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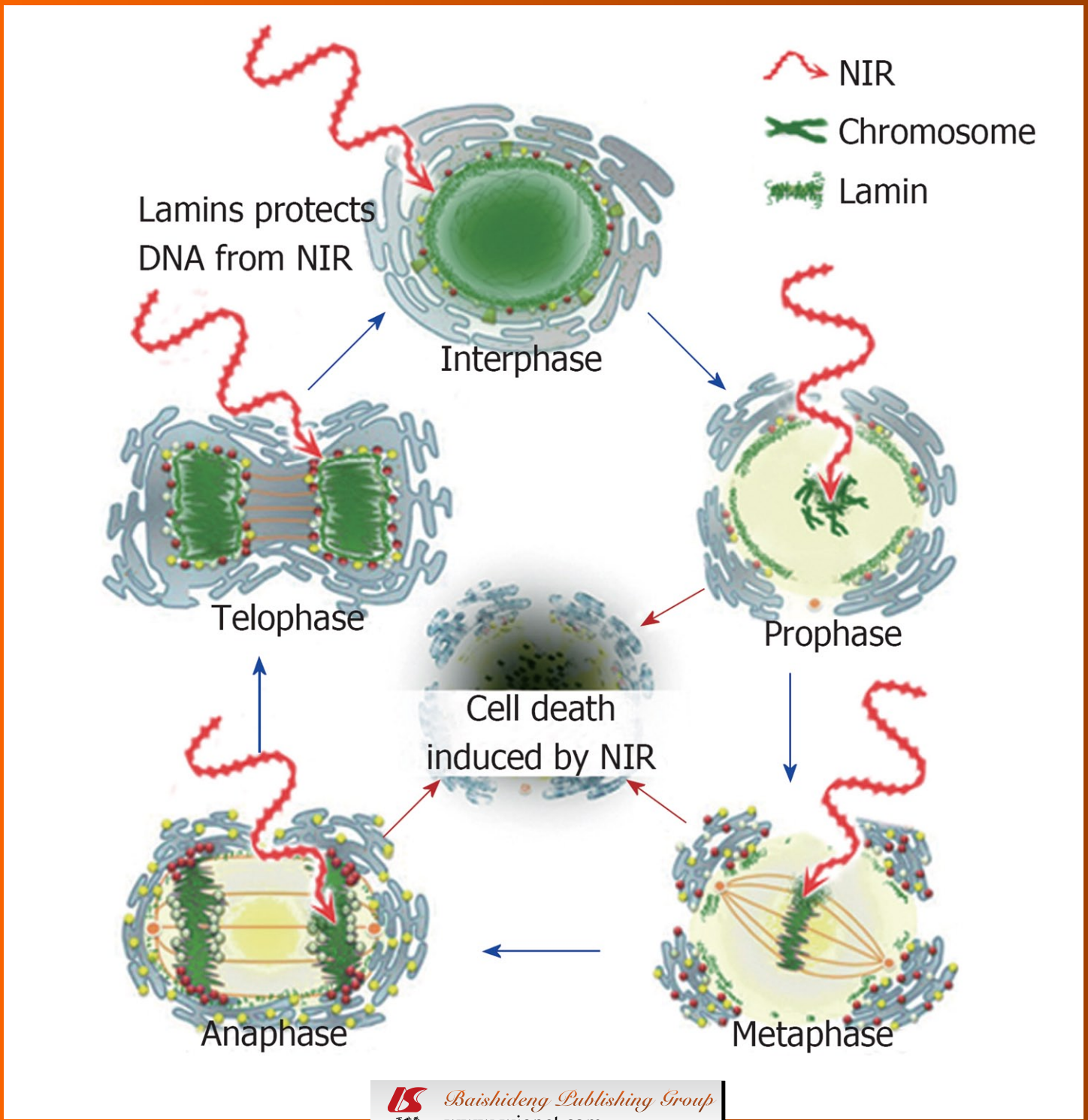

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EDITORIAL

Clinical evidences, personal experiences, recent applications

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Abstract

Management of difficult wounds can be a complex, challenging and expensive task, especially for wounds showing a slow healing process. Topical negative pressure (TNP) therapy has greatly improved difficult wounds treatment. It allows to treat patient on an outpatient management, to reduce the complication rate with shorter hospital stay, to avoid frequent dressings with expensive advanced materials and allow a lower commitment of health professionals. Vacuum Assisted Closure® (VAC®) system is a therapeutic device based on the administration of a controlled TNP introduced by Morykwas and Argenta in 1997. It is indicated in different kinds of wound, but clinical evidences are present only for few of them. In this work we summarize indications and recommendations for VAC® therapy and we analyze the actual better choice of treatment based on evidences and personal experience in order to stimulate further studies. Finally we introduce recent applications of VAC® system such as Prevena®, VAC Instill® and VAC Via®. Prevena® is a system based on TNP indicated in the management of closed wounds that present risk factors for dehiscence. VAC Instill® is a system that allows to associate TNP and topical administration of solutions, such as antibiotics or disinfectants, to treat specific type of wounds. VAC Via® is a device based on TNP, characterized by little dimension and a preset system that allow the treatment of little wounds for 7 d, with no impairment for the patient. The aim of our paper is to describe a report of VAC® therapy use in order to stimulate further studies and to define the level of evidence of VAC® therapy.

