancing microvessel stabilization and promoting microvessel maturation[22].

Using a deep tissue wound in a porcine model it was shown that a maximum fourfold increase in blood perfusion occurs when suction of 125 mmHg is applied to a PU foam. It was also shown that higher suction levels of 400 mmHg and above inhibit blood flow as the capillaries distort. In healthy human skin suction levels of up to 300 mmHg applied to a PU foam cause a fivefold increase of blood flow while suction on a Polyvinyl Alcohol (PVA) foam results in a threefold increase[23].

Topical negative pressure has been shown to stimulate vessel proliferation and neo-angiogenesis. Topical negative pressure applied to chronic wounds of 16 patients (-125 mmHg) in preparation for reconstruction with free or pedicled flaps has been shown to considerably increase blood vessel density, reaching a maximum of approximately 200% in contrast to the vessel density prior to treatment[24].

Modulation of inflammation: MDWT promotes active wound healing by simultaneously inducing inflammation while removing harmful components of inflammation such as infiltrating leucocytes, cytokines, and matrix metalloproteinases. Wounds treated with MDWT display increased cellularity of wound exudate with elevated erythrocytes and leukocytes, along with increased gene expression of leukocyte chemoattractants, such as CXCL5 and IL-8[25].

Topical negative pressure with reticulated open cell foam (ROCF) has been shown to increase expression of various pro-healing anabolism-related genes. This includes increased expression of extracellular matrix genes resulting in increased production of the proteoglycans epiphycan and fibronectin. Other genes found to be upregulated include CD163 and macrophage scavenger receptor 1 which are involved in macrophage signalling[26].

Cellular responses-proliferation, differentiation, and migration: Cells have long been known to undergo proliferation and division when exposed to mechanical stresses[27]. Consequently, cells can be induced to undergo these cellular functions by exposure to dynamic physical inputs. MDWT is largely based on this principle; the tissue microdeformation stimulates cellular proliferation enhancing wound healing. This effect has been shown to upregulate angiogenesis and epithelialization in chronic wounds in a rabbit model[28].

Studies using a diabetic mouse model found that application of short (6 h) intermittent MDWT results in increased expression of Ki-67, a marker for proliferation. The level of strain induced in the tissue by MDWT is the same level of strain required to induce cell proliferation *in vitro*[13].

It is believed that isometric tension is heavily involved in promoting cellular proliferation[29]. In the absence of isometric tension, growth factors and cell attachment to ECM proteins are essential but insufficient for cellular proliferation. Chronic wounds tend to lack the structural scaffolding needed for cell adherence and hence the development of isometric tension. Consequently cells undergo spherization and apoptosis. Suction applied

during MDWT is believed to generate the necessary forces within the tissues that enable isometric tension and hence cellular proliferation[13].

In addition, gene ontology enrichment analysis of tissue treated with MDWT has shown increased epithelial cell migration in the tissue[25]. Analysis of histologic penetration depth showed increased endothelial migration in tissues, whereas migration assays indicated enhanced dermal fibroblast migration[30,31]. MDWT also enhances migration of resident skin mesenchymal cells and circulating progenitor cells into granulation tissue[32].

Interestingly, although migration and proliferation of epithelial cells is increased by MDWT, differentiation is decreased. By downregulating keratin genes, such as KRT1 and KRT2, and major cornified envelope genes, such as annexin A9 and loricrin, MDWT inhibits keratinocyte differentiation[25]. This decrease is believed to be due to the changes induced in the wound tissue matrix as mesenchymal stem cell lineages are highly specific to the mechanical characteristics of the ECM. For example, mesenchymal stem cell neurogenesis, myogenesis, and osteogenesis are guided along soft, stiffer and rigid matrices, respectively[33]. Overall, MDWT is believed to promote wound healing by modulating cellular proliferation and migration, whilst inhibiting epidermal development and maturation[25].

Granulation tissue formation: MDWT affects the proliferation stage of repair by inducing robust tissue granulation, cell proliferation, and blood vessel sprouting. Research on mast cell-deficient mice has shown that all three processes require early and continuous activation by mast cells[34]. Collagen maturation is strictly dependent on mast cells in order to proliferate and remodel. Interestingly, MDWT application in mast cell-deficient mice, has no effect on collagen maturation, as expected, but does induce an increase in collagen production. In the control mice, both production and maturation were increased. Consequently, collagen production is not believed to be dependent on mast cells[34].

MDWT relies heavily on mechanotransduction, whereby mechanical forces are transduced by cells into biological triggers for various processes, including gene expression[35,36]. Mechanotransduction signalling in MDWT is a relatively new area of study. The current theory supports that molecules in the hypoxia pathway, such as nitric oxide, are involved[18].

In vitro studies using tissue engineering bioreactors have held a dominant role in simulating the *in vivo* micromechanical environment and the foam-wound interface. For example, tissue analogues subjected to topical MDWT for 48 h in a 3-dimensional bioreactor model of the wound bed environment displayed that fibroblast cell bodies undergo morphological change, from elongated bipolar to thickened morphology. Another observation following this treatment was the presence of dense actin cortical structures[37].

Research on a 3-dimensional fibrin matrix model found that MDWT increases cytochrome c oxidase levels, energy charge, and the adenosine triphosphate (ATP)-adenosine diphosphate (ADP) ratio in fibroblasts. The increased energy was found to be utilized by healing biomechanisms. Two important factors required for collagen production during granulation formation, growth factor TGF-β and platelet-derived growth factors (PDGF) α and β, were also shown to increase with simultaneous application of subatmospheric pressure and a reticulated open-cell foam. In addition to upregulating collagen formation, PDGF α and β upregulate glycosaminoglycans and fibronectin synthesis in fibroblasts[31]. Upregulation of fibroblast growth factor, TGF-β1, Type I collagen α1, and smooth muscle actin α2 messenger RNA expression has also been observed in cells 48 h after been exposed to a suction, foam or perfusion bioreactor[32].

The rate of granulation formation with NPWT therapy with a PU foam was measured in a porcine model by determining the decrease in wound volume over time. Increased rates of granulation formation were seen with continuous (63%) and intermittent (103%) application of suction. Continuous treatment is believed to be less effective than intermittent treatment because the cells in the wound become accommodated, and hence less responsive, to continuous physical forces[38].

Intermittent suction application inactivates capillary autoregulation, hence increasing tissue perfusion, and enables the production of new cellular components by allowing time between cycles of cell division for the proliferating cells to rest. Continuous stimulation on the other hand is believed to switch off mitosis. Despite this, many clinicians prefer to use continuous treatment for the first 48 h, before switching to the intermittent mode, because it is better tolerated by patients[39].

Alterations in bioburden: Changes in bioburden occur as a result of NPWT. However, studies related to this have produced mixed results. One study showed that NPWT results in decreased presence of non-fermentative gram-negative bacilli, but increased load of Staphylococcus aureus[40]. Other studies found no significant difference in bacterial levels when foam dressings were used with and without suction. These experiments, however, used nonviable tissue and focused primarily on the effect of suction on bacterial load[41]. It is believed that the decreased bacterial load occurs due to an interplay of multiple factors, not just due to the effect of suction[42,43]. Experiments on foam material found high bacterial loads in sonicated foams, and very high polymicrobial bacterial loads in all foams studied[44]. Porous PU foams on high suction (125 mmHg) were found to have a lower level of bacteria than PVA foams on lower suction. In addition, increased angiogenesis and blood perfusion may increase infection resistance by increasing inflow of oxygen in the wound tissue.

CLINICAL APPLICATIONS OF NPWT

NPWT has been used to treat wounds in numerous different anatomical locations, with different levels of

complexity and varying pathologies. The following section will review the evidence available on the application of NPWT in different wounds.

Open wounds

Basic applications of NPWT: At its most basic application, NPWT has been used in the management of open wounds, where the foam is directly applied to the wound bed. Common targets are poorly healing ulcers such as those caused by diabetes, venous or arterial pathologies and pressure necrosis.

More specifically, NPWT has been found to promote wound area reduction, wound bed granulation and clearance of microbial infection in diabetic foot ulcers[45]. NPWT has been associated with a higher rate of limb salvage[46]. Furthermore, treatment of diabetic, arterial and venous ulcers in high-risk patients using NPWT results in a higher rate of successful closure, with the greatest difference seen in venous ulcers[47]. When NPWT is applied earlier on in the treatment these wounds display faster healing times[47]. In nonoperative treatment of scleroderma ulcers, NPWT has been found to prevent digit amputation[48]. In the treatment of pressure ulcers, NPWT has been shown to reduce the surface area, volume and depth of wounds, to enhance granulation and to decrease the likelihood of hospitalisation[39,49,50]. Vowden K NPWT may also be effective in treating nonhealing deep-pressure ulcers covered by soft-necrotic tissue which require rapid formation of granulation tissue[51]. It is important to be noted that NPWT needs to be used concurrently with disease specific treatment, for example medical treatment for vasculitis and pyoderma gangrenosum[52].

In the treatment of surgical wounds, NPWT often acts as the pre-treatment before a skin flap or graft, or before secondary closure with NPWT. More specifically, in the excision of melanoma, NPWT enhances both functional (improves vascularity) and cosmetic (scar reduction) outcomes[53], whereas in the postoperative treatment of lymphangioma in children it is believed to decrease the risk of recurrence and infection[54].

Skin graft and dermal scaffold recipient site preparation: NPWT is often used to prepare a recipient site for skin grafts and dermal scaffolds. Large wounds, where granulation tissue spans the entire wound, can be rapidly closed with autologous skin grafting. One prospective RCT investigated the efficacy of NPWT prior to skin grafting in patients with acute traumatic wounds. NPWT improved total successful graft uptake, decreased regrafting, and required shorter lengths of hospital stay[55].

Dermal scaffolds are often used in wounds where tendon or bone is exposed to induce vascularization of the wound bed in preparation for skin grafting[56,57]. Concurrent treatment with NPWT and dermal scaffolds (Matriderm, Dr Suwelack Skin and Health Care AG, Billerbeck, Germany) enhances the contact between the wound surface and the scaffold and is believed to result in scars with higher elasticity and more natural skin pigmentation, and a decreased occurrence of postoperative wound contamination one year post-operatively[58].

Combination therapy: Various bioactive factors have been incorporated in NPWT to enhance efficacy.

Silver has been used in various wound dressings and has proven useful in burn care[59]. In NPWT therapy, silver was added to the coating of the PU foam in order to decrease the bacterial load in the wound. In a goat model of complex infected orthopedic wounds, silver dressings placed beneath the negative pressure dressings resulted in a decrease in the bacterial load, most notably in the numbers of *S. aureus*[60]. The MDWT foam can be modified to contain silver in order to act as an antimicrobial agent, as has been used in wound bed preparation for substantial split-thickness skin grafts (STSGs) to treat recalcitrant venous stasis ulcers[61]. However, silver-infused dressings are not always indicated[62].

A combined treatment of NPWT, platelet-rich plasma (PRP), STSGs and bilayered acellular matrix grafting was found to completely heal a large necrotizing fasciitis wound in a patient with diabetes[63]. Furthermore, one study used a combination therapy of PRP and NPWT on patients with sternal osteomyelitis and sinus tract after thoracotomy. The treatment regimen was PRP gel on the day of surgery followed by continuous NPWT for 20 d. This combination therapy was found to shorten the sinus tract sealing time, wound healing time, and length of hospital stay. Secondary repair surgery was also avoided[64].

Instillation therapy is the injection of fluid, such as normal saline, into the wound through a port on the NPWT connecting tube to enhance wound healing (Figure 7). This technique has been successfully applied in massive venous stasis wounds to reduce bacterial concentrations in the wound prior to STSG. A single-delivery-instillation system, whereby a series of intermittent cycles of MDWT was followed by a single injection of dilute sodium hypochlorate solution, appeared to create good wound bed preparation[65].

In continuous-instillation MDWT a second port is connected to the continuous-drip system, which can allow continuous instillation of a fluid, for example insulin, to decrease the time required for wound healing[66]. In full-thickness excisional wounds in a porcine model, NPWT with simultaneous irrigation with polyhexanide biguanide (PHMB) or saline showed improved wound healing with either irrigation solution when compared with NPWT alone[67]. Other factors which can be instilled are dilute Betadine, doxycycline, phenytoin and lactoferrin. Further research is needed to investigate the efficacy of this concept[68]. Instillation MDWT has been recommended in patients with multiple comorbidities with difficult wounds, although without high level of evidence to support these recommendations[69].

Further examples of adjuvants include platelet gel, activated protein C, arginine-rich dietary supplements, and Manuka and Leptospermum honeys. Platelet gel, added to the wound bed following initial NPWT, has been used in

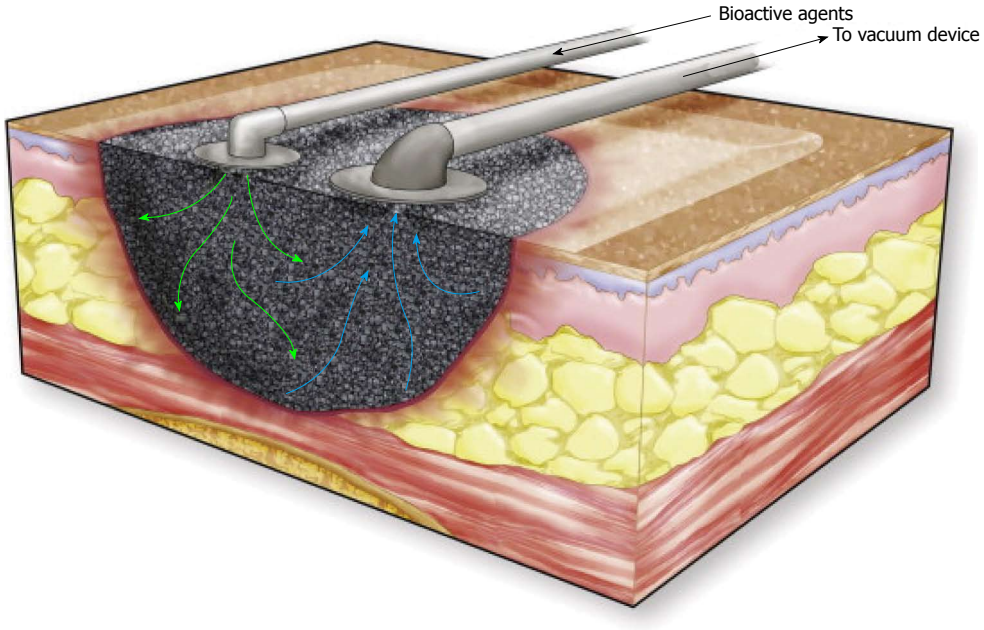

Figure 7 Instillation vacuum-assisted closure[2]. Fluid, such as normal saline, is instilled into the wound through a port on the connecting tube to enhance wound healing. Reproduced from, Huang C, Leavitt T, Bayer LR, Orgill DP. Effect of negative pressure wound therapy on wound healing. *Curr Probl Surg* 2014; 51: 301-331. Copyright 2016 by Elsevier.

the treatment of a nonhealing ileocutaneous fistula leading to complete wound healing[70]. In orthopedic wounds, activated protein C, an anticoagulant, was injected into the wound bed resulting in a decrease in the area and depth of the wound and an increase in granulation tissue formation[71]. Studies on the use of arginine-rich dietary supplements, which are believed to enhance local circulation at the wound bed, have shown that treatment with the supplements results in complete healing of infection-induced wound dehiscence with only one month of treatment and no recurrence at the 6-mo follow-up[72]. Leptospermum and Manuka honeys have been used in the treatment of a nonhealing postsurgical wound and an abdominal phlegmonous lesion, respectively[73,74].

NPWT in burns: NPWT has been found to preserve perfusion in acute partial-thickness hand burns[75]. It has also been used as a dressing over a dermal substitute in burn wounds, where it was believed to have no effect on graft adherence, but did improve long-term scar elasticity[76]. When NPWT was used with porcine acellular dermal matrix (ADM) dressing as combination therapy in deep burn wounds it was found to decrease wound exudate and bacterial load and promote wound healing[77]. NPWT has also been used in a patient with major third and fourth-degree high voltage electrical burns to enhance granulation tissue formation in preparation for skin grafting. Through the use of NPWT, major chronic soft tissue defects in the right leg were covered and amputation was avoided[78].

Treatment of deep infected wounds: The efficacy of NPWT in deep wounds has been studied using soft tissue blast injuries in porcine models. In these models, NPWT was found to decrease bacterial load, inhibit infection-induced tissue necrosis, and induce early initiation of granulation tissue formation[79]. Research on humans has shown that NPWT is effective in controlling infection, specifically in thoracic and abdominal wounds.

NPWT in open fractures: NPWT has also been used in the treatment of open wounds with exposed bone or joints, where it is believed to keep the wound moist, warm and sterile by preventing external contamination. The rate of wound healing in open fractures has also been shown to be expedited with NPWT[80]. Furthermore, the rate of deep infection in open tibial fractures is believed to be lower in NPWT treated wounds than in conventional treatment[81]. Treatment with NPWT in an open left knee-joint wound, induced formation of granulated wound bed which fully covered the exposed bones and joint[82]. NPWT is especially important in cases where free-flap transfer is contraindicated[82,83]. NPWT in Gustilo grade ⅢB open tibial fracture treatment helps reduce the size of the flap required but can also eliminate the need for a flap transfer all together. However, it should be noted that treatment with duration longer than 7 d was associated with higher likelihood of infection and amputation[84]. NPWT in patients with grade Ⅲ open fractures significantly reduced bacterial load at the wound site, as well as decreasing the risk of recurrent infection[85].

Deep sternal wound infection: Use of NPWT as the first line of therapy in deep sternal wound infections (DSWI) has been shown to decrease rates of early reinfections, as well as reducing numbers of late chronic sternal infections and mortality[86]. The length of hospital stay is also shortened by 1 wk[87]. In methicillin-resistant DSWIs

following cardiovascular surgery, MDWT has been shown to decrease length of hospital stay, healing time, and infection recurrence[88].

NPWT is believed to have the ability to stabilize the thoracic cage, improving hemodynamics and pulmonary status. NPWT in conjunction with a tissue flap can provide adequate control of infection preventing sepsis and hemodynamic instability[89]. In the presence of poststernotomy osteomyelitis, adequate debridement and antibiotic therapy is still necessary with the use of NPWT[90,91].

NPWT as an augmented surgical drain: NPWT enables improved drainage of the fluid which builds up in anatomical cavities or abscesses in deep wound infections. For example, application of NPWT in the treatment of a deep neck abscess reduced the need for open thoracotomy by preventing accumulation of purulent material[92]. Concurrent open window thoracotomy and NPWT was found to eradicate local infection and hence control sepsis in postoperative or recurrent pleural empyema. In complex chest wall wounds NPWT inhibited empyema recurrence and enhanced lung expansion[93]. A modified NPWT therapy has been used to treat deep cavitary defects, such as those caused by blast injuries or high-velocity projectiles. By connecting a superficial foam dressing to the surgical drain, deep cavitary defects can be converted into superficial ones. This modified therapy can apply suction deep in the wound cavity and result in a decrease in the dead space, reduced edema and lower risk of infection. In comparison to traditional VAC therapy, draining is enhanced, and the risk of deeper cavities closing off is minimized[94]. VAC therapy has been successfully used in cases of Hidradenitis suppurativa where immediate primary closure was not possible secondary to the large size of the defect. An internal VAC was found to accelerate delayed closure and reduce the rate of recurrence in hidradenitis excisions[95].

NPWT as biologic sampling device: NPWT is increasingly being used as a biologic sampling device, where mediastinal fluid is collected from the wound and cultured for microorganisms. In one study, NPWT was found to increase the rate of detection of microorganisms and was recommended as a replacement to traditional biologic sampling devices[96]. On the other hand, microbiology of NPWT specimens in patients with prosthetic vascular graft infections was found to have limited diagnostic value, with anaerobe species being the most poorly identified in NPWT foam samples[97]. Additional studies are, however, required before general conclusions on the efficacy of NPWT as a sampling device can be drawn.

Intra-abdominal NPWT: A further potential target for NPWT are deep intra-abdominal wound infections.

Specifically, in a case of acute necrotizing pancreatitis, placement of NPWT foam dressing in the opening created during lesser sac marsupialization in classical laparotomy was found to accelerate wound closure, hence improving patient outcome[98]. In addition, examination of wound secretions improved, abdominal compartment syndrome was prevented and care was overall simplified. NPWT has also been successfully used endoscopically in the treatment of rectal wall anastomotic disruptions[99].

NPWT and gynecological laparotomy: NPWT has also been used as a prophylactic measure in laparotomy wounds in patients with gynecologic malignancies. The rate of wound complications was similar in patients who received traditional treatment and those receiving prophylactic NPWT dressing, despite those receiving NPWT having significantly higher BMIs[100].

NPWT and soft-tissue sarcomas: NPWT has been shown to be safe and effective as an adjunct to wound closure in cases of wide tumor resection for soft-tissue sarcomas. Continuous suction, with pressures from -200 to -300 mmHg, was applied on the soft-tissue defects as preparation for wound closure. This treatment was found to decrease wound complications, such as post-operative infection and recurrence, while also reducing edema, draining exudate, and promoting granulation tissue formation[101].

NPWT and congenital deformities: NPWT holds potential for the treatment of congenital deformities such as giant omphalocele[102] or complex gastroschisis[103]. However the efficacy for this has yet to be established and the treatment is not approved by the Food and Drug Administration (FDA). In pediatric patients, the granulation tissue response is often much more robust than in adults, often leading to more frequent dressing changes to avoid ingrowth into the interface material.

NPWT and digestive surgery: Most recently, there have been suggestions of using NPWT in digestive surgery, however this use is yet to be established. One previous pilot study investigated NPWT use following ileocecal resection in Crohn's disease and found that NPWT shortened length of hospital stay by 70%-80%[104]. It is important to note that one major concern of NPWT use in digestive surgery is the development of enteric fistulas due to negative pressure[105]. Prophylactic NPWT at the ostomy closure wound in patients with ulcerative colitis was found to be safe with no enterocutaneous fistula formation or postoperative bleeding. However, in this particular study, no effect on the duration of wound healing was observed and the prophylactic efficacy of NPWT could not be proven[106]. Further studies are needed to prove the efficacy of NPWT in digestive surgery.

VARIATIONS OF THE TRADITIONAL NPWT SYSTEMS

Incisional NPWT

The literature supporting the use of NPWT over clean

incisions has mixed results. Clean, closed surgical incisions displayed decreased rates of seroma and hematoma formation in porcine models[107]. Decreased rates of seroma, as well as haematoma formation have also been reported in post-bariatric patients receiving incisional NPWT[108]. Topical NPWT applied to closed incisions also decreases the risk of infection[109-112]. In total hip and knee arthroplasty, NPWT has been shown to be beneficial by decreasing excessive hospital stay and achieving a more predictable length of hospital stay. Wound complications, such as superficial wound infections and prolonged wound exudate, were also reduced[113]. Furthermore, in total hip arthroplasty incisional NPWT was found to decrease the rate of postoperative seromas[114], whereas in abdominal wall reconstruction it was found to reduce the incidence of incisional wound dehiscence[114,115]. Incisional NPWT in the reconstructive surgery of poststernotomy mediastinitis was found to decrease the duration of required therapy, length of hospital stay, and failure of treatment[116]. Peri-incisional lateral stress is reduced by approximately 50% following NPWT application and the directions of these stress vectors mimicked the distribution found in intact tissue[117]. Evidence from this research has supported the development of systems such as Prevena™ Incision Management System (KCI, an Acelity company, San Antonio, TX) which is specifically designed to be used in incisional wounds. Prevena™ has successfully been used in closed sternal incisions in cardiac patients where it has been shown to result in favorable outcomes within 30 d post-surgery[118]. A recent literature review has recommended the use of incisional NPWT in all patients with high risk of developing surgical site occurrences and those undergoing a high-risk procedure or a procedure that would have morbid consequences if complications occurred[119].

In contrast, VAC therapy in high risk patients with lower extremity and abdominal wound incisions had no significant effect on infection and dehiscence rates[120]. It should be noted that one prospective analysis of 21 patients who received NPWT post primary knee arthroplasty found no benefit in wound healing with NPWT, with the only notable benefit being less wound leakage and better protection of the incisional site. This study was, however, limited by the small sample size and the results need to be validated by a larger prospective RCT[121].

Skin graft immobilization

NPWT is used in STSGs in the place of a bolster, which is traditionally used to immobilize the graft by applying gentle pressure[122,123]. NPWT stabilizes the graft, drains excess fluids, and promotes better contact for graft integration enhancing vascularisation[122-125]. NPWT has been shown to decrease the risk of reoperation in cases of congested lower extremity pedicle and free flaps by decreasing venous insufficiency and tissue edema, promoting granulation and, hence, preventing further flap necrosis[126]. Furthermore, NPWT decreases venous congestion in random local flaps used in complex ankle wounds, hence decreasing the likelihood for ischemia and distal necrosis and enhancing their viability[127]. NPWT is also used in the treatment of large back donor sites for head and neck free flaps where it is believed to decrease complications. NPWT has successfully been used in degloving injuries to immobilize skin grafts[128,129], or as adjuvant treatment with a dermal regeneration template[130].

CLINICAL CONSIDERATIONS

NPWT has been used in various wound types and its use in poorly healing wounds is FDA approved. The KCI VAC therapy system, which is widely used, lists acute, subacute, chronic, traumatic, dehisced wounds, ulcers, partial-thickness burns, grafts and flaps as indications for use in its manufacturer guidelines[131].

Contraindications

Use of NPWT is contraindicated in untreated osteomyelitis, when necrotic tissue or malignancy is present in the wound, in nonenteric and unexplored fistulas, and when there is exposed vasculature, nerves, anastomotic sites, or organs[107]. It should be noted that NPWT has been used successfully in contraindicated cases such as in cases of osteomyelitis[91], exposed organs[98], and exposed anastomotic sites[132].

Numerous potential patient risk factors that require consideration have also been identified. NPWT is contra-indicated in patients with high risk of bleeding or hemo-rrhage or those who are on chronic anticoagulation or antiplatelet treatment[133]. In addition, the patient's body habitus needs to be considered.

Direct contact of exposed tendons, nerves, vasculature and organs with PU foam under vacuum forces can also result in complications. Hence, in cases where NPWT needs to be applied in close proximity to exposed structures, these structures can be covered with a nonadherent barrier layer such as petroleum gauze and nonadherent dressings[134]. In addition, an isolation sterile bag has been described for intra-abdominal dressings in which the VAC foam is placed inside a sterile bag (3M SteriDrape Isolation Bag) whose surface has been perforated, allowing fluid drainage whilst simultaneously protecting the surrounding tissue[97].

Possible complications

Complications that have been mentioned in the literature include infection and sepsis, foam retention in the wound, tissue adherence, bleeding, and pain (Figure 8). Although in the most serious cases bleeding and infection have led to death, these complications occur very rarely[107]. Death associated with NPWT application at home or in long-term care facilities, is most commonly due to massive bleeding. Consequently, care needs to be exercised when selecting patients to apply NPWT at home, particularly in wounds of high risk for bleeding. In open abdominal

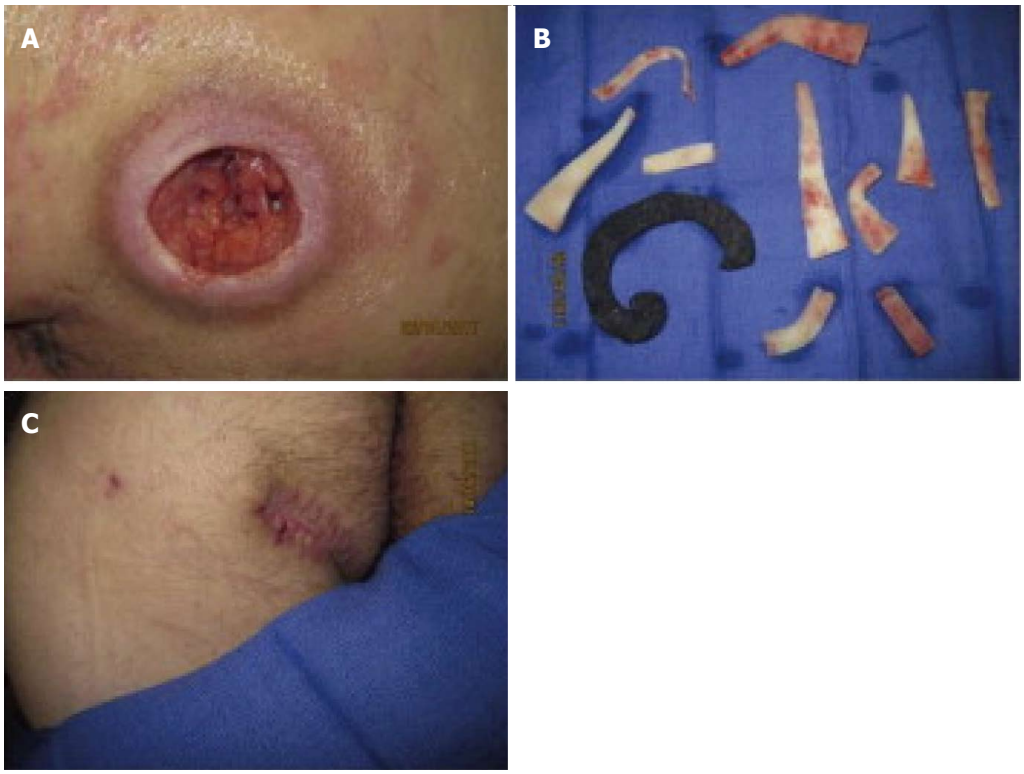

Figure 8 Infection and sepsis, foam retention in the wound, tissue adherence, bleeding, and pain[2]. A: Treatment of L-1 partial paralysis and left ischial pressure ulcer with microdeformational wound therapy for 2 m; B: Discovery of retained foam; C: Wound healing following removal of foreign material and flap surgery. Courtesy of Brigham and Women's Hospital.

wounds the tension generated on the proximal bowel of the stoma during NPWT has been seen to cause stomal mucocutaneous dehiscence[135].

The frequency of dressing changes can also affect treatment outcome. For example, in a case of NPWT treatment of a stage IV ischial pressure ulcer, spreading infections were masked, resulting in necrotizing fasciitis, as the dressing was changed at 5 d intervals[136].

Special consideration should be taken when treating blast wounds with NPWT, as application has been linked to increased rates of sepsis[137]. If applied before complete debridement is performed, it should be changed more frequently until the debridement is complete. Blast wounds have deep cavitary defects and the tail of the foam placed within the cavity has a higher chance of retention[94]. Currently, most interface materials do not have any indicator that can be visualized on X-ray. Great care must therefore be taken when changing the interface material to ensure complete removal.

FUTURE PERSPECTIVES

Interface material

Various interfaces have been developed through the years. At the moment, reticulated open-pore foams have been the most carefully studied and are considered to be able to transmit suction over long distances and to induce tissue microdeformation. Furthermore, the pore size in the foam material is believed to be directly related to the level of granulation tissue formation, where larger pores induce higher production of granulation tissue[138]. Further research related to optimal interface materials for different clinical situations is necessary.

Optimal cycling

To date, research supports that short, intermittent NPWT induces a more robust tissue response in biological systems than continuous mechanical forces[16]. However, in one study, continuous NPWT application and variable application (every 2 d for 4 h) were found to induce a similar granulation tissue response. Furthermore, very fast cycle times seem to decrease granulation tissue formation by causing damage to nascent granulation tissue[8,139,140]. Intermittent therapy is also often not adhered to by patients because of patient discomfort. Additionally, optimal cycling varies with the type of wound. A chronic ulcer, for example, may be best treated with continuous suction throughout treatment, whereas an acute wound, may respond better to continuous suction for 48 h, followed by cycles of intermittent therapy[135].

Optimal suction level

There has yet to be a definitive study that states the optimal NPWT suction level. A lower pressure is believed to be best for circumferential wounds and in cases where NPWT is used in conjunction with a free flap.

Adhesives

A limitation of the currently available NPWT devices is the inability to obtain a good seal at the edges of the device

which compromises the maintenance of suction. Further development of materials that enable better adhesion on curved and moist surfaces is necessary to allow use of the devices in difficult wounds.

CONCLUSION

NPWT may have proven successful as an adjunctive therapy in a wide variety of wounds. However, the currently available systems are still novel, and the number of high-level clinical studies investigating NPWT is lacking. More RCTs are needed to elucidate the details of NPWT efficacy, particularly in terms of its different indications and modalities. Overall, NPWT continues to hold great promise and with further research on the optimal parameters of its application this management option stands to continue to improve wound healing and patient care.

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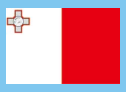

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REVIEW

Review of the initial treatment and avoidance of scald injuries

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Abstract

Scald injuries, which describe burns to living tissue from hot liquids, are a very common injury that occur across geographical, social, economic, and national boundaries. Despite their ubiquitous nature, a complete understanding of the conditions which are required to cause scald burns is not yet available. In addition, clear guidance to medical practitioners is available through various guidelines however in actual situations, the extent of the burn is not fully known and this lack of knowledge complicates care. Here, a comprehensive review is made of the available knowledge of temperatures and scald durations which lead to skin-burn injuries. The range of volumes and liquid temperatures are typical of those found in heated consumer beverages. This review can help medical practitioners design initial treatment protocols and can be used by manufacturers of hot-liquid products to avoid the most severe burns. Next, within the context of this ability to quantify burn depths, a review of current burn treatment guidelines is given. Included in this review is a visual recognition of the extent of burns into the dermal layer as well as decision guidelines for selection of patients which would benefit from referral to a dedicated burn center. It is hoped that by bringing together both the quantified burn-depth information and current treatment guidelines, this review can be used as a resource for persons in the medical, manufacturing, beverage service, and other industries to reduce the human impact of scald injuries.

Key words: Scald injury; Skin burns; Biological heating; Hot beverages; Burn depth

Core tip: This paper presents a concise summary that relates hot-beverage spills to burn injury risk. Not only can this paper be used to predict the depth of burn injuries, but it can also show how service temperature and cooling time can be set to reduce the threat of injury. Results are presented in simple to use tables and graphs for ease to medical practitioners.

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INTRODUCTION

Burn injuries are a common type of injury that can occur in many situations around the globe. Within the category of burn injuries, scald wounds caused by hot liquids are among the most common. Scald injuries can occur in kitchens, baths, industrial and manufacturing environments, restaurants, and other locations. The extent of scald injuries can vary from mild to death causing. Mild burns are almost always treated without medical attention, while extreme burn injuries often result in referral to dedicated burn centers. Because of the large variation in harm caused by burns, it is important to create environments which lessen burn injuries. It is also important for medical responders to quickly and correctly categorize a burn so that appropriate treatment is initiated.

Scald burns, which here refer to any thermal injury caused by heated liquid, can occur anywhere on exposed body; however, they are most common on the skin. Since the vast majority of scalds are skin burns, they will be the sole focus of this review.

The severity of a skin burn is quantified by two measurements. The first is the depth of the burn into the tissue. The second measure is an estimation of the size of the surface area involved. Both of these measures will now be discussed.

BURN CLASSIFICATION

Burn depth

Both within the medical community as well as with the general public, the degree classification is most often used to describe burn depth. Within this classification, the description first-degree burn describes burns that kill tissue only within the outermost layer of skin (the epidermis). As a consequence, the burns generally heal quickly and without medical attention. The injuries may be painful and result in hyperemia and flaking of the necrosed epidermis following the incident.

Second-degree burns pass through the epidermal layer and into the dermis. They lead to thermal necrosis of tissue within that layer and consequently damage the skin structures which are housed there, such as hair follicles, sweat glands, capillaries, among others.

Third-degree burns pass through the dermis and enter the underlying hypodermis tissue and possibly into muscle. Since the burn completely destroys the dermis, the functions of this layer are also halted (such as blood flow and sensation). Consequently, the skin is ischemic. While it may appear hyperemic, when the skin is compressed, reperfusion of the tissue is very slow to occur if at all. The pain associated with third-degree burns is often less than that of second- or first-degree burns because the innervation to the tissue is compromised. For third-degree burns, slow healing occurs and medical attention such as surgical excision and grating is required. If large parts of the body are burned, shock, hypothermia, and infection can occur[1-3].

Within the academic and bioheat transfer community, different descriptions are used. In this community, superficial burns are the equivalent to burns of first degree. Superficial-partial-thickness burns are those that pass through the epidermis and into the external part of the dermal layer - generally not beyond the dermal midplane. Next, deep-partial-thickness burns pass through the dermal midplane and into the lower half of this layer. Finally, full-thickness burns are essentially the same as third-degree burns - they extend through the dermal layer and into underlying tissue. As with third-degree burns, they often require skin grafting[4-6]. The primary difference between the two modes of burn classification is that in the latter, a separate accounting is made for burns that either are confined to the outer half of the dermis and those that pass into the lower half of the dermal layer.

Regardless of the preferred nomenclature, it is a challenge to visually assess burn depth. Many times, the visual estimation is not accurate[5,7-10]. A summary image is provided in Figure 1 to bring together the various burn extents which have already been discussed in the accompanying text.

Burn area

Total burn surface area (TBSA) is also an important measure of injury. TBSA is most commonly reported as a % of the body area that a burn covers. With this method, the body is subdivided into major regions (head, torso, legs, arms, *etc.*). Each region is allocated a numerical value which is a typical percentage of the region compared to the total body surface. An example of such a regional breakdown is provided in Figure 2. Since many of the body regions are multiples of 9%, this regional breakdown is often referred to as the Rule of Nines. The Rule of Nines is endorsed by both the American Burn Association and the European Practice Guidelines for Burn Care. While other burn area criteria have been studied, the widespread current usage of this metric motivated its inclusion here.

More information will be provided in a later section of this report related to decision making of medical professionals. First, however, quantitative information on the depth of the burn will be provided.

Prediction of burn depth

Burn depth studies have been performed since the late 1940s. Pioneering work[11-14] quantified the complex temperature-time relationship required for burns on porcine and human skin. It was discovered that the physiologic

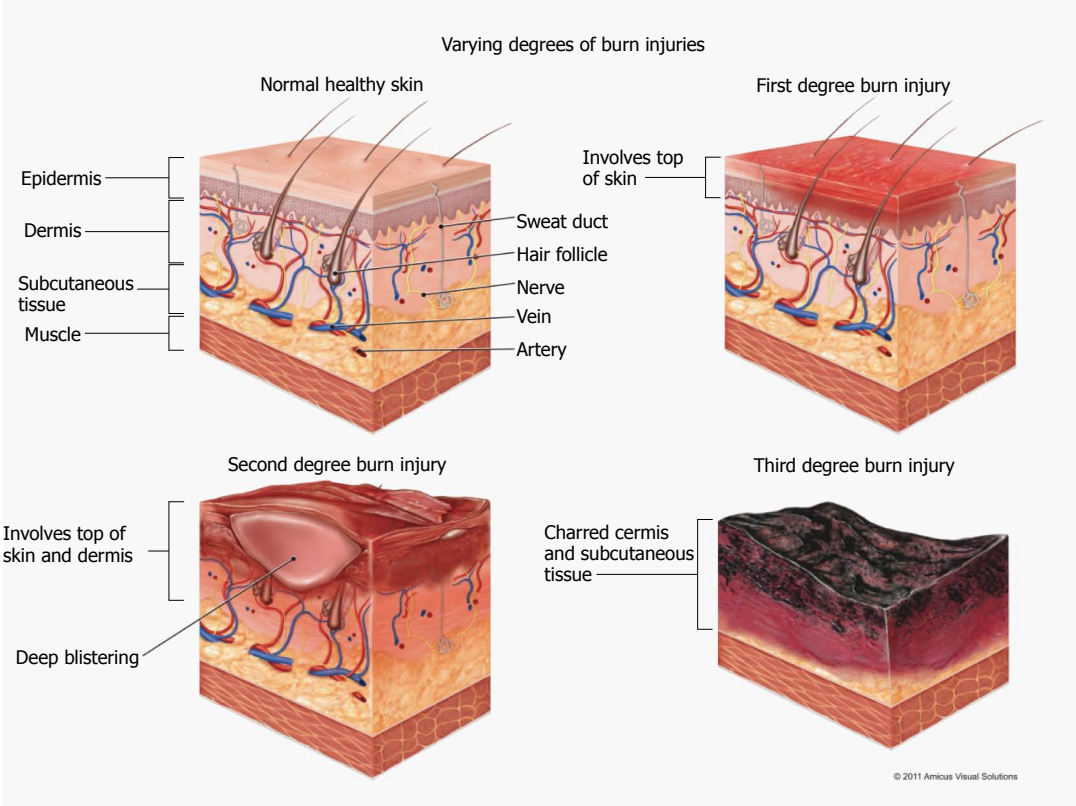

Figure 1 Illustration of burn depths and characteristics (courtesy of Amicus Medical Images).

Rule of nines for adult body surface burns	
Head and neck equal	9%
Anterior trunk equals	18%
Posterior trunk equals	18%
Upper extremities (each 9%)	18%
Lower extremities (each 18%)	36%
Perineum	1%

Rule of nines for small child body surface	
Head and neck equal	18%
Anterior trunk equals	18%
Posterior trunk equals	18%
Upper extremities (each 9%)	18%
Lower extremities (each 13.5%)	27%
Perineum	1%

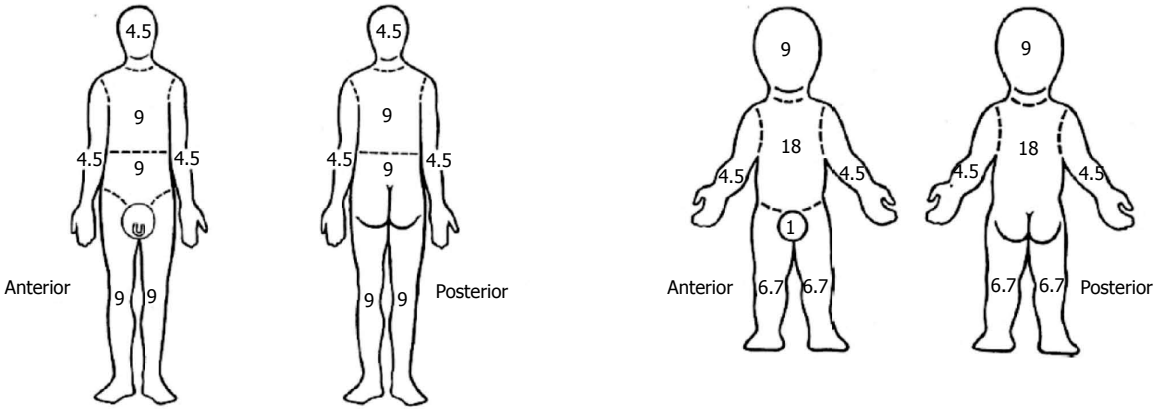

Figure 2 The Rule of Nines for adults and children (Courtesy of Brookside Associates).

response to elevated temperatures was complex and that for small increases in exposure temperature, large changes in burn injury rates were observed. The outcome of this work was a quantification of the rate of cellular damage and the amount of viable cells still within the heated zone which is expressed mathematically as:

Table 1 Injury parameters for skin tissue

Ref.	A (1/s)	Ea (J/kmol)
[14,23]	3.10e98	6.28e08
[25]	2.90e37	2.44e08
[26]	9.09e37	2.49e08
[27]	4.33e64, T < 50	24.19e8, T < 50
	9.39e104, T > 50	6.70e8, T > 50
[13,24]	3.10e98	6.28e08
[28]	2.19e124, T < 50	7.78e8, T < 50
	1.82e51, T > 50	3.25e8, T > 50
[29]	1.43e72	4.57e08
[29]	2.86e69	4.61e08
[29]	4.32e54, T < 50	4.16e8, T < 50
	9.39e104, T < 60	6.65e8, T < 60
[30]	3.1e98, T < 55	6.27e8, T < 55
	5e45, T > 55	2.96e8, T > 55
[31]	2.19e124, T < 50	7.82e8, T < 50
	1.82e51, T > 50	3.27e8, T > 50
[27]	4.33e64, T < 50	4.18e8, T < 50
	9.39e104, T > 50	6.69e8, T > 50

$$\text{Damage index} = \Omega = \ln [c(0)/c(t)] = \int A e^{-(Ea/RT)}\, dt \quad (1)$$

Here, C represents the concentration of viable cells either initially or at some time t. A is the frequency factor (1/s), E_a is the activation energy (J/mol), R is the universal gas constant (8.3143 J/mol-K), T is the temperature in Kelvin, e is the constant 2.718, and t is the time (s)[15-31]. The fitted terms are obtained through experimental correlation, and they depend on the tissue type and body location. To illustrate the wide-ranging values of these parameters, Table 1 has been prepared.

The prediction of injury [through Equation (1)] is achieved by solving for the conduction of heat through perfused tissue using the Pennes model[32] which is expressed in Equation (2).

$$(\rho c)_t (\partial T_t/\partial t) = k (\partial^2 T_t/\partial x^2) + S_{met} + (\rho c)_b \omega (T_b - T_t) \quad (2)$$

The calculation method outlined here has a long history of use and has been corroborated with experimental results. Results from those works have been adopted to predict skin burns using modern computational techniques[33-57]. An outcome of these efforts is the ability to predict the distribution of an injury parameter throughout the various layers of tissue that have been heated. Values of are taken to correspond to completely necrosed tissue as they generally represent tissue which has too few viable cells to regenerate.

In the present study, focus is given on a subclass of scald burns - those caused by hot beverages. While the spill scenario can vary dramatically (volume of liquid spilled, temperature of liquid, spill pattern, presence or absence of clothing, speed of spill, thickness of skin, ability of victim to remove heat and apply cooling duration of hot liquid cooling prior to spill, among others), it is possible to generalize the results in a way that can provide meaningful information to treating physicians. To enable the generalization, the following ranges of parameters were used in the experiments.

Volume of liquid spilled: 8-16oz (237-473 mL).

Temperature of liquid spilled: 158 ℉-203 ℉ (70 ℃-95 ℃).

Type of clothing: 1 layer of a cotton shirt.

Spills of cups that had caps as well as cups without caps.

Other parameters, such as the constitution of the cup, the presence or absence of an insulating sleeve, *etc.* had a very small impact on the results and so for simplicity are not included here[46].

The experiments, which were carried out involving spills on living human tissue and on a tissue surrogate are described in[46] and are not discussed in detail here. The experiments were carried out in typical ambient conditions of about 20 ℃. The temperature during the cooling period for an 8 ounce (237 mL) beverages without a protective cover are shown below in Table 2. Corresponding information for covered beverages are provided in Table 3. These tables are followed immediately by information for larger volume beverages (16 ounces) both with and without protective caps (Tables 4 and 5).

The calculations were continued until the temperatures within the tissue reduced to levels which would no longer cause injury. Interested readers are invited to references[46] and which discuss both the cooling effect[56], the impact of rapid cooling after a burn, and the duration of time needed to bring tissue temperatures to safe levels.

From the experiments and calculations completed[46], verified by a simplified model[56] and by the comparison between models and physical observations which were contained therein, it is possible to create a visual reference which allows the estimation of burn risk caused by hot-liquid spills. The reference is provided in Figure 3.

The information presented in Figure 3 and the preceding tables can be brought together in a simple to use manner as seen in Tables 6-9. These tables list the initial beverage temperature, the volume, and the cooling time which should occur to bring the beverage to a low enough temperature so that a threshold mid-dermal burn may not occur. Table 6 corresponds to small (237 mL) cups cooling with a protective cap; Table 7 is the counterpart for the no-cap situation. Tables 8 and 9 present information for 473 mL cups with and without a protective cap, respectively.

These data show that beverage service temperatures, which are often in excess of 180 ℉ are at levels which have the potential to cause serious physical harm. Furthermore, some beverage service temperatures are above the preferred temperature for the consumers[57-61]. It seems reasonable to promote the service of beverages at temperatures which are both preferred by consumers and safe so that serious mid-dermal burns are unlikely. The cooling results set forth here are corroborated by other mutually reinforcing studies[62-64].