Key words: Topical negative pressure; Wound; Vacuum Assisted Closure®; Diabetic foot; Pressure ulcers

Peer reviewer: Bruno Sarmento, Professor, Department of Pharmaceutical Sciences, Advanced Health Sciences Institute, R Central de Gandra 1317, 4585-116 Gandra, Portugal

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INTRODUCTION

Management of difficult wounds can be a complex, expensive and time consuming task.

The increasing age of general population and life style changes (sedentary life, metabolic syndrome) can led to higher incidence of chronic wounds and lesions in patients with poor general conditions (vascular disease, diabetes).

Direct consequences are a higher number of patients in relative good general status affected by chronic wounds requiring higher costs for health care system due to hospitalization, outpatient management, frequent dressings and commitment of health professionals.

Topical negative pressure (TNP) therapy has greatly improved difficult wounds treatment. It allows to treat patients on an outpatient base, reduce the complication rate with lower hospital stay, avoid frequent dressings with expensive advanced matherials and so there is a lower commitment of health professionals. The possibility

to manage the therapy with a relative comfortable instrument allows the patient to carry out daily activities.

The use of negative pressure in clinical practice date back to ancient times. It was described in Chinese medicine in combination to ago puncture[1] thanks to its hyperaemic effect. In 1841, Junod used heated glass cup applied on the skin to create vacuum and stimulate circulation[2]. Different techniques of TNP application were later described. In the 1980s, in the Russian literature, the use of TNP in combination with aggressive debridement was reported to significantly reduce bacterial counts in suppurative wounds[3]. In 1989, Chariker *et al*[3] applied TNP therapy in patients with incisional or cutaneous fistulas using moist gauze placed over the wound surface and a flat drain placed over the gauze covered by a bio-occlusive dressing. Fleischmann *et al*[4] in 1993 described the application of TNP trough a foam dressing observing the formation of granulation tissue and wound cleaning.

Morykwas *et al*[5] elaborated a system composed by a polyurethane (PU) foam covered by a semi occlusive dressing and connected to a vacuum source to induce TNP on wound in animals. This work was the start point for the production of the Vacuum Assisted Closure® (VAC®) system by Kinetic Concepts Inc. (San Antonio, United States).

VAC® SYSTEM

VAC® device is made up by (Figure 1): (1) Vacuum source; (2) Foam dressing: it is the interface between the vacuum source and the wound. Its essential role consists in the uniform administration of TNP on the whole wound surface, even in difficult anatomical sites (e.g., groin). Other systems use a moist gauze fill in the wound as interface; (3) The foam can be made by PU (black) that is hydrophobic and presents big holes (400-600 μm), polyvinyl alchool (white) that is hydrophilic and with small holes or PU combined with Silver (gray) with an improved bacteriostatic effect; (4) Foam choice depends on wound characteristics and supposed treatment's goal; (5) Semi occlusive transparent adhesive drape fixed on heal skin, all around the wound to isolate it from the external environment; (6) An adhesive disk (Pad) positioned on an hole created in the drape and connected to the vacuum source trough a suction drain; (7) A reservoir connected to the drain; and (8) A processor that elaborate signals from the different components of the device and that shows dysfunction (e.g., air leakage). In particular KCI developed the Therapeutic Regulated Accurate Care (TRAC®) pad system that controls continuously the pressure at the wound bed and not only the one derived from the vacuum source; it allows the clinician to diversify the intensity of the negative pressure and provides a even setter distribution of negative pressure at the wound bed. The SensaTRAC® system allows to monitor and maintain the desired pressure at the wound area for a constant administration of the therapy, it allows to reduce clogging of pipes and false alarms using an advanced computational fluid dynamics and to use Smart Alarms® for maximum patient safety. All these possibilities led to an easy and effective application of VAC® Therapy and improved patient comfort.

The direct effect of VAC® is to create a wet environment with a sterile and close dressing.

TNP administer by VAC® Therapy creates forces that, applied to the wound bed, are able to develop an environment that promotes wound healing. These forces can be distinguished in macro-deformations and micro-deformations.

Macro-deformations consist in a visible stretching that occurs when the negative pressure shrinks the foam. The direct effect is to close the wound edges, to allow an uniform distribution of pressure at the whole wound bed and to remove the exudates and infectious materials.

Micro-deformations are the modifications present at the cellular level. The direct effect is to reduce oedema, to promote perfusion, to increase cells proliferation and migration and to promote granulation tissue formation.

The final effects of VAC® Therapy leading to promote wound healing could be so resumed in: (1) Remove infectious materials; (2) Provide an adequate protection against infection; (3) Remove exudates; (4) Reduce oedema; (5) Provide a moist environment; (6) Increase blood flow promoting perfusion; and (7) Promote cell migration and proliferation during granulation tissue formation.