It should also be noted that while the above tables correspond to typical adults and children (whose skin thickness is approximately 70% that of an adult), great care must be given to their use[55,65,66]. Also, as summarized in[55], skin thickness varies by body location[67-70]. For locations or persons whose skin is thinner than that used in the current study, lower temperatures or longer cooling durations are recommended. On the other hand, for persons whose skin

Table 2 Cooling of an 8 ounce (237 mL) heated beverage without a protective cap

Cooling time (min)	Service temperature, ℃ (℉)					
	70 (158)	75 (167)	80 (176)	85 (185)	90 (194)	95 (203)
0	70	75	80	85	90	95
5	58.1	61.9	61.9	69.5	73.4	77.2
10	50.4	53.4	53.4	59.5	62.5	65.5
15	45.1	47.6	47.6	52.6	55.2	57.7
20	42.4	44.6	44.6	49.1	51.4	53.6
25	42.2	44.4	44.4	48.9	51.1	53.3

Table 3 Cooling of an 8 ounce (237 mL) heated beverage with a protective cap

Cooling time (min)	Service temperature, ℃ (℉)					
	70 (158)	75 (167)	80 (176)	85 (185)	90 (194)	95 (203)
0	70	75	80	85	90	95
5	62.5	66.7	66.7	75.2	79.5	83.7
10	56.9	60.6	60.6	67.9	71.6	75.3
15	52.5	55.8	55.8	62.3	65.6	68.8
20	49.5	52.5	52.5	58.4	61.3	64.3
25	47.7	50.5	50.5	56.1	58.8	61.6

Table 4 Cooling of a 16 ounce (473 mL) heated beverage without a protective cap

Cooling time (min)	Service temperature, ℃ (℉)					
	70 (158)	75 (167)	80 (176)	85 (185)	90 (194)	95 (203)
0	70	75	80	85	90	95
5	61.5	65.7	69.8	74	78.1	82.3
10	55.9	59.5	63.1	66.7	70.3	73.9
15	51.9	55.1	58.3	61.5	64.7	67.9
20	49.6	52.5	55.5	58.5	61.4	64.4
25	48.9	51.8	54.7	57.5	60.4	63.3

Table 5 Cooling of a 16 ounce (473 mL) heated beverage with a protective cap

Cooling time (min)	Service temperature, ℃ (℉)					
	70 (158)	75 (167)	80 (176)	85 (185)	90 (194)	95 (203)
0	70	75	80	85	90	95
5	65	69.5	74	78.5	83	87.5
10	61.5	65.7	69.8	74	78.1	82.3
15	58.8	62.7	66.6	70.5	74.4	78.3
20	57	60.7	64.4	68.1	71.8	75.5
25	56	59.6	63.2	66.8	70.4	74

Table 6 Cooling times required for various service temperatures in order to cause threshold mid-dermal burns, 8-ounce (237 mL) cups with a protective cap

Service temperature		Cooling time for adult mid-dermal burns (min)	Cooling time for children mid-dermal burns (min)
(℃)	(℉)		
95	203	8	12
90	194	5	9
85	185	2	6
80	176	Not applicable	3

is thicker than 2 mm, higher temperatures and/or shorter cooling durations can be used.

In addition to skin thickness, clothing type and the ability of someone to remove heat quickly and apply cool or cold temperatures should be a consideration. For persons whose mobility is limited, such as children or elderly, a spill

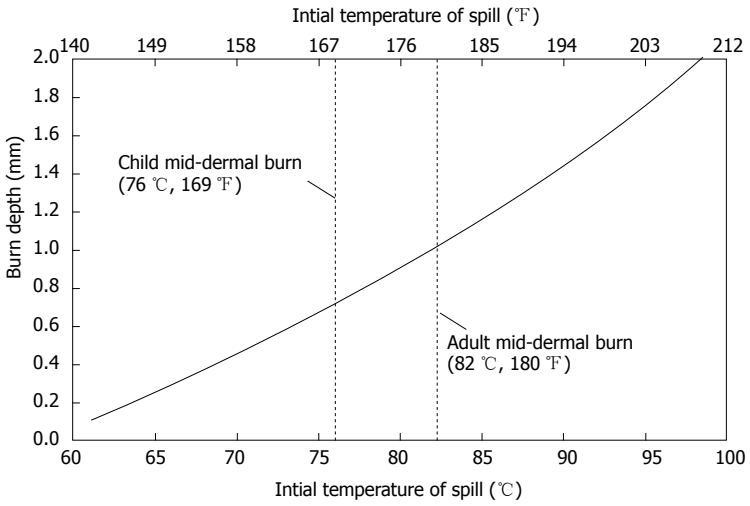

Figure 3 Burn depth and spill temperature relationship with annotations for mid dermal burns in adults and children.

Table 7 Cooling times required for various service temperatures in order to cause threshold mid-dermal burns, 8-ounce (237 mL) cups without a protective cap

Service temperature		Cooling time for adult mid-dermal burns (min)	Cooling time for children mid-dermal burns (min)
(℃)	(℉)		
95	203	4	6
90	194	2	4
85	185	1	3
80	176	Not applicable	1

Table 8 Cooling times required for various service temperatures in order to cause threshold mid-dermal burns, 16-ounce (473 mL) cups with a protective cap

Service temperature		Cooling time for adult mid-dermal burns (min)	Cooling time for children mid-dermal burns (min)
(℃)	(℉)		
95	203	11	18
90	194	7	12
85	185	2	8
80	176	Not applicable	3

Table 9 Cooling times required for various service temperatures in order to cause threshold mid-dermal burns, 16-ounce (473 mL) cups without a protective cap

Service temperature		Cooling time for adult mid-dermal burns (min)	Cooling time for children mid-dermal burns (min)
(℃)	(℉)		
95	203	6	9
90	194	4	6
85	185	2	4
80	176	Not applicable	2

may remain in contact with skin for a longer duration than for someone who quickly removes the source of heat (the spilled liquid and any saturated clothing). Consequently, for these mobility-challenged persons, lower temperatures and/or longer cooling durations are recommended.

With respect to clothing, it has two competing effects. First, clothing can insulate the skin against the hottest temperatures of the liquid. Second, the clothing can hold the hot liquid against the skin, extending the scald and delaying cooling. From a heat transfer perspective, a first responder should immediately remove the source of heat by removing saturated clothing if possible. In addition, the responder should apply cool/cold temperatures to quickly reduce the skin temperature. Room temperature liquids are often available and an excellent choice. It is recommended that if cool liquids such as room temperature water or other beverages are available nearby, they can be applied directly to the burn location and even through clothing. Burns occur

very quickly and even a few second delay in the application of cooling can make an impact on burn depth.

Not only does cooling reduce temperatures and thereby reduce burn depth[55-56], but it also provides palliative relief[71-84]. Many of these studies have investigated the speed at which cooling should be applied to maximize the benefit. Others have considered the optimal temperatures for the cooling. While the consensus is that temperatures in the range of 10 ℃-20 ℃ (50 ℉-70 ℉) are effective, in our opinion, speed is of critical importance. A delay of a second or two can make the difference between a superficial-partial-thickness burn and a deep-partial-thickness burn. In some instances, ice is used to cause cooling. Ice should be used with care, because very cold temperatures can cause vasoconstriction which inhibits blood flow to the injured region and slows healing. Extended application of cold temperatures can even cause cryological injuries[85-92].

BURN ASSESSMENT

Depth of the burn, TBSA involved, and the location of the burn all are necessary to develop a treatment plan. Burn depth occurs on a continuum and accurate assessment of burn depth is often difficult immediately after the injury[3,6-10,13-21]. Burn depth assessment helps predict which injuries will require excision and grafting as deep-partial-thickness burns and full-thickness burns often require this treatment.

First-degree (superficial) burns are red, have a dry surface, and typically are associated with discomfort. These burns do not blister. The affected skin will blanch with pressure and quickly reperfuse. A typical sunburn is an example of a first-degree burn.

Superficial second-degree (superficial-partial-thickness) burns are painful and form blisters. The surface under the blister is typically red, hypersensitive and moist. This surface will blanch with pressure.

Deep second-degree (deep-partial-thickness) burns blister and may be less painful than superficial partial thickness burns. The tissue underlying the blister will be moist and may appear mottled, red, or even white. Reperfusion after blanching is slow or absent. Sensation of the damaged tissue maybe diminished when tested with pin prick.

Third-degree (full-thickness) burns extend into subcutaneous fat or connective tissue. These injuries appear white or tan and are insensate. They do not blanch as there is no perfusion to this area of the burn due to damage of the capillaries.

Fourth-degree (full-thickness) burns extend into deep structures such as muscle or bone. These injuries are easily identified.

The size of the burn is estimated based on the percentage of total body surface area involved. Only partial-thickness burns and deeper are used when estimating TBSA burned. This estimation informs intravenous fluid resuscitation needs and is used to determine if a patient would benefit from a referral to a burn center. A common method for estimating TBSA burned is the Rule of Nines as described above. This method is endorsed by the American Burn Association, but several other methods exist. For smaller burns, the patient's hand (palm and fingers) can be used as a reference as this surface area is approximately 1% TBSA.

The final aspect of the initial burn assessment involves noting the area of the body involved. Partial thickness and deep burns involving the face, hands, feet, perineum, genitals, and major joints often require consultation with a burn center.

INITIAL MANAGEMENT AND TREATMENT CONSIDERATIONS FOR SCALD INJURIES

Prehospital care

Immediate removal of the burn source and cooling of the affected area is critical to prevent further tissue damage. Cooling is most easily accomplished by application of cool or even room temperature water. If immediate removal of any overlying clothing is possible this may be done before application of water. Otherwise, liquid can be poured directly on porous clothing to begin the cooling process. Cool water is a safe, effective, and soothing intervention. Therefore, continue with the application of cool water until the burning process is completely halted.

Initial emergency center care

Serious burns require initial treatment at an emergency center. A complete review of the initial care of the burned patient is beyond the scope of this paper. The following text will therefore focus on how the burn assessment informs subsequent treatment. After any life threatening injuries and medical complications have been addressed, the burning process has been halted, and any necessary analgesics have been administered a burn assessment can be performed. The clinician will need to assess all burns noting location and depth. Next, TBSA burned can be estimated using only partial thickness burns and deeper for this calculation.

Initial fluid resuscitation

Fluid loss through damaged skin and loss into the interstitial space can result in hypovolemic shock and thus inadequate tissue perfusion. This can lead to not only viable skin becoming nonviable, but also to end organ dysfunction. Resuscitation with intravenous fluid is the mainstay for addressing and preventing burn shock. As noted previously, first degree burns are not included in the TBSA estimation for fluid resuscitation calculations[2,3]. Adult patients with less than 20% TBSA affected and pediatric patients will less than 10% TBSA affected can often be managed with oral hydration alone[3]. Larger burns require intravenous fluid resuscitation with crystalloids and ringer's lactate solution is commonly

used. Multiple formulas exist for estimating intravenous fluid needs in the first 24 to 48 h after a burn. The Parkland Formula is one of the most popular. This formula uses the variables TBSA burned and patient weight in kilograms. The Parkland formula estimates the milliliters of intravenous fluid to be given in the first 24 h after the burn occurs. Half of the volume is administered over the first 8 h and the second half of the volume is administered over the following 16 h.

The Parkland Formula: Milliliters of IV fluid = 4 x TBSA burned as percent x weight in kilograms (3)

BURN CENTER REFERRAL CRITERIA

The American Burn Association has published guidelines to help clinicians determine which patients would benefit from referral to a burn center[1].

Criteria recommended by the American Burn Association for burn center referrals are: (1) Partial thickness burns greater than 10% of body area; (2) burns of hands, feet, face, genitals, perineum, or major joints; (3) third degree burns; (4) electrical burns (including lightning); (5) chemical burns; (6) inhalation burns; (7) burns in patients with pre-existing conditions that could complicate management; (8) concomitant trauma which increases morbidity or mortality risk; (9) burns of minors treated in hospitals without qualified personnel or equipment; and (10) burn injury which requires social, emotional or rehabilitation intervention.

CONCLUDING REMARKS

Here, a two-fold presentation of information is given. First, the relationship of liquid temperature to burn depth is showcased with an easy-to-use graph. Included in the results is information regarding how the cooling time between hot-beverage service and a spill incident will reduce burn depth. With this information, it is possible to predict, within a reasonable degree of certainty, the depth of a burn injury. In addition, required beverage cooling times to avoid mid-dermal burns are listed.

In addition, the information presented here can be used by the beverage service industry to make safer hot-liquid beverages. Often times, service temperatures are above those preferred by consumers and these elevated temperatures pose an unnecessary risk of injury.

While the focus in this study was on mid-dermal burns, it should be recognized that lesser burns can also be injurious. Also, readers should recognize that mid-dermal burns can be caused at lower temperatures on areas where the skin is thinner, when victim mobility is challenged, or when the situation makes difficult the removal of the source of heat and the application of cooling.

With respect to medical care, there are a number of care phases that occur. First care starts prior to arrival at a medical center and involves the removal of heat and application of cooling. Next, there is a stage of initial medical care which may include fluid resuscitation. For severe burn situations, referral to a burn center is made. Guidance for all these care phases is provided here with reference to published guidelines.

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MINIREVIEWS

Cutaneous implications of essential oils

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Abstract

Essential oils (EOs) as home remedies and for health benefits have been used for millennia, but with the recent surge in the popularity of natural products, these oils have garnered increased attention. EOs are complex natural mixtures obtained plant materials, and have demonstrated potent biological effects *in vitro*. They have commercial value in the food, cosmetics, and fragrance industries, and also have also experienced a steady rise in personal and home use as part of aromatherapy. Currently, widespread acceptance and use of EOs is limited by a lack of large-scale clinical trials in humans. In addition, they are associated with notable side effects such as contact and allergic dermatitis, among a myriad of rare but serious systemic side effects. This review is intended to provide the clinician with key background information and biology of essentials oils, identify key trials demonstrating benefits, and describe adverse effects, with a focus on cutaneous presentations.

Key words: Essential oils; Photosensitization; Contact dermatitis; Aromatherapy

Core tip: Essential oils (EOs) have been used as home remedies for millennia. Currently, widespread acceptance and use of EOs is limited by a lack of large-scale clinical trials in humans. In addition, EOs are associated with notable side effects such as contact and allergic dermatitis, among a myriad of rare but serious systemic side effects. We review the current usage of EOs and identify pertinent cutaneous manifestations.

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INTRODUCTION

Essential oils (EOs) are complex volatile substances extracted from plants, and used in food, cosmetic, and

Table 1 Commonly used essential oils (botanical origin)

Tea tree oil (*Melaleuca alternifolia*)
Jasmine absolute (*Jasminum officinale*)
Sweet bay (Laurel) oil (*Laurus nobilis*)
Cedarwood oil (*Juniperus virginiana*)
Patchouli oil (*Pogostemon cablin*)
Ylang-ylang oil (*Cananga odorata*)
Lemongrass oil (*Cymbopogon spp.*)
Clove oils (*Eugenia caryophyllus*)
Jasmine absolute (*Jasminum officinale*)
Sweet bay (Laurel) oil (*Laurus nobilis*)
Neroli oil (*Citrus aurantium* flower)
Peppermint oil (*Mentha piperita*)
Narcissus absolute (*Narcissus poeticus* Flower Extract)
Lemon oil (*Citrus medica limonum*)
Eucalyptus oil (*Eucalyptus globulus*)
Orange oil (*Citrus aurantium dulcis*)

fragrance industries. They have gained the attention of the medical community for their biologically active effects and therapeutic potential for many illnesses. In addition, EOs are also experiencing a tremendous growth in aromatherapy and home use for their reported health benefits[1]. EOs are well-known allergens and photosensitizers; however, there is a paucity of data on the dermal exposure of essential oil use in the United States. In addition, the production and use of EOs is not currently standardized or regulated and may pose an occupational hazard for those with close and repeated contact with EOs. With increasing popularity of essential oil consumption, clinicians can expect to come across more cases of cutaneous and systemic reactions to these complex substances. This review provides the most updated and relevant scientific information related essential oil use, primarily pertaining to cutaneous involvement.

BACKGROUND

EOs are secondary metabolites found in plants[1]. They are derived from plant material, such as leaves, stems, flowers, bark, and roots[1]. Common methods used to extract the components include steam distillation, or mechanical expression; oils produced with the aid of chemical solvents are not considered true EOs[1]. The major chemical composition of EOs includes terpenes, esters, aldehydes, ketones, alcohols, phenols, and oxides[2]. A given essential oil contains varying amounts of each of these compounds, which imparts a particular fragrance and determines its therapeutic characteristics[2]. In contrast, a fragrance is chemically made to mimic the smell of a plant or flower.

EOs can be divided into two main distinct biosynthetic origins: The terpenes and terpenoids, and the aromatic and aliphatic components[3]. There is great interest in the main biologically active component of EOs - terpenes and terpenoids. Terpenes are a large and diverse class of organic compounds that consist of five-carbon bases[4]. Some terpenes, such as the diterpenes, are the building blocks for biologically active compounds such as retinol, retinal, and taxol[1]. Diterpenoids have antioxidant, antimicrobial, anticancer, anti-inflammatory, wound healing, antihypertensive, analgesic, and anxiolytic activities[5-7].

APPLICATIONS OF EOS

Currently, of the approximately 3000 EOs that have been described, 300 are commercially important[8,9]. The use of EOs is common in food flavoring, fragrance, and cosmetic industries. The United States Food and Drug administration has classified most EOs as "generally recognized as safe" at specified concentration limits[3].

EOs comprise the key ingredient in aromatherapy, which is rapidly growing in popularity worldwide[10-13]. Many spas, massage therapists, and practitioners of alternative medicine provide aromatherapy. The most commonly used EOs in aromatherapy include patchouli, cedarwood, lavender, tea tree oil, along with citrus-scented oils such as bergamot, lemon, and orange oils (Table 1). The oils are usually applied to the skin, but can also be given orally, by inhalation, or by diffusion through the air. Currently, aromatherapy products do not need approval by the FDA[13].

Little is known about consumption habits and exposure to EOs, especially in the United States. The most comprehensive study of usage patterns was a 2014 study, which focused on the 12 most types of EOs among 1507 participants in France[14]. Information about types of EOs used, skin areas exposed, frequencies and quantities were collected. Lavender (*Lavanda)* species are the most used EOs among both females and males, followed by *Eucalyptus* oil (Table 2)[14]. The study notably pointed out the increased prevalence of female users for almost all types of Eos[14]. In addition, females tend to apply EOs on their face and neck, while males applied the products on the chest[14].

MEDICINAL USES

EOs are composed of many biologically active molecules, which may have promising therapeutic benefits in many diseases and ailments. EOs have been recognized for their antibacterial, antiviral, antifungal, and insecticidal properties, which led to their acceptance and wide-spread use in the food industry[15-19]. Pre-clinical studies have shown that in addition to aforementioned properties, EOs also demonstrate potent anti-inflammatory, and antioxidant activity[20-22]. Because of the great number and variety of constituents, EOs do not have specific cellular targets. They exert their cytotoxic effects through disruptions in the structure and functions of key intracellular lipids and proteins[2]. In eukaryotic cells, EOs can change the fluidity of membranes, which become abnormally permeable resulting in leakage of radicals, cytochrome *C*, calcium ions and proteins[2]. Permeabilization of outer and inner mitochondrial membranes leads to cell death through apoptosis and

Table 2 Usage patterns of essential oils by gender (percentage of use)

	Females	Males
Essential oils	Lavender (60%)	Lavender (50%)
	Eucalyptus (35%)	Eucalyptus (42%)
	Menthol (28%)	Ylang ylang (21)
	Ylang ylang (28%)	Tea Tree (19%)
	Tea Tree (24%)	Citrus (19%)
	Citrus (24%)	Menthol (18%)
	Vanilla (17%)	Vanilla (16%)
	Rosemary (16%)	Pine (15%)
	Ravintsara (16%)	Rosemary (14%)
	Pine (11%)	Neroli (9%)

necrosis[2]. Similar cytotoxic effects were observed *in vitro* in many gram positive and gram negative bacteria of relevance to the food industry including *S. aureus* and *E. coli*[2].

Bottom of form

Of all the EOs, tea tree oil (TTO) is arguably the most recognized and investigated compound in dermatology. Numerous studies have demonstrated its tolerability and efficacy and against *P. acnes*[22-24]. A 1990 singe-blind randomized controlled trial (RCT) in 124 patients showed that 5% TTO gel has a comparable efficacy to that 5% benzoyl peroxide lotion[22]. In 2007, a double-blind RCT was performed in 60 patients with mild to moderate facial acne vulgaris[23]. A significant difference between TTO gel and placebo was observed based on decreases in total lesion counts and acne severity index scores[23]. Most recently, the results of a 2016 phase II pilot study assessing tea tree oil for the treatment of mild to moderate acne further demonstrated its efficacy, and favorable side-effect profile[24]. No serious adverse events were reported in this study and side effects were limited to self-resolving peeling, dryness and scaling[24]. In addition, tea tree oil has shown promising results for other common dermatologic ailments such as seborrheic dermatitis[25-27]. A 2002 single-blind parallel controlled trial of 126 patients with mild to moderate dandruff showed that the use of 5% TTO shampoo showed 41% improvement in dandruff, as measured by quadrant-area-severity score, compared with 11% in the placebo group ($P < 0.001$)[27].

EOs have also been studied for the treatment of alopecia areata. A double-blind RCT involving 86 patients showed that a mixture of thyme, rosemary, lavender, and cedarwood EOs massaged into patients' scalps produced significant improvement when compared with the carrier oils alone (improvement in 54% and 21% of patients, respectively, $P = 0.08$)[28]. The efficacy of the treatment was evaluated at initial assessment and 3 and 7 mo after treatment by dermatologists' visual scoring of photographs and a computerized analysis of traced areas of alopecia[28]. However, the study had limited external validity, as the extent and severity of the alopecia areata in the subjects were not mentioned. At this time, there are no further clinical trials using EOs for alopecia areata.

There is little doubt that EOs may have great relevance to the field of dermatology, and more studies should be performed given all of their *in vitro* findings. Further work on the antimicrobial, antiviral and antifungal effects of EOs may have immense potential in the treatment of dermatological diseases. Indeed, a 2012 study showed that a combination of TTO with iodine was superior to iodine alone in the treatment of molluscum contagiosum virus in 53 children[29]. Moreover, EOs may have benefits in other cutaneous maladies, such as hyperpigmentation. The efficacy of α-bisabolol, a terpene derivative of the essential oil of *Matricaria chamomilla,* exerts an inhibitory effect on melanogenesis[30]. In a 2010 study, α-bisabolol was evaluated in an 8-wk clinical trial of 28 Asian females, and led to a significant decrease in hyperpigmentation[31].

ADVERSE EFFECTS

While safety testing on EOs has shown minimal adverse effects, the use of EOs still poses risks and allergic responses that clinicians should be aware of. Under normal conditions of established use, most oils appear to have a good safety profile[12]. The majority of adverse events are mild, but serious toxic reactions from some EOs have been observed, including abortions or abnormalities in pregnancy, neurotoxicity manifesting as seizures or retardation of infant development, bronchial hyperreactivity, and hepatotoxicity[12]. Accidental ingestion by young children has occasionally proved fatal[32]. Repeated exposure to topical lavender and tea tree oils was associated with the development of prepubertal gynecomastia in a case-series of 3 subjects[33]. This outcome was reversible upon discontinuation of the oils, and was attributed to the mild estrogenic and anti-androgenic activities of lavender and tea tree oils[33].

Notably, the majority of adverse effects of EOs are cutaneous in nature. The field of dermatology has encountered an increase in the frequency of allergic reactions to EOs, likely secondary to the growing popularity of topical use of EOs[12]. EOs are known sensitizers, and there is extensive evidence linking them to cases of contact allergy and allergic contact dermatitis[34,35]. One case of airborne contact dermatitis secondary to sensitization after inhaled aromatherapy has also been described[36]. As EOs age, they are often oxidized so their chemical composition changes, and may become more allergenic or prone to irritation[13]. The most common allergens are ylang-ylang oils, lemongrass oil, jasmine absolute, sandalwood oil, and clove oil[13]. However, in clinical practice, it may be difficult to identify specific EOs in many cases. For example, in aromatherapy, the practitioner commonly uses undefined mixtures of EOs without specifying the plant sources.

In addition, many EOs contain chemicals prone to causing sensitization, including limonene, linalool, citral, and cinnamyl alcohol (Table 3)[14]. This is most commonly seen with citrus oils, such as bergamot, lemon, lime, and orange, which contain foucoramins, in addition

Table 3 List of commonly used essential oils (botanical origin) and allergenic ingredients

Ylang-ylang oil (*Cananga odorata*)	Linalool, Benzyl benzoate, Benzyl salicylate, Geraniol, Isoeugenol, Eugenol
Lemongrass oil (*Cymbopogon* spp.)	Citral, Geraniol, Limonene, Trans-isocitral, Eugenol, Linalool
Clove oils (*Eugenia caryophyllus*)	Eugenol, Isoeugenol
Jasmine absolute (*Jasminum officinale*)	Benzyl benzoate, Linalool, Eugenol, Benzyl salicylate, Isoeugenol
Sweet bay (Laurel) oil (*Laurus nobilis*)	Linalool, Limonene, Eugenol, Geraniol
Neroli oil (*Citrus aurantium* flower)	Linalool, Limonene, Geraniol, Citral
Peppermint oil (*Mentha piperita*)	Menthol, Limonene, Linalool
Narcissus absolute (*Narcissus poeticus* Flower Extract)	Benzyl benzoate, Cinnamyl alcohol, Isoeugenol
Lemon oil (*Citrus medica limonum*)	Limonene, Citral, Linalool, Geraniol
Eucalyptus oil (*Eucalyptus globulus*)	Limonene
Orange oil (*Citrus aurantium dulcis*)	Limonene, Linalool, Citral
Patchouli oil (*Pogostemon cablin*)	Cinnamyl alcohol

to limonene, linalool, and citral. Linalool, a terpene derivative found in many EOs, is the most sensitizing components in many EOs[36]. It is a fragrant chemical also found in lavender, ylang-ylang, and jasmine oils[36]. Cinnamyl alcohol is found in patchouli oil[15]. Factors influencing risk of photo-sensitization also include the amount of product applied and the area of exposure. This is important as the major study determining exposure patterns of topical essential oil use found that females tend to apply to areas such as the face and neck, thus placing themselves at greater risk of photosensitive reactions[14].

NEED FOR FURTHER RESEARCH

Although it is well established that allergic contact dermatitis can result from essential oil use, the allergens in EOs are largely unknown. Moreover, patch testing currently does not provide accurate or particularly reliable information on EOs, as many EOs lack standardization in manufacturing and production[37]. Finally, larger scale studies on exposure patterns are needed to reliably estimate the use of EOs. Many patients struggle with chronic cutaneous diseases and often wish to try to "natural" or "alternative" therapies, without being aware of the potential allergenic side effects.

CONCLUSION

The use of EOs, which are complex volatile substances with strong odors, has long been established in the fragrance and cosmetic industries. In addition, EOs have notable effects as antimicrobial agents, and are widely used in food industries. In recent times, EOs in the form of aromatherapy have experienced a resurgence in their popularity. They are notable for causing allergic and photosensitivity reactions, along with serious but rarely occurring side effects. More controlled clinical studies are needed to determine the benefits and risks of plant-derived products, especially EOs, in dermatology. This review describes historical and current results from scientific studies of essential oil components and highlights the areas in need of further research.

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ORIGINAL ARTICLE

Retrospective Study

Use of a selective enzymatic debridement agent (Nexobrid®) for wound management: Learning curve

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Abstract

AIM

To evaluate the efficacy of Nexobrid® in the initial management of burns and lessons learned with the procedure.

METHODS

From January 27th 2015 until January 25th 2016, 25 patients aged between 18-94 years old with deep partial and full thickness burns were treated with Nexobrid® covering 1%-30% of their total body surface area (TBSA). The debridement was applied in the first 96 h post-injury following the protocol suggested for Nexobrid®. In patients with burns of more than 15% TBSA a second application of Nexobrid® was performed. After the removal of the product - 4 h post application and after a 2 h period of wet dressing - we used several products to cover the wound like Suprathel®, Biobrane®, Mepitel® with wet dressing, silver sulphadiazine 1% cream, and in some cases even autografts. We treated patients with inhalation injury as well. All the procedures were done under deep sedation, regional blocks in extremities or general anaesthesia in the intensive care unit room or in the operating theatre.

RESULTS

After these first 25 cases, we have observed that patients with partial thickness burns treated with Nexobrid®, experienced great benefits in the reduction of the need for autografting compared with the standard of care. This is

because after selective enzymatic debriding of the burn scar we can distinguish different wound beds, which can coexist in the same patient, and we also managed to associate each one to its ability to epithelize. In major burns, besides the improvement in wound healing, we observed an important improvement in their general state. This may be because SIRS significantly improved through a bloodless debridement of necrotic tissue, decreasing the requirements of vasoactive drugs and fluid resuscitation. Circumferential burns also benefited from enzymatic debridement, observing a decrease in the number of compartment syndromes and the need for escharotomies. At present, we have not observed a positive effect in the evolution and outcome of major burns with inhalation injury.

CONCLUSION

The introduction of Nexobrid® shows significant improvement in burn treatment. Cumulative experiences are necessary to adapt its application in all Burns Centres.

Key words: Burns; Eschar; Debridement; Enzymatic debridement; Wound bed; Nexobrid®; Epithelialization; Dermis preservation; Autograft

Core tip: Burns continue to be a common injury in western countries. It is difficult to assess the severity of burns, but knowing its mechanisms as well as its characteristics can be of help. An alternative to surgical debridement is the enzymatic or chemical debridement, although past reports that used it with patients show that its efficiency is limited. Nexobrid® is a new enzymatic debridement agent. We show our learning curve with it.

Palao R, Aguilera-Sáez J, Serracanta J, Collado JM, Dos Santos BP, Barret JP. Use of a selective enzymatic debridement agent (Nexobrid®) for wound management: Learning curve. *World J Dermatol* 2017; 6(2): 32-41 Available from: URL: http://www.wjgnet.com/2218-6190/full/v6/i2/32.htm DOI: http://dx.doi.org/10.5314/wjd.v6.i2.32

INTRODUCTION

When a thermic, electric or chemical aggression acts in the skin for the necessary time and with enough intensity, then a local injury known as burn occurs. Nowadays, burns continue to be a common injury in western countries. Many of these burns will need urgent medical attention, hospital admission, and even surgery[1]. It is difficult to assess the severity of burns, but knowing its mechanisms as well as its characteristics can be of help. Nonetheless, the majority of burns present with different degrees in all it's extension through the skin. Consequently, it can be extremely complicated to differentiate between a superficial partial thickness burn and a deep partial thickness one[2,3]. The diagnosis of burn depth is really important in order to plan the treatment. While the epidermal and superficial partial thickness burns will heal spontaneously, the deep partial thickness as well as the full thickness burns will need surgery[4]. For the latter, the tangential debridement followed by the coverage with skin autograft within the first five days after suffering the injury, is considered to be the current standard of care[5-7]. An alternative to such surgical debridement is the enzymatic or chemical debridement, although past reports that used it with patients show that its efficiency is limited, it is a slow process and increases the infection risk due to maceration of necrotic tissue[8]. Since 2004 many articles have been published on the use, efficiency and security that NexoBrid® (enzymatic debridement) provides. NexoBrid® consists of a mixture of proteolytic enzymes enriched in bromelain, which is extracted from the stem of the pineapple plant[9-13]. The purpose of this manuscript is to share the experience acquired during the learning process with this enzymatic debridement used in the Burns Unit of Vall d'Hebron University Hospital at Barcelona.

MATERIALS AND METHODS

The Burns Unit of Vall d'Hebron University Hospital at Barcelona is the top reference center for Catalonia, Balearic Islands (Spain) and Andorra. Every year we receive approximately between 400 and 500 burns related entries. We also receive, but to a lesser extent, other entries due to exfoliative skin illnesses.

We considered initial entries of the learning curve the first 25 cases, which received the enzymatic debridement treatment. These were done between January of 2015 and January of 2016. We worked with the enzymatic debridement in the circumstances where there was at least an intermediate partial thickness burn with an extension not above 15%, according to the product indication, unless we organized the therapy in two separated days if the patient achieved a total enzymatic debridement of 30% of its total body surface area. Based on our experience we now have our own recommendations regarding its indications based on our learning and when not to use it. As it is a painful process pain management is indicated. We do this particularly at the extremities in which we can perform locoregional nerve block, or we can also do it either in the extremities or trunk if the patient has been intubated with sedoanalgesia for whatever reason.

The technique is always performed in a sterile environment, either the theater or the same room for major burns, removing devitalized tissue. Then, we will proceed to mix both components of the product, creating the Nexobrid® gel. After that, we will delimit the area to treat with a trail of Vaseline in order to avoid spillage of the product out of the treatment area. Once we have done this, we will proceed to use the cream - creating a uniform fine layer of 1.5-3 mm thick - over the area of the body that we want to debride. Afterwards, we will cover the extremity with a transparent plastic wrap so that the lotion will not move during the 4 h that the product

Table 1 Patients treated with Nexobrid® (January 2015-January 2016)

Patient	Age	Sex	Etiology	Extension (%)	Depth	Time to escarectomy (d)	Treated area	Pre debridement dressing	Post debridement dressing	Surgery	Time to complete healing (d)
1	24	W	Scald	2	DPT	4	Foot	SSD	Mepitel one	Yes	35
2	31	M	Flame	20	SPT and DPT	1	Hands and lower limbs	SSD	Mepitel one	No	21
3	33	M	Flame	60	DPT and FT	0	Trunk and upper limbs and foot	SSD	Mepitel one	Yes	15
4	46	M	Chemical	6	DPT and FT	4	Trunk	SSD	Biobrane	Yes	19
5	90	M	Flame	4	DPT and FT	2	Forearm and foot	SSD	Suprathel	Yes	33
6	58	M	Flame	53	DPT and FT	0	Hands and lower limbs	SSD	Biobrane	Yes	Exitus
7	18	W	Scald	2	SPT and DPT	1	Lower limbs	WD	Suprathel	Yes	30
8	64	M	Scald	10	MPT	3	Lower limbs	SSD	Suprathel	No	14
9	58	M	Contact	1	SPT and DPT	3	Foot	WD	Suprathel	Yes	20
10	44	M	Deflagration	15	SPT and DPT	1	Upper limbs	WD	Suprathel	No	27
11	69	M	Deflagration	8	SPT and DPT	4	Upper limbs	WD	Suprathel	No	21
12	51	M	Scald	2	SPT and DPT	2	Upper limbs	Nitrofurazone	Biobrane	Yes	51
13	21	M	Flame	10	SPT and DPT	1	Upper limbs	WD	Aquacel Ag	No	16
14	56	M	Flash	5	MPT and DPT	4	Hands	WD	Suprathel	No	19
15	40	M	Deflagration	6	SPT and DPT	2	Upper limbs	WD	SSD	No	22
16	94	W	Flame	10	DPT and FT	4	Trunk and upper limbs	WD	SSD	Yes	21
17	81	M	Flame	2	SPT and FT	2	Lower limb	WD	WD	Yes	31
19	72	W	Deflagration	14	MPT	1	Lower limbs	WD	Suprathel	Yes	27
20	38	M	Deflagration	7	DPT	1	Hands	WD	Biobrane	Yes	38
21	63	M	Flame	65	MPT and FT	0	Lower limbs	SSD change to WD before 24 h	Mepitel and Nitrofurazone	Yes	23
22	46	W	Scald	4	MPT	2	Lower limb	WD	Suprathel	No	37
23	62	M	Flame	18	SPT and DPT	1	Upper and lower limbs	WD	Aquacel Ag	Yes	36
24	56	M	Flame	28	SPT and DPT	2	Lower limbs	WD	SSD	Yes	EXITUS
25	38	W	Abrasion	1	DPT	2	Hand	WD	Aquacel Ag	No	17

SPT: Superficial partial thickness; MPT: Mid partial thickness; DPT: Deep partial thickness; SSD: Silver sulfadiazine; WD: Wet dressing; W: Women; M: Man.

needs in order to work. Always remember that we must try to maintain a uniform layer of gel when we cover the extremity with the plastic wrap. After the 4 h we remove the product as well as the plastic wrap, and the rest of necrotic tissue, vaseline, exudate and bleeding. We do this with an intense brushing or scratching with the scraper. Then, we apply a wet dressing with normal saline solution 0.9% that we will leave until the next day. Once we remove the wet dressing we must apply a new one that varies according to the appearance of the treated wound bed. In the Discussion we elaborate on what we use in each step.

RESULTS

Between January 2015 and January 2016 we treated 25 patients (Table 1), 19 of them were men, 6 women. Their mean age was 52.6 years old (ranging from 19 to 94 years old). The etiology of their burns was flame in 11 cases, deflagration in 5 cases, scald in 5 cases, electrical flash in 1 case, chemical burn in another one, abrasion in 1 case, and finally one case of contact burn. The mean burned body surface area was 14.4% (ranging from 1% to 65% TBSA).

In all cases patients received enzymatic debridement treatment in their extremities, and 3 cases also required enzymatic debridement treatment of their anterior trunk. As mentioned previously, this was done within 4 d of injury. It is important to highlight that in most cases the treatment was successful (it didn't go well in 5 cases). The reason was 4 of the cases had received local silver sulphadiazine 1% cream during more than 24 h before being treated with the enzymatic debridement. This caused the consolidation of the characteristic pseudo-eschar that this cream forms. This explains why it was unsuccessful. In the fifth case, we believe that the treatment didn't work due to the use of an insufficient amount of the product.

Pre-Nexobrid® treatment, local dressing employed was silver sulphadiazine 1% cream in 9 cases. As mentioned, in 4 of those this was used for more than 24 h which lead to incomplete eschar debridement. In the rest of patients the enzymatic debridement was performed within the first 24 h (in 3 of them), or wound dressing was replaced with wet dressing also within the first 24 h (2 patients). In 15 cases a wet dressing of normal saline solution and

chlorhexidine was used. In one case, initial dressing was silicone sheets and nitrofurazone cream. The mean burned area treated with enzymatic debridement was 6.5% (ranging from 1% to 30%).

We essayed with a wide range of possibilities regarding local dressings once we have already performed the enzymatic debridement, and also after placing wet dressing: Suprathel® (9 cases), Biobrane® (4 cases), silver sulphadiazine (3 cases), Aquacel Ag® (3 cases), Mepitel one® (3 cases), Mepitel® and nitrofuazone cream (1 case), wet dressing (1 case).

Fifteen patients underwent surgery to cover the debrided areas with skin grafts. The other 10 patients showed spontaneous epithelialization. Those patients who needed surgery (apart from the 4 patients that died) healed within an average of 30.45 d, whereas those who didn't need surgery within 22.30 d.

Each patient has been followed-up until today, so they are still receiving the same post-burn care than the patients that have been treated with the standard treatment (tangential debridement plus skin graft coverage). The post-burn care means: Use of silicone patches, pressure therapy, massages, hydration, rehabilitation, and so on. As mentioned, 4 patients died, 3 of them because of a bad systemic evolution that caused a multiple organ failure, while the other death was due to a respiratory insufficiency in the context of smoke inhalation that caused burn in the air way.

DISCUSSION

When a new technique is first introduced we always need a period of time in order to learn its different new aspects. Once we verified the debriding capacity of the product, and with the knowledge of the publications on it, then we had some doubts about which where the most suitable circumstances in which we should use the product, how to assess the wound bed after the procedure or which local dressings to apply on it, that's what we want to discuss here from our experience.

Where to use Nexobrid®

In our opinion, this product should be used to treat circumferential burns that can lead to a compartment syndrome; intermediate and deep partial thickness burns as well as burns where there are different degrees, full thickness burns. We consider that children, elderly people and major burns victims, could specially benefit from this procedure for their specific circumstances. Now we will proceed to elaborate on the benefits of using the product in each of the circumstances mentioned above.

Compartment syndrome: When there is a suspicion that the patient is suffering a compartment syndrome in any of the extremities it is, in our opinion, one of the clearest cases in which we should use the product. It has been proved that the first 30 min after employing the product the compartment pressure descends below 30 mmHg. This descent will stand even after removing the product[10]. Eliminating the secondary rigid eschar from the circumferential burn will allow the expansion of the muscles, which consequently will eliminate the possibility of suffering compartment syndrome[12]. None of the 25 patients that we debrided with such technique required surgical escharotomy. It is true that the surgical escharotomy effects are immediate in relation to the compartment pressure fall, however we also need to highlight that an expert surgeon as well as basic surgical staff are needed. Sometimes the expert surgeon can't treat victims fast enough, which subsequently will cause the victims to suffer irreversible pain. Furthermore, surgical escharotomy is not exempted from possible complications such as haemorrhages, loss of fluids, subcutaneous tissue infection, and so on[10].

Partial and full thickness burns: NexoBrid® can help us diagnose intermediate partial thickness burns. These burns are the ones that due to their appearance are difficult to classify upon initial presentation. This also occurs with superficial partial thickness burns and the deep partial thickness ones. The clinical assessment performed by an expert surgeon on the depth of a burn is only accurate in two-thirds of the examined cases[14]. There are some equipment that help us to differentiate burn depth, such as Laser Doppler Imaging, which allows to clearly differentiate depth, because it informs about the status of the dermic vascularization with an positive predictive value around 90%[14,15]. However, NexoBrid® has a considerable advantage against this equipment, as it shows the wound bed itself thus facilitating diagnosis, at the same time we are doing the escharectomy. Another advantage of the product is that it reduces the time elapsed between the burn injury and complete burn eschar removal[13]. Later we will talk about how to assess the wound bed after enzymatic debridement. Nowadays there are no publications that exactly delineate the interpretation of the wound bed in intermediate partial thickness burns.

Children and elderly people: In children and elderly people we tend to be more conservative in the surgical aspects as they are more delicate patients than others. Both types of patients have less epithelial reserve, while only elderly people have commonly associated comorbidities[16,17]. We believe that Nexobrid® is an ideal medical tool. First of all, it allows us to predict if the burn will need to be treated in a conservative manner or a surgical debridement is necessary, and it also let us know how to handle such burn (conservative or surgical treatment). What is more, the extension of the area treated will be smaller in comparison to standard therapy[12,13]. If we limit the surgical areas, we will consequently limit the extension of the donor site, where we obtain the skin graft that will cover the debrided part of the body[13]. Moreover, if we manage to avoid surgical debridement bleeding will also be avoided[13]. However,

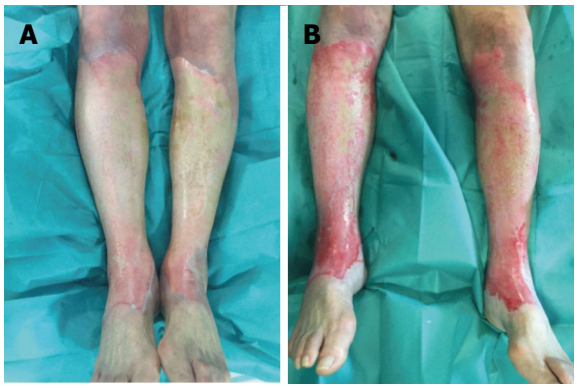

Figure 1 Patient treated with silver sulphadiazine cream for more than 24 h in the pre-Nexobrid® treatment. A: Patient where silver sulphadiazine cream was applied in the pre-Nexobrid® treatment for more than 24 h; B: After 4 h of exposure to Nexobrid®, the incomplete removal of eschar is shown.

we must say that no child has participated in this research in our Unit.

Major burn victims: In relation to major burn patients, we think that an early enzymatic debridement can contribute many benefits to them. Firstly, we consider that by reducing the time until the complete escharotomy, we are also reducing the amount of time in which the body is producing cytokines and inflammatory mediators as a systemic response to the burn[18,19]. So, we believe that the syndrome caused by the systemic inflammatory response will be minor. Additionally, early removal of the necrotic tissue can lead to a reduced incidence of sepsis. There are no publications that support our arguments, but still we consider that it is a reasonable argument that needs to be studied in the future. Finally, it is also important to say that as these patients tend to show poor overall state, we believe that by limiting surgical aggression from tangential debridement this will be beneficial to them.

When not use Nexobrid®

On the other hand, we will not follow this principle in superficial partial thickness burns, as it doesn't result in any benefit. We also will not use it in electric burns because they have a complex injury mechanism and employing it would be useless. It also won't be used in small burns where the cost outweights the benefits. We will not employ it in burns that had been treated during more than 24 h with silver sulphadizine cream or dressings with silver as the pseudo-eschar formed over the burn limits the debriding action of the product, as is shown in Figure 1. We can support this information with the other experiences present in the bibliography[9]. However, if the silver sulphadiazine has been working less than 24 h, then we will proceed to remove the pseudo-eschar through an intense scratching (with a surgical brush or scraper), and after that we will use Nexobrid®.

After 24 h the pseudo-eschar cannot be completely removed. This is the reason why we apply a wet dressing with normal saline 0.9% to the patients that we initially believe can benefit from enzymatic debridement (Nexobrid®), while we wait.

Wound bed diagnosis

As previously stated, we believe Nexobrid® is a great tool for proper diagnosis of burn depth. Actually, the selective debridement allows us to perform a precise diagnosis of the total depth of the burn, through a direct view of the skin structure and vascular patterns[12].

The current publications recommend grafting as soon as possible those wound beds that do not present valid dermic remainders; while those valid dermic remainders will be protected with an allograft or with a dressing that will consequently allow the epithelisation during 3 wk, the time in which the areas that remain denuded will be then grafted[12]. This has been one of the most difficult aspects to understand, as until now we associated a white wound bed without much bleeding to a deep dermic burn. But there is nothing in relation to the pre-debridement inspection with the post Nexobrid® debridement one. However, when we were reviewing our clinical cases we managed to distinguish different dermic wound beds after performing enzymatic debridement with Nexobrid®, and we also managed to associate each one to its ability to epithelize. So, after using Nexobrid® we can face four different wound beds, which obviously can coexist in the same patient, because a burn can have different depths. Now we are going to analyse the different wound beds (Table 2).

Type Ⅰ: Dermic wound bed with abundance of small diameter pin-point bleeders (uniform shades of red to pink). This bed corresponds to a superficial dermic burn (Figure 2).

Type Ⅱa: Dermic wound bed with a sparse pattern of larger diameter bleeders (irregular shades of pink to white) that it is not depressed in relation to the surrounding healthy skin, or the own bed surface skin burn. It corresponds to an intermediate/deep dermal burn, but the loss of tissue thickness cannot be macroscopically observed (Figures 2 and 3).

Type Ⅱb: Dermic wound bed with a sparse pattern of larger diameter bleeders (no shades, white colour) that it is depressed in relation to the surrounding healthy skin, or the own bed surface skin burn. It corresponds to a deep dermal burn where the loss of its tissue thickness can be macroscopically observed (Figures 3 and 4).

Type Ⅲ: Fatty wound bed. It corresponds to a full thickness burn (Figure 4).

The importance of all this, in our experience, is that the types Ⅰ and Ⅱa will heal spontaneously within a maximum period of 30 d; whereas the types Ⅱb and Ⅲ won't heal spontaneously over a period of 30 d, so we will consider covering the burns with skin autografts. Despite 30 d for burns, at risk of hypertrophic scarring, is more time than the classically accepted for a spontaneous epithelialization (3 wk), it has been seen that in a long-

Table 2 Wound bed classification after debridement with Nexobrid®

Wound bed	Appearance	Depression	Type of burn
Type Ⅰ	Abundance of small diameter pin-point bleeders (uniform shades of red to pink)	No	Superficial PT
Type Ⅱa	Sparse pattern of larger diameter bleeders (irregular shades of pink to white)	No	Mid/deep PT
Type Ⅱb	Sparse pattern of larger diameter bleeders (no shades, white colour)	Yes	Deep PT
Type Ⅲ	Fatty	Yes	PT

PT: Partial thickness.

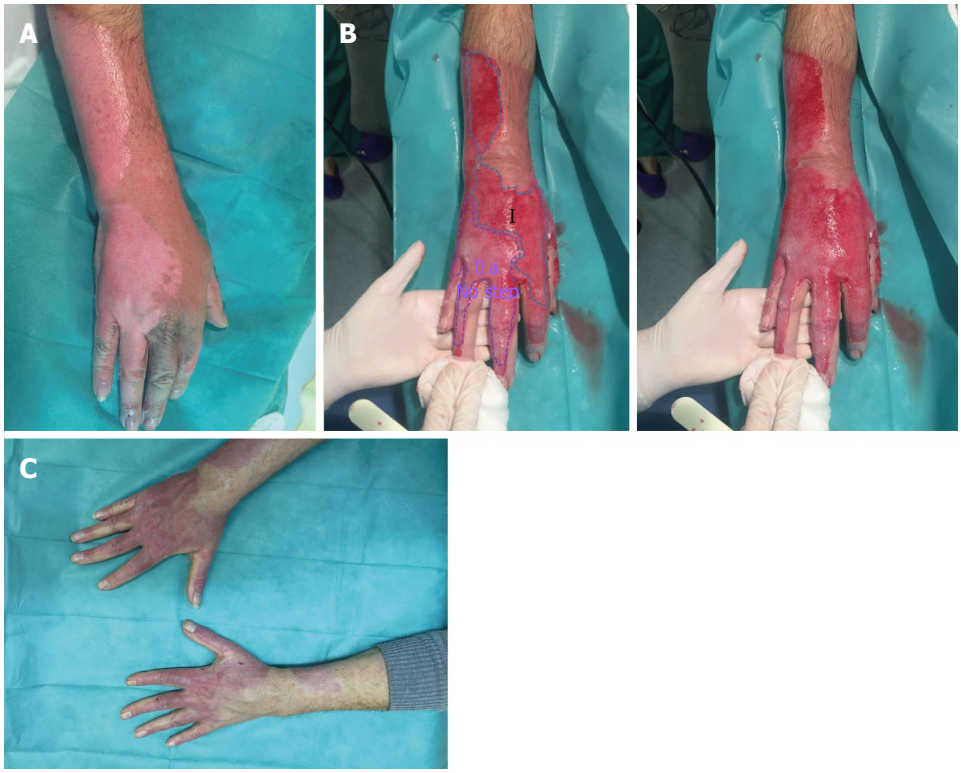

Figure 2 Wound bed Type Ⅰ and Ⅱa. A: Burn before Nexobrid® treatment; B: Burn after Nexobrid® treatment with two different wound bed. Type Ⅰ, with abundance of small diameter pin-point bleeders (uniform shades of red to pink, superficial partial thickness burn). Type Ⅱa, with a sparse pattern of larger diameter bleeders (irregular shades of pink to white colour), not depressed either in relation to the surrounding healthy skin or the own bed surface skin bed (mid/deep partial thickness burn); C: Outcome 38 d post-burn.

term outcome the burn scars treated with Nexobrid® are not inferior than the ones who are subjected to the standard treatment[13]. We think that two factors can have an influence on this. On the one hand, the spontaneous epithelialization in a inflammatory bed is different from the one produced in a clean dermal base, and secondly, the effectiveness of the postoperative care of these scars.

We believe that the difference between types Ⅱa and Ⅱb is the amount of epithelial reserve available for wound healing by reepithelialisation. When we talk about epithelial reserve, we are referring to the presence of cells capable of generating a new healthy epithelial tissue. In this case it would be the basal cells of the epidermis, which are damaged in both types (Ⅱa as well as Ⅱb). However, these basal cells of the epidermis are in continuity with the basal sebaceous gland cells and the cells of the outer hair shaft, as both share embryologic development. These cells have the ability to form new keratinocytes that migrate into the wound[9]. In addition, the cells of the protuberance, structure located in the hair follicle below the sebaceous glands, are pluripotential cells that can reconstitute all the epithelial lineages after suffering an insult, including the interfolicular epidermis, albeit they are not involved in the normal process of epidermal renewal. Furthermore, it has been proved that no less than 25% of the new cells that have repopulated a wound derive from this structure[20].

It's obvious to think that in deep dermal burns healing by regeneration of a healthy epithelium will depend on the number of these structures that have survived the injury. According to our observations the beds type Ⅱa maintain a sufficient epithelial reserve for healing, while the beds type Ⅱb don't (if we are macroscopically able to see a depression it is logical to think that the remaining dermis corresponds to deeper layers, and therefore is poorer in these areas).

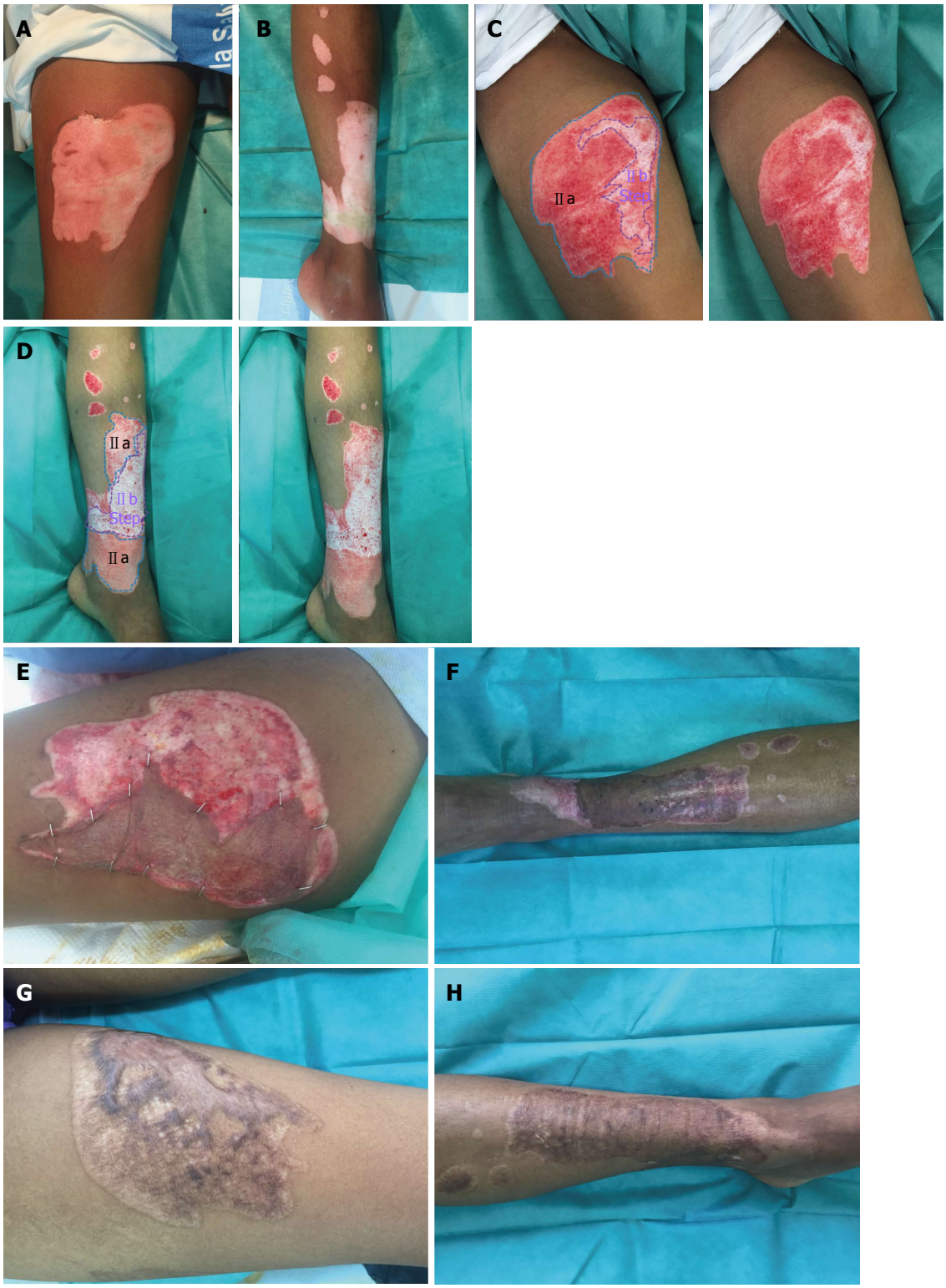

Figure 3 Wound bed Ⅱa and Ⅱb. A and B: Burn before Nexobrid® treatment; C and D: After Nexobrid® treatment with two different wound bed. Type Ⅱa and Type Ⅱb, sparse pattern of larger diameter bleeders (no shades, white colour) that it is depressed in relation to the surrounding healthy skin, or the own bed surface skin burn (Deep partial thickness burn); E and F: Autografting after two weeks; G and H: Final outcome after 6 mo.

This explanation should be taken carefully in areas of thin skin, as well as in children and elderly people who already have a thin skin. In a minor skin thickness it can be assumed that an injury that doesn't produce this macroscopic dermal depression, if it is able to destroy the epithelial reserve so that the injury cannot heal by regeneration. Therefore, we should also be cautious in areas without hair or with patients that have suffered a hair removal treatment that removes the hair follicle. These areas will have less epithelial reserve.

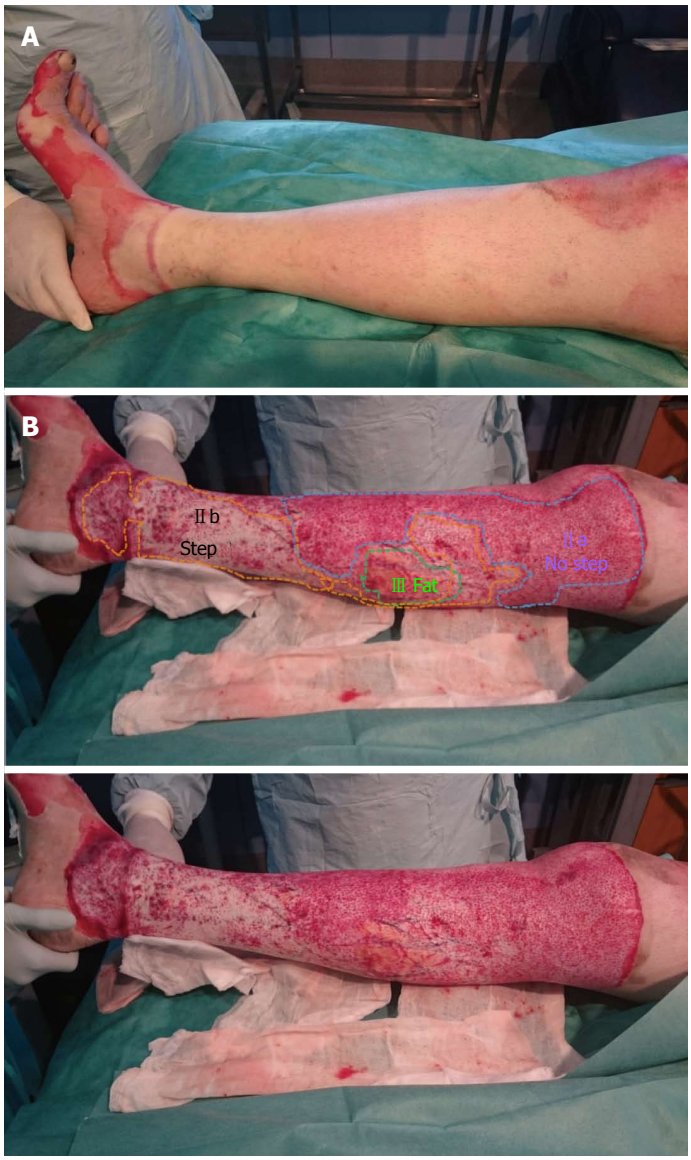

Figure 4 Different wound beds in the same burn. A: Burn before Nexobrid® treatment; B: After Nexobrid® treatment with three different wound bed. Type Ⅱa, Type Ⅱb and Type Ⅲ, with a fatty wound bed (full thickness burn)

Factors that can influence wound healing

Once we have done the initial assessment of the wound bed after practicing the enzymatic debridement, we must be aware that there are some factors that can have an influence in relation to the evolution of the wound healing. Factors that may lead to the stasis zone or even cause irreversible damage. These factors are infection, edema or prolonged hypotension[21]. The latter can occur to major burns patients for reasons such as distributive shock and the use of vasoactive drugs which may difficult the healing due to bad peripheral perfusion.

To sum up, once we have already performed the enzymatic debridement treatment and while we are waiting for the spontaneous healing or for the coverage with skin autografts, it is very important to remember that we must keep the wound bed wet in order to prevent it from drying out and therefore deepening, even more important than with a regular wound. As we previously stated, we will use different creams and dressings that we can easily find in our Unit: If we believe the wound bed to be type Ⅱb or Ⅲ, then we will have to do surgery, but first it is really important to previously apply to the patient some dressings to keep the wound bed hydrated. For example, dressings such as an hydrocolloid type that must be changed every 48 h until the moment that the general conditions of the patients and the availability of the operating rooms allow us to perform the surgery. If on the other hand we consider the wound bed is type Ⅰ or Ⅱa, then the injury will heal spontaneously, so that we will only have to apply a dressing that does not interfere and promotes spontaneous epithelization. At this moment, our first choice to cover the wound bed is Suprathel® and nitrofurazone cream with Mepitel®. On Suprathel® we place a non-adherent meshed dressing and finally, dry gauzes to finish the dressing. We keep this for 10 d (despite the fact that at the fifth day we should have a look and check that there haven't been setbacks. Depending on the state of the affected area, after the 10th day we continue using the same treatment or change it. With nitrofurazone cream with Mepitel® we change the dressing every 48-72 h.

When we introduced the enzymatic debridement with

Nexobrid® in our armamentarium we could only use the nitrofurazone cream in one case, because the Producer stopped the production for some months. However, now it is available again, so we have introduced its use after Nexobrid® treatment of new patients (25 patients more since January 2016, 50 patients totally), combined with a silicone meshed non-adherent dressing (Mepitel®).

Our choice, to use one or the other, depends on either if the patient is going to be treated as in-patient or as out patient. In in-patients, we prefer to apply the nitrofurazone cream combined with Mepitel®, because it favours their comfort. We change the dressings every 2-3 d, which consequently allow their cleaning. On the other hand, in out patients we prefer to apply Suprathel® because it reduces the amount of dressing changes and controls.

It is important to highlight that we have used silver sulphadiazine 1% cream, but the pseudoeschar formation promotes delayed healing and the appearance of hypertrophic tissue granulation.

When we decide that autografting is necessary in type ⅡB and Ⅲ wound bed, we usually wait at least 3-4 d before doing it, because in our first patients some skin grafts failed when the surgery was performed in the first two days after the debridement. Our opinion is that some of the eschar and product still remain on the wound bed for several days after debridement. If we wait these days before surgery, we have removed them and then, the skin grafts intake is much better.

The introduction of the new enzymatic debridement agent Nexobrid® in our Burn Centre has shown significant improvement in wound healing in general and in the overall state of major burn patients. Cumulative experiences are necessary to adapt its utilisation to other Burn Centres.

COMMENTS

Background

When a thermic, electric or chemical aggression acts in the skin for the necessary time and with enough intensity, then a local injury known as burn occurs. Nowadays, burns continue to be a common injury in Western countries. Many of these burns will need urgent medical attention, hospital admission, and even surgery. The majority of burns present with different degrees in all its extension through the skin. Consequently, it can be extremely complicated to differentiate between a superficial partial thickness burn and a deep partial thickness one. The diagnosis of burn depth is really important in order to plan the treatment. While the epidermal and superficial partial thickness burns will heal spontaneously, the deep partial thickness as well as the full thickness burns will need surgery. For the latter, the tangential debridement followed by coverage with skin autograft is considered to be the current standard of care. An alternative to surgical debridement is enzymatic or chemical debridement, although past reports that used it on patients show that its efficiency is limited, it is a slow process and increases the infection risk due to maceration of necrotic tissue. The introduction of a new selective enzymatic debridement agent (Nexobrid®) in armamentarium for burn wound management has provided us some new concepts in the initial management and wound healing as well. In this study, the authors show learning curve of the procedure, lessons learned, advantages and disadvantages compared to the standard of care.

Research frontiers

Nexobrid® is a selective enzymatic debridement agent for burn wound management. The results of this study contribute to a better understanding the procedure and to avoid mistakes in its use.

Innovations and breakthroughs

The efficacy of Nexobrid® for burn wound management has been previously well established. In this study, the authors show learning curve of the procedure and give some advises for a better understanding of the remaining wound bed after debridement, which can help in the diagnosis of burn depth and the plan of treatment.

Applications

This study suggests that Nexobrid® is useful for burn wound management, specially the mid-partial, deep-partial and full thickness burns which can benefit in the reduction of the need for autografting compared with the standard of care. In major burns, besides the improvement in wound healing, the authors observed an important improvement in their general state.

Peer-review

The manuscript is an interesting and well written study.

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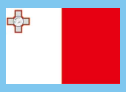

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Contents

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Contents

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MINIREVIEWS

Atopic eczema treatment now and in the future: Targeting the skin barrier and key immune mechanisms in human skin

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Abstract

The skin facilitates a number of key roles but its functioning can be impaired by disease. Atopic eczema is a chronic inflammatory disease where the skin barrier has become leaky, and inflammation occurs. It affects up to 20% of children and 3% of adults worldwide, manifesting as red itchy patches of skin with varying severity. This review aims to investigate the leaky skin barrier and immune mechanisms from the perspective of potential novel treatments. The complexity of atopic eczema as a disease is what makes it difficult to treat. Genome-wide association studies have highlighted possible genetic variations associated with atopic eczema, however in some cases, individuals develop the disease without these genetic risk factors. Loss of function mutations in the filaggrin gene are one of these associations and this is plausible due to its key role in barrier function. The Th2 immune response is the link with regards to the immune mechanisms as atopic inflammation often occurs through increased levels of interleukin (IL)-4 and IL-13. Eczematous inflammation also creates susceptibility to colonisation and damage by bacteria such as Staphylococcus aureus. Potential novel treatments are becoming ever more specific, offering the hope of fewer side effects and better disease control. The best new treatments highlighted in this review target the immune response with human beta defensin 2, phosphodiesterase-4 inhibitors and monoclonal antibodies all showing promise.

Key words: Atopic eczema; Novel treatment; Filaggrin; Skin barrier; Immune dysfunction

Core tip: Atopic eczema (atopic dermatitis) is an itchy inflammatory skin disease with complex aetiology, including impairment in barrier function and concomitant inflammation. Increased understanding of the molecular

mechanisms in eczema pathogenesis has opened up opportunities for new therapeutic targets. This review summaries current understanding and highlights some novel treatments in development.

Bell DC, Brown SJ. Atopic eczema treatment now and in the future: Targeting the skin barrier and key immune mechanisms in human skin. *World J Dermatol* 2017; 6(3): 42-51 Available from: URL: http://www.wjgnet.com/2218-6190/full/v6/i3/42.htm DOI: http://dx.doi.org/10.5314/wjd.v6.i3.42

INTRODUCTION

Atopic eczema is a prevalent disease with substantial morbidity

Atopic eczema (also called atopic dermatitis) is a skin disease that has shown a rise in prevalence in Africa, Eastern Asia and Western Europe[1]. It is a chronic inflammatory disease that manifests as red patches of itchy skin and in severe cases excoriated or infected lesions[2]. Inflammation is believed to occur when the skin barrier becomes leaky and an immune response is stimulated; *vice versa*, the inflammatory response can itself impair the skin barrier function[3].

There are two forms of eczema: Atopic, when an increased IgE response occurs, and non-atopic when this response is not observed. Eighty percent of cases are atopic[4] and the feature of atopy (raised IgE) is what relates the disease to other allergic responses such as food allergies, allergic rhinitis and asthma which can all show an IgE response. The so-called "atopic march" describes the progressive acquisition of atopic diseases in a step-wise manner throughout childhood[5]. Therefore children affected by one atopic disease will often show phenotypes of the others too[5]. Atopic eczema is predominantly a childhood disease that affects up to 20% of children[6] and this is one of the reasons why it is among the most common skin diseases worldwide[2]. In the 2010 WHO article into the global burden skin diseases, atopic eczema was ranked first by causing the most number of days that people were not at full health[7]. The effects of atopic eczema are not limited to skin. Children with more extreme atopic eczema suffer from reduced sleep and increased psychological problems[8]. Atopic eczema not only has a large effect on the health of the sufferer but it also has a substantial economic effect. In the United States, the direct cost for the treatment of atopic eczema may be as high as $3.8 billion per year[9], studies in the United Kingdom are not recent enough to compare as one of the most recent was in 1996[10,11]. This shows from an economic stance that research into a more cost effective treatment is of great importance.

Atopic eczema is a complex trait and current treatment options are sub-optimal

The development of specific treatment modalities in atopic eczema is difficult due to the complexity of this disease. For example, there are a number of strong genetic risk factors associated with the disease and variations in these genes are often seen in atopic eczema; however in a subset of cases, a mutation is present but there is no disease[12]. Another feature involved with atopic eczema is environmental allergens such as dust or animal hair which can precipitate the disease or elicit a flare up. Therefore the disease is now believed to be caused by a combination of both genetic and environmental factors[13]; this complexity is why treatments are only partially effective and why there is currently no cure[14].

Atopic eczema arises due to interactions between a leaky skin barrier and the immune response that occurs both in the skin and the systemic circulation; therefore current treatments aim to reduce the inflammation and repair the skin barrier at sites of inflamed or dry skin. Due to the complexity and range of severity of the disease, there are a number of different treatments[15]. These have been summarised in Figure 1. The most commonly used treatment is the application of emollients; these act by increasing the lipid content in the stratum corneum (outermost layer of the skin) to repair the barrier, thereby improving hydration[15]. However, in all but the mildest cases emollients are insufficiently effective so a combination therapy is used with another agent targeting the inflammatory response. Topical corticosteroids act through the corticosteroid-receptor complex to downregulate synthesis of the proteins involved in inflammation[16]. Topical corticosteroids come in different forms from sprays to creams and ointments but more potent steroids must be used sparingly as they have been found to reduce dermal thickness[17]. Topical calcineurin inhibitors also target the immune mechanisms and act by binding to intracellular protein macrophilin-12, thereby decreasing the production of inflammatory cytokines interleukin (IL)-4 and IL-13; this treatment does not decrease dermal thickness[18,19].

Other treatments include wet-wraps[15,20], oral antihistamines[13] and phototherapy[21] where ultraviolet light is administered to the skin for its immunosuppressive effect. Atopic eczema sufferers frequently have to undergo two or more treatments (Figure 1), one for the disease itself and the other for co-existent bacterial or viral infection[22].

Staphylococcus aureus (*S. aureus*) is a bacterium that may be carried in the nose and flexural skin of some individuals and on the apparently healthy skin of atopic individuals. In individuals with atopic eczema it can cause infections within actively inflamed lesions and lead to increased skin barrier damage[22]. There is a more permissive environment for the growth of *S. aureus* because atopic skin shows a reduction in the expression of antimicrobial peptides[23]. Topical corticosteroids have been found to reduce the colonisation by *S. aureus*[24], but the most effective treatment involves combining these topical corticosteroids with an antimicrobial preparation[25]. However, this combination therapy only shows

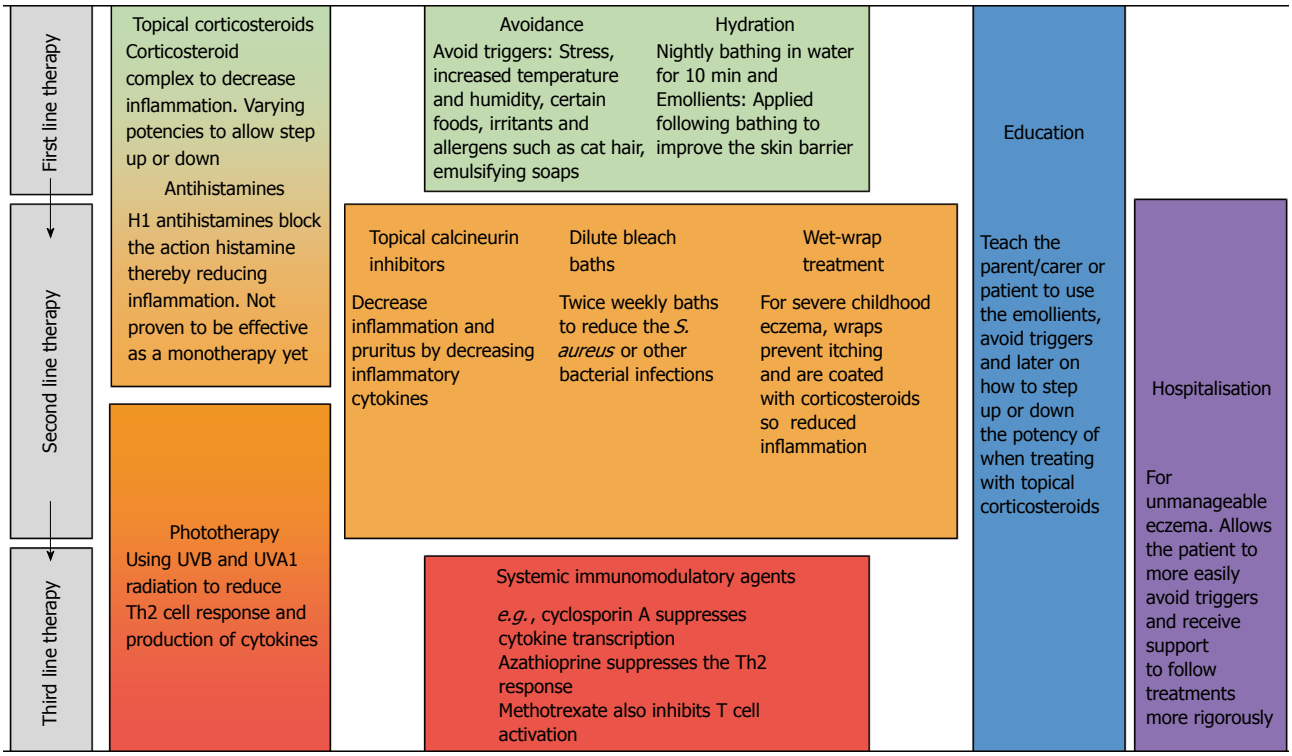

Figure 1 Current treatment options for atopic eczema. A summary of current treatment for atopic eczema, showing stepwise progression for more severe or treatment-resistant disease[13,15-18,20,21].

efficacy in the short-term as over a long period there is no significant benefit in comparison to corticosteroids alone. Therefore a more effective treatment is required to prevent *S. aureus* re-infection.

The stepwise approach to treating atopic eczema, shown in Figure 1, highlights the varying severity in this disease. It also illustrates the range of treatments in use, because of the variation in individual response to each therapy. The currently available treatments target atopic eczema in a rather non-specific way; it is hoped that novel treatments, such as monoclonal antibodies, will be able to target the specific problem(s) in each individual's atopic eczema.

WHAT IS KNOWN ABOUT BARRIER FUNCTION AND IMMUNE MECHANISMS IN ATOPIC SKIN?

This review will focus on the skin barrier and the immune mechanisms of the skin and how irregular function of both lead to atopic eczema, as well as the novel and theoretical treatments designed for targeting each component of the disease.

The skin barrier plays an essential role in protecting the body against the entry of allergens and loss of water

The skin is the largest organ in the body[26] and it plays a number of key roles in survival. A central function is to act as a physical barrier to prevent the entry of allergens and irritants while also vitally retaining water within the body[4]. The skin is composed of three main layers: epidermis, dermis and hypodermis[27]. The outermost layer of the epidermis is called the stratum corneum (Figure 2); this contributes to the control of trans-epidermal water loss (TEWL)[28], *i.e.,* water lost through evaporation. The stratum corneum includes 18-20 layers constructed from dead cells containing keratin called corneocytes; this is surrounded by a matrix of lipids mainly consisting of ceramides and cholesterol[29]. The epidermis provides the physical skin barrier function through the matrix of lipids but also through corneodesmosomes and tight junctions with the stratum granulosum layer below[29].

An essential component of the barrier function of the skin is filaggrin (filament-aggregating protein), an intracellular protein[30] important for formation of the stratum corneum[31]. Filaggrin is formed from the dephosphorylation and proteolysis of profilaggrin when the keratinocytes in the stratum granulosum are undergoing differentiation to the corneocytes of the stratum corneum[32]. Filaggrin monomers bind to keratin molecules to strengthen the filament network and contribute to the changes in shape of keratinocytes as they mature into corneocytes. Filaggrin also plays a key role in control of TEWL. Filaggrin undergoes proteolysis to release hygroscopic amino acids at the surface of the stratum corneum, when the outer skin starts to become dehydrated. These amino acids contribute to natural moisturising factor (NMF) for the skin, maintaining hydration of the stratum corneum and controlling TEWL[33]. Another key role played by filaggrin

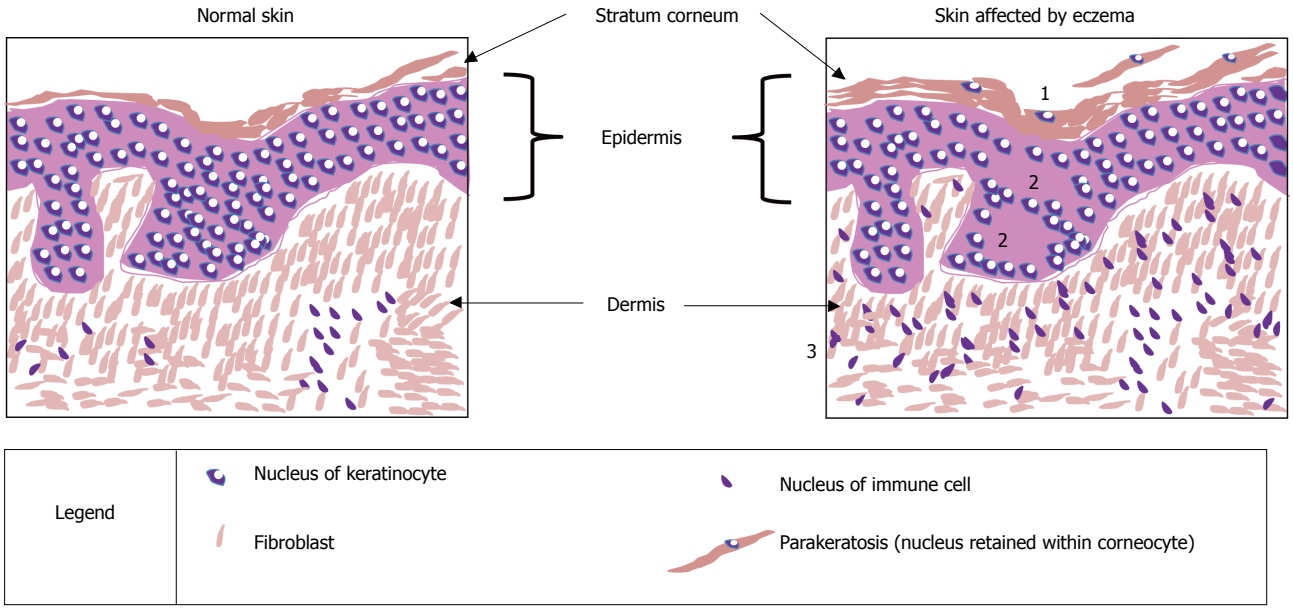

Figure 2 Histological features of atopic eczema. This figure represents sections of skin biopsies, stained with haematoxylin and eosin, to highlight the changes that can be observed under a light microscope, comparing skin affected by atopic eczema and a control sample. Three characteristic features of atopic eczema are illustrated: Increased thickness of the stratum corneum (hyperkeratosis and parakeratosis) is caused by a disruption to the cornification process; spongiosis occurs when there is a reduction or damage of the proteins involved in tight junctions, thereby leading to uncontrolled movement of fluids in the paracellular space; infiltration of the dermis by immune cells is a sign of the immune response as a primary feature of atopic eczema itself or in response to the entry of allergens through a leaky skin barrier. The effects of eczema: 1: Increased thickness of stratum corneum; 2: Spongiosis - oedema (water retained between cells); 3: Increased number of immune cells.

and its degradation products is in the control of skin pH. The acidic pH of skin acts as an antimicrobial defensive mechanism to limit bacterial colonisation[34]. If the pH of the skin is increased, filaggrin proteolysis can contribute acidic amino acids to return it to the optimal slightly acidic pH[34].

Tight junctions hold the keratinocytes together, control the flow of fluids paracellularly and are key as they act as another barrier; the stratum corenum acts as the first physical barrier to allergens and irritants while tight junctions form the second[35]. This barrier is particularly important if the stratum corneum becomes diseased, since the tight junctions provide a second line of defence against allergens, to prevent their entry into the skin and the resultant immune response.

Atopic eczema has profound effects on the skin barrier of an affected individual

The difficulty in describing the causes of atopic eczema are that the mutations or genetic variants being proposed as the culprits of the skin barrier dysfunction only occur in a proportion of affected individuals. There have been a number of genetic studies aiming to highlight potential risk factors for atopic eczema; they have discovered links between certain mutations or genetic variants that are associated with increased risk for the disease[36-40]. The majority of candidate gene association studies point to null mutations in the filaggrin gene, *FLG*, and genes involved with the type 2 T helper lymphocytes (Th2 cell) function[41,42]. Loss of function mutations in *FLG* were first identified in 2006 and this remains the strongest genetic risk factor for atopic eczema identified to date[43].

The section above highlighted the importance of the protein filaggrin in a number of key roles involved with producing the skin barrier; therefore it is understandable that a loss of function mutation in *FLG* may increase the risk of atopic eczema. Other related diseases such as ichthyosis vulgaris, atopic asthma, allergic rhinitis and food allergies are also often associated with mutations in filaggrin[44]. Filaggrin is key in cross-linking keratins to flatten the shape of cells, in the stratum corneum; consequently null mutations will lead to malformed corneocytes and allergens may be able to enter through this leaky skin barrier and incite an inflammatory response[26]. In atopic eczema there is an increased rate of TEWL and again it is possible that filaggrin may play a role, as null mutations mean filaggrin cannot be degraded to form NMF, hence skin hydration is reduced[26]. Another often vital part of the disease is the colonisation by bacteria and this is more likely to occur in the alkaline conditions of the skin when filaggrin is absent or reduced in amount[45]. This is one of possibly several factors that allows binding of bacteria such as *S. aureus*, and it can contribute to the development of atopic eczema or worsen its severity[46]. The main mechanism by which *S. aureus* damages the skin barrier is through secretion of SspA/V8 protease. This protease acts to degrade the proteins in the corneodesmosomes in the stratum corneum but also proteins in the tight junctions of the stratum granulosum, thereby compromising both elements of the skin barrier and allowing entry of allergens and irritants[47,48].

In some cases of atopic eczema it has been shown that key proteins involved with tight junction function, claudin-1 and claudin-23, are reduced[35]. It was believed that mutations in the filaggrin gene may also affect tight junction functionality, however mouse models demonstrated that filaggrin insufficiency did not have a direct effect[49]. Other mouse models have demonstrated the importance of claudin-1 in maintaining normal levels of TEWL: When mice lack this protein, they die within a day[50]. On closer inspection, it was observed that claudin-deficient mice died of dehydration as a result of increased TEWL and this was due to non-functioning tight junctions[50]. Therefore, the reduction in claudin-1 seen in atopic eczema patients may contribute to their increased TEWL and dry skin. Tight junctions are vital for paracellular control of fluids, as well acting as a physical barrier, and what is often observed with atopic eczema is spongiosis, where oedema is occurring between the keratinocytes in the epidermis (Figure 2).

Another characteristic of atopic eczema which can be seen as scaliness (white flaky skin) when directly observing the skin, or by light microscopy of a histological section of diseased skin, is an increased thickness of the stratum corneum[51]. Normally epidermal cells undergo transformation from keratinocytes of the stratum basale, in the lower epidermis, to corneocytes of the stratum corneum, in the upper epidermis, and begin to shed off the skin; however in atopic eczema this cornification process is disrupted[52]. In atopic eczema the keratinocytes retain their nucleus and remain attached instead of shedding, contributing to the thickened stratum corneum. This feature can also be seen in Figure 2.

Immune dysfunction plays a key role in eczema pathogenesis

The balance of immune mechanisms in the skin is a closely regulated process, which involves a number of different immune and non-immune cells interacting to protect the body from pathogens[53]. However, this balance is susceptible to a number of diseases. Above, we have mostly described how skin barrier dysfunction leads to an increased immune response thereby causing atopic eczema; nevertheless the disease may also be caused by immune dysfunction leading to skin barrier damage. It has been demonstrated that IL-4 and IL-13, the two cytokines that are greatly increased in atopic eczema, are able to significantly decrease the expression of filaggrin[54]. When IL-4 and IL-13 were incubated with keratinocytes for 24 h they decrease the expression of filaggrin[54]. Hence these two interleukins can cause damage to the barrier *via* their effects on keratinocyte differentiation[54]. This study also highlighted that environmental allergens such as soap and detergents would cause the same damaging effects through increased levels of IL-4 and IL-13[54]. A different study demonstrated that histamine may also contribute to immune dysfunction causing a leaky skin barrier and atopic eczema[55]. This study again observed keratinocyte differentiation as a measure of barrier damage but also investigated the important barrier proteins keratin 1 and keratin 10, loricrin and filaggrin[55]. The study showed that expression of these proteins was reduced by as much as 80%-95% in the presence of histamine thereby affecting keratinocyte differentiation and the skin barrier[55]. The final part of this study demonstrated that histamine also caused down-regulation of the claudins involved in tight junction formation and therefore this may also contribute to the leaky skin barrier in atopic eczema[55].

The adaptive and innate immune responses have both been highlighted as possibly playing a role in atopic eczema[56]. The candidate gene and genome-wide association studies mentioned earlier have illustrated that variation in genes involved with the adaptive response of the Th2 cells is associated with risk of atopic eczema. In a number of cases of atopic eczema there will be increased levels of the Th2 cell and its cytokines IL-4 and IL-13; these are important for instigating inflammation[56]. IL-4 is key for production of eosinophils and importantly IgE, which then acts through Fc-εRI receptors to cause mast cells degranulation, stimulating inflammation[57]. IL-13 has not been as extensively studied in skin, however its mechanism of inflammation appears to occur through interacting with the IL-4Rα receptor[58]. Another mechanism by which atopic eczema may occur is when someone begins to scratch, causing mechanical damage. The traumatised keratinocytes release thymic stromal lymphopoietin (TSLP), another cytokine. Studies have demonstrated that TSLP levels are increased in skin affected by atopic eczema compared to normal skin[59]. TSLP acts on dendritic cells which activate Th2 cells producing IL-4 and IL-13 resulting in a cycle of increased inflammation and atopic eczema[59,60].

The innate immune system may also play a role in causing an individual's atopic eczema. One of the first lines of response to pathogens is by antimicrobial peptides which are secreted and activated once toll-like receptors (TLR) identify pathogens[61]. Defects in these TLRs have been implicated in potentially allowing the colonisation of bacteria and therefore instigating atopic eczema[62]. A study using a mouse model found that mice with defective TLR4 or TIR-domain-containing adapter-inducing interferon-β (TRIF) had increased levels of TEWL, resulting in atopic eczema[62]. The peptides themselves are found to be reduced in eczema-affected skin and therefore fail to prevent colonisation and damage by pathogens such as *S. aureus* or infection with herpes simplex resulting in eczema herpeticum[63]. Cathelicidin and human beta defensin 2 (hβD-2) have been shown to be reduced in atopic eczema, lowering the threshold for this damage to occur[64,65]. *S. aureus* releases alpha and delta toxins which activate the adaptive immune response resulting

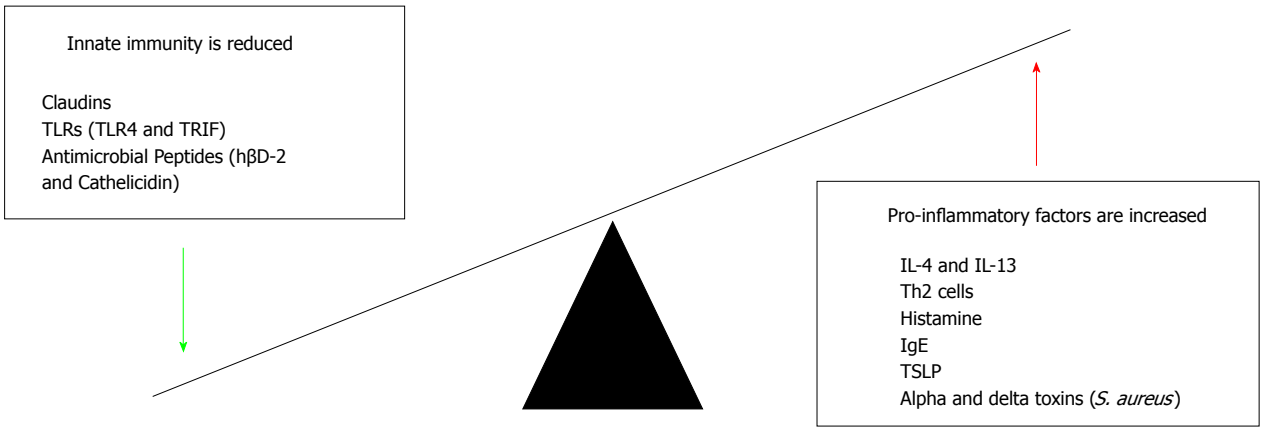

Figure 3 Immune dysfunction in atopic eczema. This figure summaries the number of immune factors discussed in the review. Increased and decreased levels of different factors contribute to the pathogenesis atopic eczema. TLR: Toll-like receptors; hβD-2: Human beta defensin 2; *S. aureus*: *Staphylococcus aureus*; IL: Interleukin; TSLP: Thymic stromal lymphopoietin.

in increased Th2 cell activity[53,66] and driving further inflammation (Figure 3).

HOW CAN THIS KNOWLEDGE BE APPLIED?

Novel treatments target the leaky skin barrier and immune mechanisms in eczema

This knowledge of the molecular mechanisms in skin barrier function and immune response is creating opportunities for novel treatment approaches for atopic eczema, summarised in Figure 4 and Table 1.

One potential therapeutic avenue may involve using vitamin D to decrease the severity of atopic eczema; studies have shown that it is important in both barrier repair and modulation of the immune mechanism[67,68]. A study in mice demonstrated that those treated by phototherapy had greatly increased levels of filaggrin which also lead to decreased time for barrier repair to occur[69]. This was believed to be due to the action of vitamin D on keratinocytes to increase levels of calcitriol, thereby normalizing the faulty keratinocyte differentiation seen in atopic eczema, to improve barrier function[69,70]. Oral supplementation of vitamin D has not shown a therapeutic effect, so alternative methods of administration are required.

The knowledge of a central role for dry skin in atopic eczema has stimulated interest in the development of bespoke emollients as treatment for xerosis[71]. In one study a standard emollient (the control) was compared to an emollient cream containing 5% urea, a skin ceramide N-stearoyl phytosphingosine (NP) and lactate[71]. When skin that had previously been treated with the cream containing ceramide NP was changed to the control there was an increase in TEWL from 11.58 to 11.94 g/m^2 per hour; this suggested that skin barrier function was improved more by using investigated cream than the control[71]. However this improvement between the creams may be due to the sodium lauryl sulfate in the control having an emulsifying effect and increasing barrier damage[71]. When hydration was also considered, the application of the ceramide NP cream showed greater hydration compared to the control, suggesting improvement of the stratum corneum barrier[71]. There is the possibility of damage if the ceramide NP cream is used with atopic eczema as it increases pH slightly and further work is needed to define the optimal emollient treatment for atopic eczema.

Another potential treatment aimed at the leaky skin barrier involves using a synthetic elastic "second skin"[72]. This skin is made of a cross-linked polymer (XPL) and has been used initially as anti-ageing solution where it can be applied to remove signs such as wrinkled skin; it has demonstrated dramatic results, especially around the eyes[72]. It has been subsequently proposed as a potential treatment for atopic eczema as the XPL will act as an extra skin barrier, for up to 24 h, preventing entry of allergens or irritants to affected areas of skin[72]. However this very interesting application remains speculative, as no research has yet been conducted.

It has recently been highlighted that increasing levels of the antimicrobial peptide hβD-2 can be used to reduce damage caused to the skin barrier by *S. aureus*[48]. In atopic eczema there are reduced levels of hβD-2 so its IL-1β defensive mechanism cannot prevent damage by the SSpA/V8 protease[48]. It was demonstrated that purified recombinant or synthesised hβD-2 could decrease skin barrier damage by 15% and 10% respectively[48]; this may be a useful avenue for future topical treatments.

Phosphodiesterase-4 (PDE-4) inhibitors can be taken orally to prevent cyclic-AMP degradation in cells involved in immune mechanisms of atopic eczema; however, this often leads to side effects such as nausea and diarrhoea[73]. An ointment based PDE-4 inhibitor has therefore been developed called crisaborole; it is one of the few non-steroidal based ointments developed recently[73]. It has just finished phase 3 clinical trials and has demonstrated improvements as high as 41%

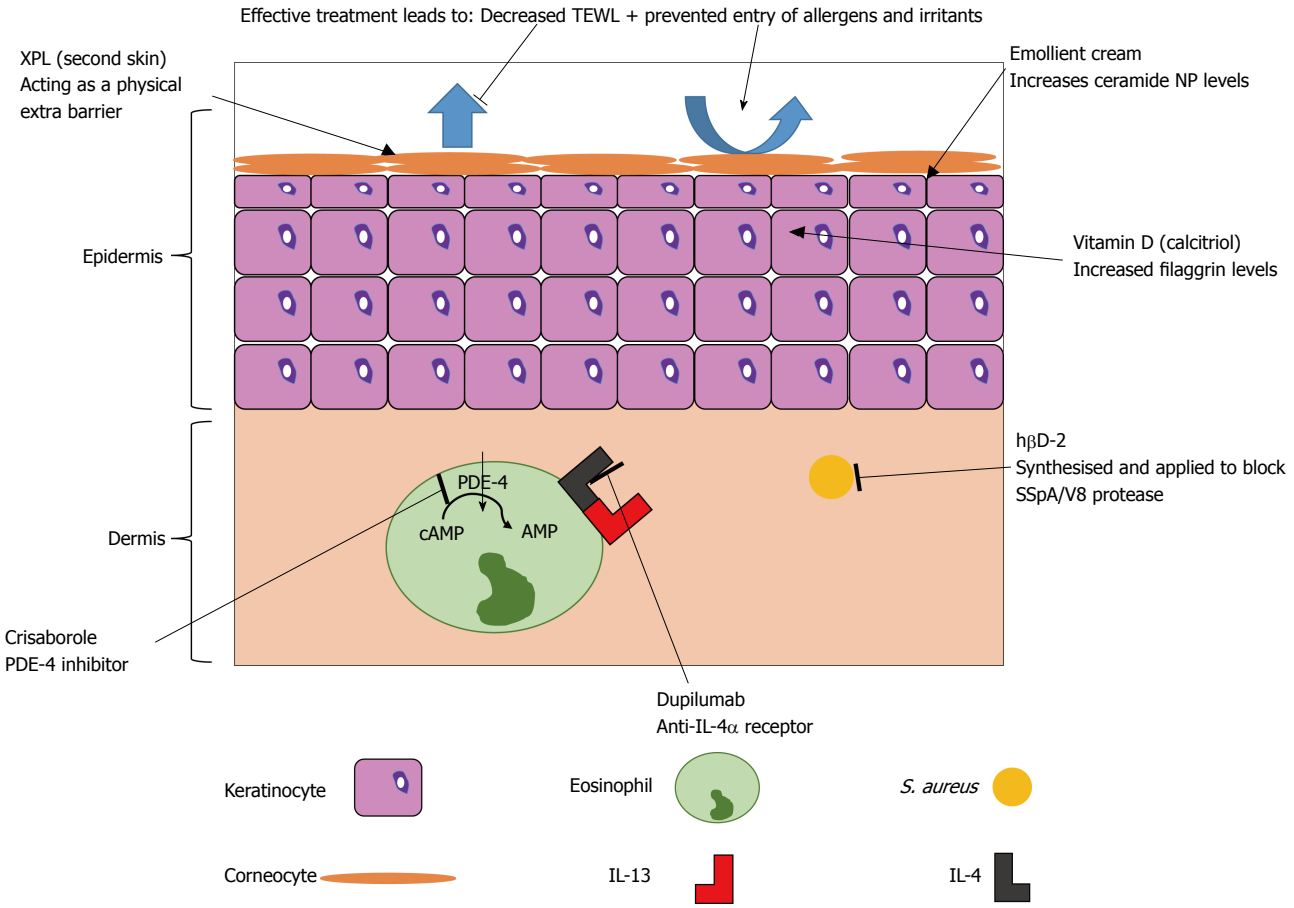

Figure 4 Novel treatment targets in atopic eczema. This figure highlights the keys roles of treatment: to decrease TEWL, prevent entry of irritants and allergens into the skin and to decrease the action of the immune response. TEWL: Trans-epidermal water loss; IL: Interleukin.

Table 1 Novel therapeutic strategies targeting atopic eczema

Repairing the damaged skin barrier	Reducing atopic inflammation
XPL (second skin)	Crisaborole
Emollients with increased ceramide NP levels	Dupilumab
Vitamin D (calcitriol)	hβD-2

Novel therapeutic strategies and mechanisms of action in atopic eczema. XPL: Cross-linked polymer; hβD-2: Human beta defensin 2.

compared to a placebo moisturiser, in terms of atopic eczema severity scores[73]. This drug may soon be approved by the FDA for treatment of atopic eczema.

A novel treatment that presents the greatest opportunity to powerfully target atopic eczema inflammation involves using monoclonal antibodies which are currently being developed to treat several different atopic diseases[74]. Currently one of the only commercially available monoclonal antibody treatments for atopic disease is omalizumab which is licenced for the treatment of asthma[74]. It targets the IgE Cε3 domain which leads to decreased severity in asthma and has the potential to be used in atopic eczema[74].

However a more promising monoclonal antibody treatment is dupilumab, which is an anti-IL-4α receptor, so stops the action of IL-4, thereby preventing the inflammation by both IL-4 and IL-13[74]. It is currently showing promising results in phase 2 trials (up to 85% of patients showing a 50% reduction in eczema severity score)[75] and phase 3 trials (in which up to 38% of patients were clear or almost clear after 16 wk of treatment)[76]. Drawbacks of this treatment are that it involves an injection which is more invasive than the other treatments and that the long-term safety is currently unknown[74].

CONCLUSION

Atopic eczema is a complex and chronic inflammatory disease of the skin that affects a large proportion of people. The pathomechanisms include a leaky skin barrier and an immune response: Both are able to occur first thereby causing the other. The problems associated with atopic eczema extend far beyond skin disease, affecting a whole family and not just the individual or child affected, causing mental health problems as well as economic impact. Mutations in the gene encoding filaggrin (*FLG*) have been highlighted as an important part of the disease; filaggrin plays a number of roles in maintaining the skin barrier so this is plausible. However, not every case of atopic eczema

has these null mutations in *FLG* and the same can be seen with the immune mechanisms of the disease. The Th2 cell response often occurs in atopic eczema and is central to causing the atopic inflammation. Bacterial infection contributes to atopic eczema pathogenesis and this is potentiated *via* reduced antimicrobial peptides or mutations in filaggrin leading to a reduction in the acidic pH of skin.

The multitude of causes is what has brought about the variety of treatments for atopic eczema. Different treatments are effective or ineffective in different individuals. The ideal treatment for atopic eczema would be able to target and repair the leaky skin barrier but also normalise the increased immune response of atopic skin. In milder atopic eczema, the best treatments often involve educating patients and children to avoid their own triggers and more education may improve overall treatment. Novel treatments have become more specific in targeting molecular mechanisms in atopic eczema, which, it is hoped, will make them more effective and with fewer side effects. However a considerable amount of research is still required to develop the most effective treatment to target both key mechanisms - the skin barrier dysfunction and immune response - to fully control this complex disease.

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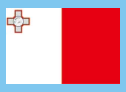

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Quarterly Volume 6 Number 4 November 2, 2017

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Skin-gut axis: The relationship between intestinal bacteria and skin health

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Abstract

The gut microbiome is an emerging area of interest in medicine. Imbalances in the gut microbiome have been linked to a number of disease states such as obesity and type 2 diabetes. The relationship between normally residing intestinal bacteria (the *gut microbiota*) and their potential role in the pathogenesis of skin diseases is an area of research for which we are only beginning to understand. Small studies have demonstrated underlying changes in the gut microbiome of patients with certain dermatological diseases. Interestingly, studies suggest that probiotics may have a role in the treatment of atopic dermatitis. However, the concept of the "skin-gut axis" is a newly emerging and important avenue of investigation, still lacking in pathobiological explanations. This review will introduce and describe the intestinal microbiome as it relates to skin health in a complex communication network between the immune system, endocrine system, metabolic system, and nervous system.

Key words: Gut microbiome; Skin; Bacteria; Probiotics; Dermatology

Core tip: The intestinal microbiome is a complex and dynamic bacterial community that plays an important role in human health. Alterations in microbiota composition have been related to different intestinal and extra-intestinal diseases such as psoriasis and rosacea. Studies have reported beneficial interactions between the human body and its microbiota and modulation through prebiotics and probiotics may prevent or resolve such diseases. Although the mechanisms for how the gut and skin communicate are not fully understood the association likely involves a complex connection between the nervous, immune, and endocrine systems as well as environmental factors.

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INTRODUCTION

The role of the gut microbiome as an important determinant of human health and disease has emerged as an exciting niche of research in many areas of medicine. An imbalance in the gut microbiome has been linked to obesity, type 2 diabetes, atopy and inflammatory bowel disease (IBD)[1]. Furthermore, the relationship between normally residing intestinal bacteria (the *gut microbiota*) and their potential role in the pathogenesis of skin diseases is an area of research for which we are only now starting to gain an understanding. The small and large intestines provide residence for a vast community of bacteria and their metabolites and by-products, which we call the *gut microbiome*. Similarly, thousands of microbial organisms and their by-products inhabit the skin, referred to as the *skin microbiome.* In both the gut and the skin, a harmonial balance in these microflora is important in maintaining homeostasis[2]. The skin and the gut have more similarities than one would suppose, and in fact, there is budding interest in learning how the skin and gut communicate and influence the health of one another[3]. Both contain rich vascular supply, diverse microbial communities, and act as vital interfaces between the internal human body and the external environment. Additionally, the skin and gut both operate as neuro-immuno-endocrine organs, and participate in essential communication with the nervous system, immune system, and endocrine system. The "brain-gut axis" has been documented extensively in the literature, and was first described in 1930 when Stokes and Pillsbury attributed depression to altering the gut microbiome, leading to inflammatory skin diseases[4]. However, the "skin-gut axis" is a newly emerging and important avenue of investigation, still sparse in pathobiological explanations. This review will introduce and describe the intestinal microbiome as it relates to skin health in a complex communication network between the immune system, endocrine system, metabolic system, and nervous system.

HUMAN INTESTINAL MICROBIOME

The "gut microbiome" refers to the diverse community of microbial organisms that normally inhabit the bowel and their metabolites/byproducts[5]. There are more than 100 trillion bacteria present in the human gastrointestinal tract, consisting of over one thousand different species colonizing the intestines[6,7]. A large proportion of the organisms found in the gut microbiome belong to two phyla: *Firmicutes* and *Bacteroidetes*[5]. The density of the bacterial populations within the bowel differs by anatomical location. For instance, the density is approximately 10^{2-3} colony forming units (CFU) per gram in the proximal ileum and jejunum, compared to the ascending colon which has approximately 10^{11-12} CFU per gram[8]. There is significant variation in the gut microbiome communities among healthy individuals[9]. The gut microbiome is relatively stable, however, studies have demonstrated that antibiotic therapy, international travel, and illness can all alter the normal gut microbiome. Aging can also lead to a shift in the predominant species within the gut microbiome. Research currently suggests that our long-term dietary patterns could have a large impact on the composition of our gut microbiome[6].

The role of the gut microbiome is thought to include proper development and functioning of the immune system, protection against infections, digestion of polysaccharides, and synthesis of vitamins[7]. The symbiotic relationship between resident gut bacterial flora and the host is vital to the normal immune system development and homeostasis of the host and regulation of epithelial growth and differentiation[10].

PROBIOTICS/PREBIOTICS

Probiotic supplementation has become increasingly popular, with many commercially available products in capsule, powder, beverage, and food forms. According to the Food and Agricultural Organization of the United Nations and the World Health Organization, probiotics are considered to be "live microorganisms which when administered in adequate amounts confer a health benefit on the host"[11]. The most frequently used bacteria are from the *Lactobacillus* and *Bifidobacterium* genera[12]. There has been evidence to suggest that they are useful in the treatment of irritable bowel syndrome (IBS), diarrhea, and lactose intolerance[13]. Probiotics may alleviate abnormal alterations of the gut microbiome, referred to as "dysbiosis". Dysbiosis of the gut microbiome has been linked to metabolic disorders, gastrointestinal infections, IBD, and irritable bowel syndrome (IBS)[14]. Probiotics are thought to provide therapeutic benefits *via* multiple mechanisms. Firstly they are believed to prevent pathogenic bacteria from colonizing the gastrointestinal tract, which would otherwise subsequently lead to disease. Secondly, they are thought to improve the barrier function of the colonic mucosa. Thirdly, probiotics may help modulate the immune system, which may help shift away from pro-inflammatory immune reactivity[12]. Fourth, they may synthesize and secrete metabolites that may have nutritional benefits and anti-inflammatory effects[15]. Lastly, probiotics may even play a role in modulating central nervous system and enteric nervous system functions. In fact, in a randomized controlled trial patients with Alzheimer's disease who received probiotic supplementation for 12 wk had significant improvement in mental status score and had a significant decrease in serum c-reactive protein (Akbari, 2016 #991). Additionally, probiotic supplementation has demonstrated

improvement in multiple sclerosis symptoms and exacerbations (Dolan, 2016 #992).

Probiotics have not yet been widely studied in the treatment of dermatological diseases. Two meta-analyses failed to demonstrate any clinically significant changes in the severity of atopic dermatitis (AD) in children treated with probiotic supplementation[16,17]. However, Lee *et al*[16] found a significant risk reduction (up to 61%) of pediatric AD in those who were treated with prenatal and/or postnatal probiotics. There are even fewer studies available regarding the treatment of adults with AD using probiotics. These small studies have demonstrated that there may be a clinical benefit in adults[18-20]; however, larger trials are needed before any conclusions can be drawn. Probiotics are postulated to help in atopic dermatitis by improving the diversity of the intestinal flora, increase the barrier function of the skin and mucosa and by producing a mainly Th1 response[13].

Prebiotics are non-digestible carbohydrates that help stimulate the growth of certain bacteria in the gut, which can lead to an improvement in the health of the host[21]. A review by Osborn *et al*[22] of four clinical trials found that there was a statistically significant reduction in the incidence of infant eczema with prebiotic supplementation of galactoligosaccharides and fructooligosaccharides (RR 0.68). It has been demonstrated that milk glycoproteins are able to select for and stimulate the growth of *Bifidobacteria longum infantis (B. infantis)* in the gut microbiome[23]. This is of clinical importance as *B. infantis* supplementation can reduce the risk of necrotizing enterocolitis in preterm infants. *B. infantis* colonization of the gastrointestinal tract is associated with improved immune response to vaccination and weight gain[24].

However, further studies need to be conducted into the use of prebiotics and probiotics before recommendations regarding their use in the treatment or prevention of dermatological diseases can be made.

LINK BETWEEN SKIN DISEASE AND THE GUT

Gastrointestinal disorders can present with dermatological skin findings. IBD is linked to skin manifestations such as pyoderma gangrenosum, erythema nodosum, Sweets Syndrome and oral lesions[23]. Celiac disease is associated skin manifestations such as dermatitis herpetiformis, alopecia, vitiligo and oral mucosal lesions. Furthermore, psoriasis is more commonly found in patients with Crohn's disease than healthy people[24].

There is emerging evidence linking certain dermatological disorders to gut dysbiosis. However, this is not a novel topic and in fact, in 1911 a gastroenterologist named Milton H. Mack wrote, "Acne and eczema are both traceable to this fountainhead of diseases… if in a case of urticarial we look to the intestinal track, why not in eczema and acne?" [25]. Simultaneous gut and skin microbiome dysbiosis has been observed in several inflammatory skin diseases, such as rosacea, psoriasis, and atopic dermatitis[26].

Psoriasis

Interestingly, patients with psoriatic arthritis are at increased risk of developing IBD and have subclinical evidence of gut inflammation[27]. A recent clinical study including 16 patients with psoriatic arthritis, 15 with psoriasis and 17 healthy controls analysed the gut microbiome across these three groups. The gut microbiome was less diverse in the psoriasis and psoriatic arthritis groups; with a decrease in the *Coprococcus* spp. Those with psoriatic arthritis experienced a reduction in important bacterial enterotypes such as *Akkermansia, Ruminococcus, and Pseudobutyrivibrio*. It is thought that these taxanomic changes cause to a reduction in the ability of the gut to regulate immune responses, which may lead to systemic or localized inflammation[28].

In addition, a clinical trial has shown that treating psoriasis patients with probiotic *Bifidobacterium infantis* 35624 for eight weeks improved C-reactive protein (CRP), TNF-alpha and IL-6 levels. However, during this study no clinical assessments were performed after baseline. These results suggest that probiotic supplementation could modulate inflammation in this disorder[29].

Rosacea

Rosacea has been linked to *Helicobacter pylori* (*H. pylori*) infection, however the efficacy of *H. pylori* eradication in rosacea therapy is unclear[30]. Moreover, a study of 113 rosacea patients demonstrated that those with rosacea have a higher incidence of small intestinal bacterial overgrowth (SIBO) when compared to controls. Those with SIBO were treated with either rifaximin therapy for 10 d or placebo. Those who were treated with antibiotic therapy experienced an improvement in their symptoms for at least nine months[31].

Atopic dermatitis

There is a well-documented association between gut microbiome dysbioses and low diversity within the gut microbiota with the development of allergic diseases (Melli, 2016 #993). Conversely, increased microbial diversity within the gut has been associated with reduced flares in inflammatory skin diseases, such as atopic dermatitis (Marrs, 2016 #994).

PROPOSED MECHANISMS REGARDING THE SKIN-GUT AXIS

At present, there is clinical evidence suggesting a close relationship between intestinal dysbiosis and dermatologic conditions. However, the mechanistic basis behind these observations has yet to be confirmed. The association between the gut and skin likely involves a complex and multifactorial interplay between the

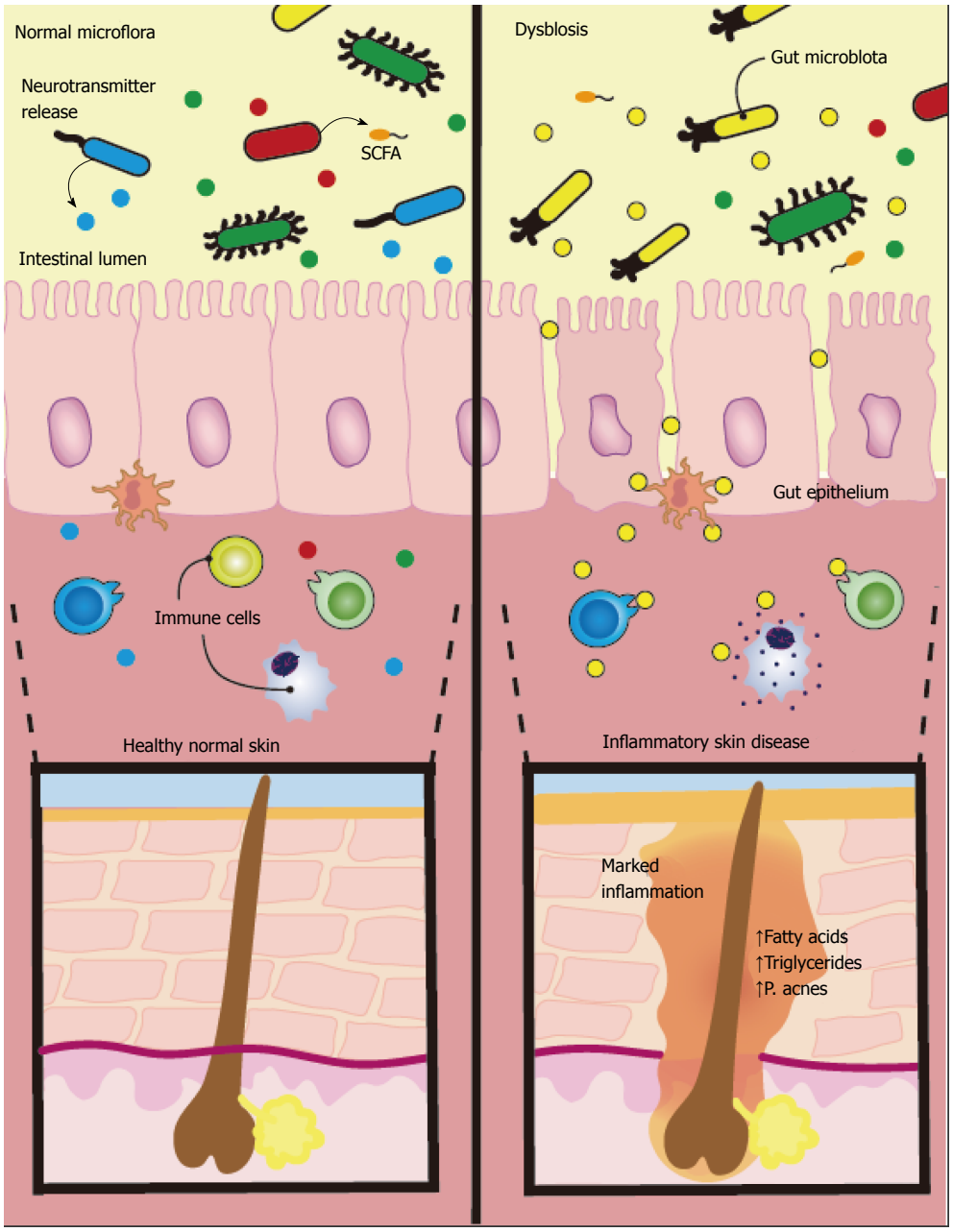

Figure 1 There is emerging evidence linking dermatological disorders to alterations in gut bacteria. Studies hypothesize intestinal flora produce neurotransmitters in response to stress that can modulate skin function. These neurotransmitters cross the intestinal epithelium enter the bloodstream and induce systemic effects. Along with neurotransmitters, the gut microflora also release short chain fatty acids (SCFAs), which can also enter systemic circulation and affect the skin. Additionally, diet may influence inflammation in the skin though nutrient signalling and release of long chain fatty acids, leading to excessive stimulation of sterol regulatory element-binding protein 1 and increased synthesis of fatty acids and triglycerides promoting *Propionibacterium acnes* overgrowth.

nervous, immune, and endocrine systems as well as environmental factors such as diet and medications (Figure 1).

Skin-gut axis and the neuroendocrine system

The "brain-gut-skin axis" has been eloquently documented by Arck *et al*[32] and Bowe and Logan[4]. It is known that psychosocial stress is implicated in both exacerbation and the initiation of various skin conditions[33]. It is plausible that the intestinal microflora produce neurotransmitters in response to stress and other external stimuli that could modulate skin function *via* neural pathways. For instance, commensal organisms in the gut can produce norepinephrine, serotonin, and acetylcholine or may evoke the release of neuropeptides from nearby enteroendocrine cells[34]. These neurotransmitters might cross the intestinal epithelium into the bloodstream and induce systemic effects[35]. Along with neurotransmitters, the gut microflora also release short chain fatty acids (SCFAs), including propionic acid, butyric acid, acetic acid, and lactic acid derived from polysaccharide fermentation from food we eat[36]. The majority of these SCFAs are produced in the large intestine, where the colon is highly efficient in the reabsorption of fatty acids, only allowing approximately

10% to remain in expelled feces[37]. The true systemic levels of SCFA derived from the colon depend on individual dietary habits, rate of SCFA production by gut microbes, and the degree of absorption through the large intestine. It is not known whether these metabolites, along with many others produced by gut microbes, are able to reach clinically significant levels in the bloodstream in order to impact the skin[38].

Immune system modulation

Health, including skin health and overall well being, require tightly integrated immune and hormone feedback systems that allow beneficial microbial to dominate in the gut and on the skin[39]. The normal gut microbial residents continuously interact with the immune system to support host homeostasis. In general, immune system homeostasis requires a proper balance of pro-inflammatory and anti-inflammatory signals and molecules in response to internal and external environmental changes. If the microbiome composition changes for any given reason, the immune system reactivity could subsequently shift and eventually lead to inflammatory skin diseases[40]. This idea was exemplified in a mouse study by Zanvit *et al* which demonstrated that mice treated with antibiotics neonatally had exacerbated imiquimod-induced psoriasis as an adult, while mice treated with the same antibiotics in adulthood had improved psoriasis (Zanvit, 2015 #990). This study demonstrates the importance of how neonatal gut dysbioses can affect skin inflammation, potentially triggering or exacerbating inflammatory skin diseases such as psoriasis later in adulthood. Interleukin-10 (IL-10) is generally considered to decrease pro-inflammatory molecules, such as IL-17[41]. Animal models have shown that probiotic supplementation up regulates IL-10 and provides beneficial skin effects[42]. In a recent article, Zákostelská *et al*[43] hypothesize that certain beneficial families of intestinal bacteria, such as lactobacilli, are able to supress the IL-23/Th17 axis, which is believed to play an important role in inflammation involved in psoriasis[43]. This suppression may occur through certain gut commensal organisms' ability to down regulate IL-23 and transforming growth factor-beta (TGF-β) expression, and preventing Th17 cell-mediated release of proinflammatory IL-17[44]. As a result of immune system dysfunction and deficiency in T regulatory cells, some autoimmune diseases can result in rampant inflammation and severe dermatitis, such as in IPEX syndrome (Halabi-Tawil, 2009 #996). The intestinal microbiome is responsible for regulating the expansion of T regulatory cells, Th1 and Th2 type cells to provide immune system homeostasis, and there has been recent research investigating how treating the gut microbiome could improve these types of skin conditions (He, 2017 #995). These are examples demonstrating the complex interplay between the immune system and gut commensal organisms. The true connection between skin health and gut bacteria induced immune system reactivity is poorly understood and still requires more extensive investigation.

Diet

Recent research continues to reveal the influence of the "western diet" in the obesity epidemic, and researchers have hypothesized that alterations in the gut microbiome due to high dietary fat intake could be partly to blame (Murphy, 2015 #997). In the literature, it is generally accepted that high fat diets lead to gut dysbioses, reflected by a decrease in *Bacteroidetes* species and an increase in *Firmicutes* species (Zhang, 2012 #998). Although the exact mechanisms are still under investigation, "western diet" induced gut dysbioses may be associated with cancer (Schulz, 2014 #999), atherosclerosis and heart disease (Gregory, 2015 #1000), insulin resistance (Carvalho, 2012 #1001), and even disorders of the central nervous system (Scheperjans, 2015 #1002). Until recently, conflicting opinions and inconclusive evidence have predominated regarding the link between diet and skin conditions. Although more mechanistic studies are warranted, there is growing evidence that diet plays an important role in the pathogenesis of skin diseases, with acne vulgaris being an example. For example, the western diet consisting of large amounts of saturated fats and high glycemic load has been strongly associated with acne[45,46]. Researchers hypothesize this occurs from problems in nutrient signalling, ultimately leading to excessive stimulation of sterol regulatory element-binding protein 1 (SREBP-1) and increased synthesis of fatty acids (ex - free oleic acid) and triglycerides in sebum that promotes flourishing *Propionibacterium acnes* growth[47]. The strong association between atopic dermatitis and food sensitivities similarly exemplifies the importance of food on the gut-skin relationship[48]. The ability of diet to both positively and negatively influence skin function demonstrates the undeniable link between the skin and gut, however, the mechanisms surrounding this connection is likely multifactorial and at present based primarily on theory. Indeed, it is difficult to detangle the direct effects of food on the skin versus food's modulation of the intestinal microflora.

CONCLUSION

The intimate relationship between the gut and skin is undeniable. Possibly, both the intestinal bacteria themselves and their metabolic by-products influence skin physiology. The mechanisms are still under study but there are a few theories: (1) bacterial products and diet could alter the physiology of the gut epithelium, resulting in different secretory products that might circulate systemically and reach the skin; (2) neurotransmitters, hormones, and other bioactive chemicals such as SCFAs derived from the gut could all act on receptors within the skin and directly alter the skin or alter the skin's commensal bacteria; and (3) ingested compounds and chemicals may absorb and have a direct effect on the skin's appearance or function[49].

Although not a new avenue of research, the relationship between the gut microbiome and skin health is emerging as an important and intriguing topic in dermatology and gastroenterology alike. It is especially important to understand how diet, medications, and psychosocial stress can influence or contribute to altered microbial communities in the gut, which may directly or indirectly affect skin health.

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CASE REPORT

Pleomorphic cutaneous xanthomas disclosing homozygous familial hypercholesterolemia

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Author contributions: Mastrolorenzo A and D'Errico A designed the report; Pierotti P performed the infectivology analyses; Mastrolorenzo A and D'Errico A collected the patient's clinical data; Giannini S and Fossi F perfomed the vascular and metabolic analyses, dyspipidemia management and critical revision; Vannucchi M perfomed the histopathological analyses; Mastrolorenzo A and D'Errico A analyzed the data and wrote the paper.

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Informed consent statement: The patient involved in this case report has signed an informed consent allowing the use of pictures and information in an anonymous format.

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Abstract

Homoxygous Familial Hypercholesterolemia is characterized by a presence of several types of cutaneous xanthomas with an abnormal lipid profile. Some of these could be pathognomonic. Although these could be initially interpreted as isolated and localized benign disorders and offered surgical treatment, it has become increasingly clear that they could be a part of a systemic pathology. Here we describe a case of this rare disorder in a 19 years old non-obese young man who presented multiple, intertriginous, tuberous and tendinous xanthomas and had an associated abnormal lipid profile with elevated low-density lipoprotein cholesterol levels. A detailed history with clinical assessment in the differential diagnosis and laboratory investigations led to a precise diagnosis.

Key words: Intertriginous xanthomas Homoxygous Familial

Hypercholesterolemia; Familial hypercholesterolemia; Dyslipidemia; Xanthomas

Core tip: This article describes a contemporary approach to the differential diagnosis of xanthomas, and the morphological classification from a review of the literature, specifically reflect the clinical findings evidenced in this case report.

Mastrolorenzo A, D'Errico A, Pierotti P, Vannucchi M, Giannini S, Fossi F. Pleomorphic cutaneous xanthomas disclosing homozygous familial hypercholesterolemia. *World J Dermatol* 2017; 6(4): 59-65 Available from: URL: http://www.wjgnet.com/2218-6190/full/v6/i4/59.htm DOI: http://dx.doi.org/10.5314/wjd.v6.i4.59

INTRODUCTION

The clinical picture of xanthomas is variable from yellow or orange dermal macules or papules, to soft or firm-hard subcutaneous plaques and tendinous nodules not attached to underlying structures, with normal-appearing overlying skin. In recent years, interest in xanthomas has been growing for several reasons, mainly because the pathogenetic mechanisms involved in the development seems to be similar to those in early stages of atherosclerotic plaques[1]. Cholesterol accumulation in tissues produces common dermatological manifestations as several types of cutaneous xanthomas[2]. The association of xanthomas with lipoprotein disorders was initially defined by Frederickson's classification[3,4]. From that phenotypic classification the recent advances in molecular genetics led to the discovery of a broad group of disorders of the lipids metabolism disclosing the relationship between the development of xanthomas and hyperlipidemias[1,5,6].

Xanthomas can be classified following clinical as well as patho-anatomical schemes, addressing special attention to the needs of dermatologists and internal medicine specialists respectively. These correlated issues gave rise to the following groups which are useful in clinical practice: Normolipidaemic xanthomas (NX), hyperlipidaemic xanthomas (HX), and necrobiotic xanthogranuloma (NXG)[1,7,8]. Nevertheless, xanthomas may be seen either as a primary disorder (primary dyslipidemia, an inherited abnormality of lipoprotein metabolism) or secondary disorder (hyperlipidemia secondary to systemic disease or medication)[1,4,9].

Cutaneous xanthomas may or may not be present with lipid metabolic disorders, usually depending on the severity of the lipid abnormality. Normolipidemic xanthomas mostly appear as diffuse flat skin lesions, while hyperlipidaemic types are polymorphous, often tuberous, and can affect either skin or tendons and joints. Recognition of these types of xanthomas may be facilitated on the basis of clinical morphology, presence or absence of inflammation, anatomic distribution, and development pattern, defining the primary type of lesion and histologic level of involvement. From a dermatological point of view these can be categorized in two specific subsets and each one with distinctive clinical associated features: (1) papulonodular xanthomas: Eruptive and tubero-eruptive xanthoma, xanthoma tuberosum (the term "tuberous" refers to the nodular character of these xanthomas) and tendineum; and (2) plane xanthomas: Plane and intertriginous xanthoma, striated palmar xanthoma and xanthelasma palpebrarum[1,4,9-11].

We report a case of a young man with multiple pleomorphic cutaneous xanthomas in association with a neglected Homoxygous Familial Hypercholesterolemia (HoFH). This article thus presents a contemporary approach to the differential diagnosis of xanthomas, and the diagnostic criteria we propose was developed after a review of the literature, and reflect the clinical findings evidenced in our patient, seen at our dermatological facility.

CASE REPORT

A 19 years old non-obese young man presented as an outpatient to our hospital with multiple, bilateral and symmetrical slow growing yellowish lesions of various forms over the dorsum of the elbows, knees, buttocks, ears, feet and hands. Biopsy of three representative and different skin lesions revealed them to be xanthomas characterized by the presence in the dermis of cholesterol crystalline aggregates surrounded by fibrosis and foamy cells (Figure 1).

On dermatological examination each lesion was defined on morphological pattern. The following clinical forms have been recognized: (1) Xanthelasma: Involving the inner canthus of the left eye (Figure 2); (2) Intertriginous xanthomas and a confluence of plane-eruptive xanthomas (Figure 3): In finger web spaces (Figure 3A), toe web spaces (Figure 3C and D), and the flexural surfaces: the ankle crease (Figure 3D), the antecubital fossae (Figure 3E and F), the popliteal fossae (Figure 3G and H) and the creases of ears (Figure 3I and J); (3) Tendinous xanthomas (Figure 4): To form a single mass localized all over the Achilles tendon just above its insertion point to the calcaneal tuberosity; and (4) Tuberous xanthomas (Figure 5): Soft skin color or yellowish nodules and tumors, with a tendency to coalesce, localized on the knees (Figure 5A and B), malleolus (Figure 5C) and buttocks (Figure 5D).

The lesions appeared at about 2 years of age on both lateral malleolus, at 3 years of age over the buttocks; they were originally asymptomatic then progressively increased in size and extent. At present time the size of the lesions varied between 1 cm × 1 cm × 1 cm to 10 cm × 5 cm (over the Achilles tendon, Figure 4) and 10 cm × 10 cm (over the buttocks, Figure 5D). On detailed clinical history the patient had symptoms of discomfort and pain in the elbows for bilateral massive

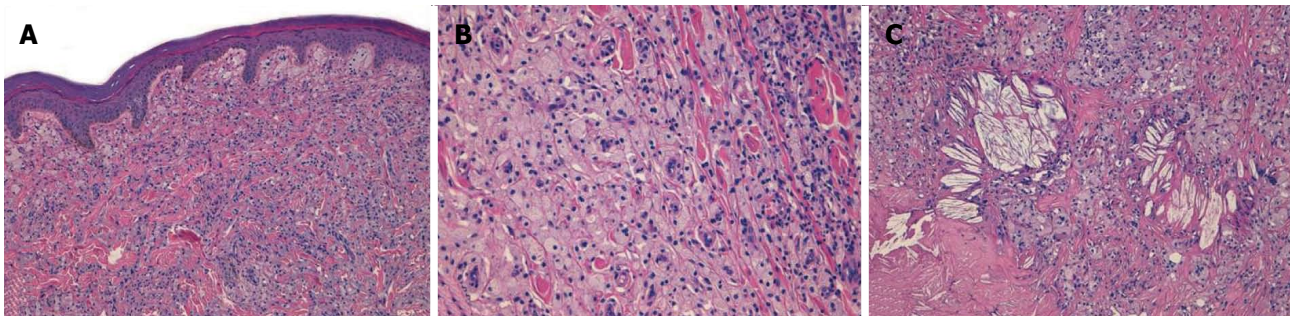

Figure 1 Histopathological examination. A: Foam cells infiltrate the superficial and deep dermis in cluster, separated by collagen fibers. Absence of any other significant inflammatory infiltrate (10 ×, EE); B: Xanthoma cells are filled with optically empty vacuoles, showing thin, well defined cytoplasmic membranes, and tend to be attached to each other. They can be multinucleate (20 ×, EE); C: Presence in the dermis of cholesterol crystalline aggregates surrounded by fibrosis and foamy cells (10 ×, EE).

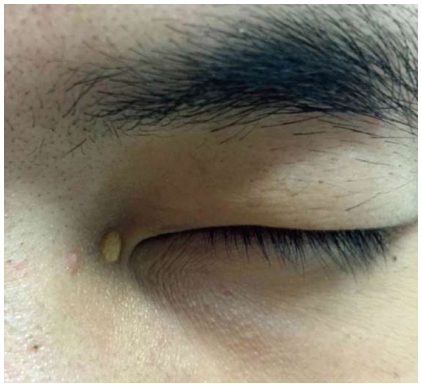

Figure 2 Xanthelasma. Single yellow-orange papular lesion on the inner canthus of the eye.

tuberous xanthomas and at the age of 8, for significantly restricted joint mobility at these sites he had surgery in China in a rural hospital. Up to day the removed lesions did not recur (Figure 6). However, the discomfort and pain due to the large size of the masses of the buttocks and the limitation of his walking distance for the Achilles tendinous xanthomas progressively worsened resulting in significant disability.

Clinical examination did not reveal xanthomatous infiltration of cornea, oral, pharyngeal, and laryngeal mucosae. The patient's family history was remarkable in that both nonconsanguineous parents had a chronic hepatitis B and high total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels. The 17 years old sister had a mild hypercholesterolemia, but no other family members have shown any other inherited disorders and such similar xanthomas. The patient's plasma TC level in the last six months ranged between 657 mg/dL and 990 mg/dL (reference value < 200), and LDL-C level was 557 mg/dL (reference value < 130). Triglycerides and high density lipoprotein cholesterol (HDL-C) levels were normal. Although not useful for the diagnosis or for clinical purposes, we also measured the plasma levels of other lipoproteins in order to better quantify the lipid profile of the patient. In particular plasma levels of apolipoprotein (Apo) A1 was normal, while the level of ApoB 345 mg/dL (reference value 55-140) and atherogenic lipoprotein (aLp) 734 mg/dL (reference value < 300) were increased.

Blood pressure was 16/11 kPa. Renal function tests, hemogram, thyroid function tests, immunoglobulins, erythrocyte sedimentation rate were all normal. The patient was suffering of a chronic hepatitis B with no current liver damage. He received a first course of entecavir therapy 0.5 mg once a day for the last 10 mo because he was tested positive for the hepatitis B "s" antigen (HBsAg), fluctuating or minimally elevated liver enzymes [alanine transaminase (ALT) 118 IU/L (reference value < 50) and aspartate transaminase (AST) 62 IU/L (reference value < 50) and very high viral load (real time HBV DNA 158000000 IU/mL)]. The patient was referred to our STDs Centre in order to establish if the dermatologic disorder was HBV-related. New test results for liver enzymes, HBV DNA, and sonography of the liver were negative.

Abdomino-pelvic ultrasonography, chest X-ray, brain magnetic resonance imaging and upper and lower gastrointestinal endoscopy revealed no abnormality. No osseous pathology was noted on plain radiographs.

The patient was referred to the Metabolic Disease Centre of the University of Florence, Centre for dys-lipidemia management. Echocardiography was normal. However, a transoesophageal echocardiogram revealed mild supravalvular aortic narrowing and a luminal irregularity of arch. The artery doppler ultrasound scan showed that the right carotid artery had the intima media 1.5 cm thick, and the right common femoral artery had formed atherosclerotic noncalcified plaques lesions and the intima media was 2.2 cm thick.

Based on the following findings including clinical picture, patient's clinical history, clinical conditions still present in his family, and pathological and serological analysis the patient was diagnosed with HoFH and multiple xanthomas.

At this time the patient is treated with a combined treatment regimen of atorvastatin (20 mg/d), ezetimibe (10 mg/d), a low dose aspirin (100 mg/d) and LDL-C apheresis therapy every two weeks while on the list for

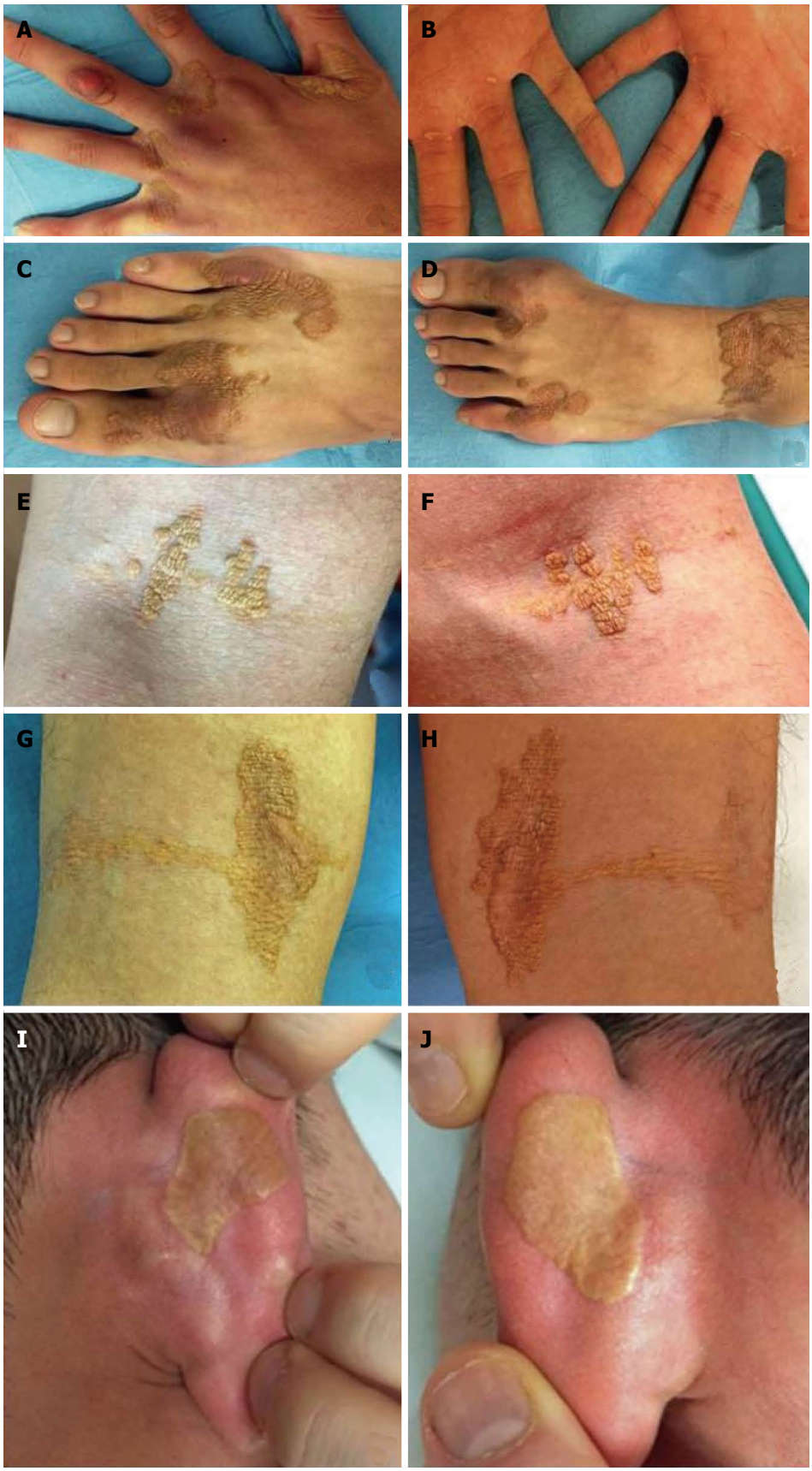

Figure 3 Diffuse intertriginous xanthomas. Usually appear in a symmetric distribution as well-demarcated and slightly elevated noninflammatory plaques of ochre-yellow or yellow-brown discoloration. Typically found in intertriginous and flexural areas. A: In finger web spaces, and in this picture with metacarpophalangeal joint tendon xanthoma; B: At metacarpophalangeal palmar crease in linear band or single papules; C: Toe web spaces; D: In toe web spaces and ankle crease; E and F: At antecubital fossae, with the "eruptive" appearance of crops of yellow dermal soft, velvety papules; G and H: In popliteal fossae; I and J: At the creases of ears in a rare pattern of "plane xanthoma" as very thin flat patches, easily clinically missed, of yellow-orange macular discoloration.

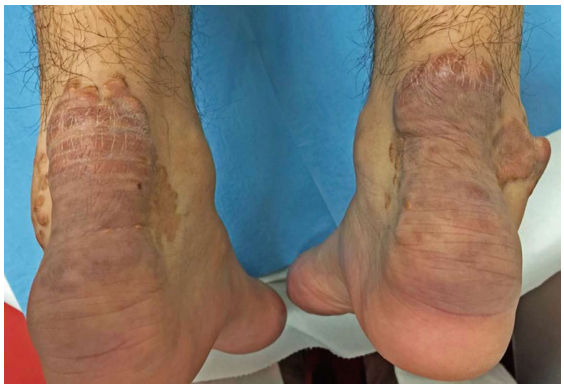

Figure 4 Tendinous xanthomas. Bilateral Xanthomas of Achilles tendon. Each swelling was localized all over the tendon just above its insertion point to the calcaneal tuberosity. They appear as firm, mobile, painless slowly enlarging subcutaneous nodules which may join together to form a single mass or multilobated masses. They are covered by reddish-brown thickened skin.

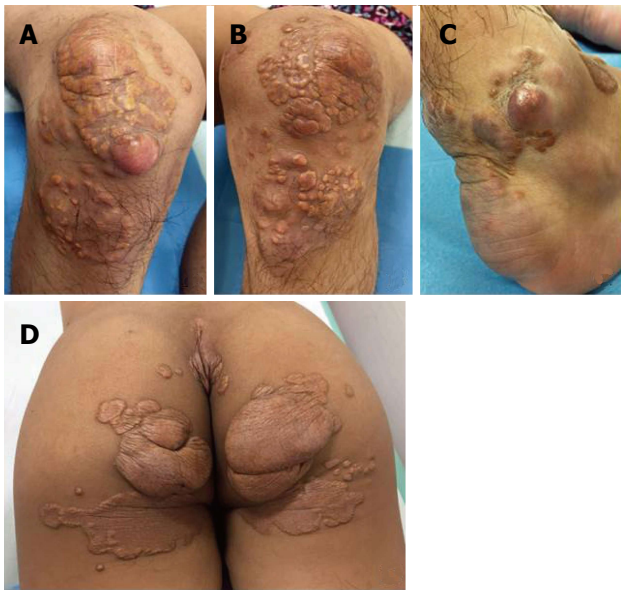

Figure 5 Tuberous xanthomas. They are very common and clinically variable. They may appear as firm, painless, red-yellow, waxy-appearing nodules located in the dermis and subcutaneous tissue, from few millimeters to several centimeters in size. They often present with a cobblestone-like pattern developing around the pressure areas such as: A and B: The knees; C: Malleolus; D: Buttocks. Lesions can join together to form multilobated masses.

anti-PCSK9 monoclonal antibody therapy.

DISCUSSION

Familial hypercholesterolemia (FH), is a primary hyperlipoproteinemia characterized by an autosomal codominant genetic disorder due to mutations in the LDL receptor gene located on chromosome 19. There are two types of FH: A Homozygous FH (HoFH), in that the individuals with two mutant LDL receptor alleles are much more affected than those with one mutant allele, Heterozygous FH (HeFH)[2,6,12]. HoFH is a rare form of inherited dyslipidemia often diagnosed early in childhood which in most cases is not detected. Originally, the

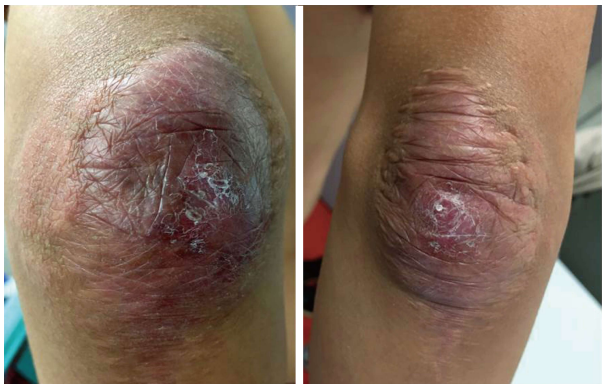

Figure 6 Bilateral massive tuberous xanthomas of the elbows did not recur after surgical excision.

prevalence of HoFH was estimated as 1 per million, with higher prevalence in countries with founder mutations, especially if consanguineous marriages were present. However, the HoFH prevalence is now estimated at one in 160000 to 300000[2,13]. The heteroxygous form is the most common with an incidence of 1 out 500, in which the patient has usually diagnosed as adult[12,13]. Despite published data, there is not agreement about how and when perform the screening in childhood but familial history of hypercholesterolemia in parents is crucial for detection and diagnosis of HoFH[2,11,14-16]. FH is a disease characterized by a triad: Elevated LDL-C, tendon xanthomas, and premature coronary heart disease[6]. HoFH should be suspected if both parents have HeFH where the probability of a child having HoFH is 1 in 4[16]. In HoFH patients, markedly elevated LDL-C concentration may be present at birth, as well as cutaneous xanthomas but generally present by the age of four. Corneal arcus is common by age ten and tendon xanthomas develop inevitably while coronary artery disease (CAD) develops from childhood on with high risk for a fatal or non-fatal coronary event by age thirty[5,13,15]. However, the presence of xanthomas increases the risk of CAD in patients with FH by as much as three fold. For a patient with cutaneous or tendon xanthomas, the probability of FH is very high; however, an absence of xanthoma does not rule out FH[6,15]. Epidemiologic data on cutaneous xanthomas are limited. Xanthomas are rarely seen before age twenty although those associated with FH are an exception. They tend to occur in both males and females without any sex predilection, develop inevitably and an exaggerated phenotype may be observed in patients with HoFH as was in our case[1,4,9,17,18]. The patient in the present study presented with multiple large xanthomas with a wide ranging distribution all over the body, and an onset at the age of two. The patient had an LDL-C level of 557 mg/dL, suggesting a high likelihood of HoFH. The patient was the offspring of two parents with HeFH, and appeared to have an inherited HoFH phenotype associated with an increased level of TC and serum LDL-C and more severe symptoms than the parents. The parents had mildly elevated levels of TC

(father 330 mg/mL; mother 300 mg/mL), which, when combined with the absence of xanthomas, suggests that the parents suffered from HeFH. Only a minority of patients with lipoprotein disorders have xanthomas thus the estimation of plasma lipid levels alone may not be enough to properly identify a specific lipid metabolic disorder, on the contrary the presence of xanthoma lesions represent a useful marker for these diseases[4]. Therefore it seems logical that skin lesions have been described as the first symptom. Cutaneous xanthomas were first introduced in the medical field by Rayer[19] in 1835, when he described "yellow lesions on the eyelids"[19,20]. In 1851, Addison and Gull observed various forms of xanthomas naming those "vitiligoidea"[20,21]. This term was soon replaced by xanthoma by W. Frank Smith in 1869 and descriptive terms were added, such as "planum", "multiplex" and "tuberosum"[10,12,22]. The unique association of FH and tendon xanthomas was reported by Fagge in 1873[6,23]. Xanthomas are seen in 40%-50% patients of FH and HeFH is the most common cause. Of the affected individuals 50% to 75% may complain of tendon xanthomas that rarely have been reported in the setting of normal plasma levels of cholesterol. The prevalence increases from 7% in the third decennium to 50% in the sixth decennium[1,4,10,15]. They are not palpable in up to 20% of individuals. Thus, to identify these xanthomas sonography is the most appropriate technique and is superior to clinical assessment, and even if not present an abnormal texture and thickening of Achilles tendon were demonstrated in 68% of subjects with FH[1,24,25]. Xanthelasma are seen in 23% of cases but they are the least specific of all xanthomas representing the vast majority of cases (> 95%) and because they are seen in many hyperlipidaemic and normolipidaemic states. About 65% of adult patients with xanthelasma may show normal plasma lipid levels. Tuberous xanthomas are reported in 10%-15% of cases and intertriginous xanthomas occurring occasionally[1,10]. The presence of tuberous and intertriginous xanthomas in a child with a markedly elevated plasma cholesterol level is strongly suggestive of HoFH. Intertriginous xanthomas have not been seen in the HeFH, in which plasma LDL-C are less markedly increased. In contrast, tuberoeruptive xanthomas are associated with several forms of hyperlipoproteinemia and rarely occur in patients with FH[1,4,9,10,12,16]. From detailed literature review and according to European Atherosclerosis Association Guidelines[6,13,16,26] our patient has met clinical criteria for a definite diagnosis of HoFH, even in the absence of a mutation on genetic testing, and was based on the following data: (1) High serum TC and LDL-C levels with normal triglyceride levels; (2) Appearance of xanthomas in the first decade of life; (3) Documentation of mildly elevated levels of LDL-C and TC and absence of xanthomas in both parents and in one of the siblings; (4) The presence of signs of atherosclerosis; and (5) The presence of multiple large xanthomas with a wide ranging distribution and above all, the rare pathognomonic intertriginous xanthomas, which have been described as a dermatological marker of this homozygous type.

In conclusion, this case highlights the importance of proper identification of nodular lesions and a differential diagnosis of specific subtypes of xanthomas by physicians and especially dermatologists. Xanthomas cannot be considered as simple cosmetic lesions as they are the earliest clinical indicators of lipidemic disorders. The publication of individual cases seems beneficial since this case study of HoFH wants to emphasise that this disorder remains critically under-diagnosed, and a delayed diagnosis could have potentially devastating consequences because these patients progress rapidly to atherosclerotic changes leading to aortic stenosis and CAD. Nonetheless a very important problem in these patients is that most of them do not feel ill enough until a severe CAD takes place.

ARTICLE HIGHLIGHTS

Case characteristics

Cutaneous xanthomas may or may not be present with lipid metabolic disorders, usually depending on the severity of the lipid abnormality.

Clinical diagnosis

Polymorphous cutaneous xanthomas in Homozygous Familial Hypercholesterolemia (HoFH).

Differential diagnosis

The presence of specific lesions represents a useful marker to properly identify a specific hyperlipidaemic disorder.

Laboratory diagnosis

High serum total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels with normal triglyceride levels.

Pathological diagnosis

Presence in the dermis of cholesterol crystalline aggregates surrounded by fibrosis and foamy cells.

Experiences and lessons

HoFH is a rare form of inherited dyslipidemia now estimated with a prevalence of one in 160000 to 300000.

Treatment

Atorvastatin, ezetimibe, low dose aspirin and LDL-C apheresis.

Related report

The presence, the clinical and dermatological features of multiple large xanthomas with a wide ranging distribution and above all, the rare pathognomonic intertriginous xanthomas, have been described as a dermatological marker of the HoFH.

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