The reported physiological effects were described in clinical or animal studies. Morykwas *et al*[5] demonstrated that a negative pressure of 125 mmHg increase the vascularisation at 4 times, while higher negative pressure induce capillary collapse with blood flow reduction. Fluid suctions led to oedema reduction with a consequent lower external pressure on capillary and blood flow increasing. This effects is particularly evident with PU foam thanks to bigger holes.

Another aspect studied by Morykwas *et al*[5] was granulation tissue formation induced by TNP; it resulted increased of 63% with continuous TNP and of 103% with intermittent regimen, compared to classical dressings. This result was explained by cells adaptation to continuous physical forces. Other favourable effects of intermittent TNP are blood flow increase due to deactivation of the auto regulatory capillary system, and the number of mitosis, due to the "relax" period in which cells are able to produce new structural components. The disadvantage of intermittent therapy is higher pain than the one experienced by patients with the continuous regimen.

Some Authors proposed to start VAC® with continuous -125 mmHg for 48 h and then switch to an intermittent regimen.

Cellular proliferation induced by mechanical forces is a well known concept in plastic surgery (e.g., tissue expansion, osteogenic distraction)[6,7]. TNP induces tissue deformity with a mechanical stress that stimulate angiogenesis and cellular proliferation.

Other described effects induced by VAC® are the reduction of substances present in the exudates that hin-

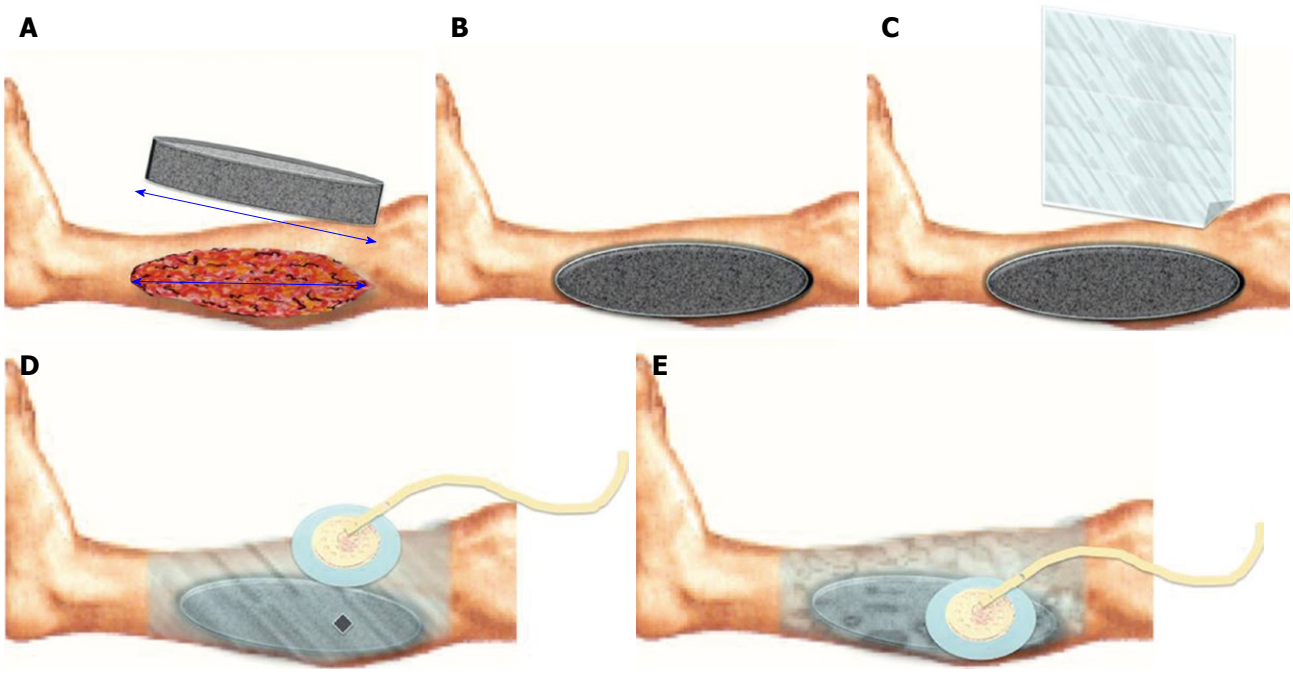

Figure 1 Vacuum Assisted Closure® system. A: The foam is placed over the wound with a size equal or little bigger than wound's dimension; B: A drape is placed over the foam to cover it completely and to attach it on the around normal skin; C: A hole is made on the drape over the foam; D: The track pad is placed over the hole; E: Starting therapy led to the foam size reduction due to negative pressure.

der wound healing, bacterial grow reduction due to the closed system that on one hand prevent external contamination and on the other hand enable an amplification of physiological antimicrobial agents thanks to blood flow increasing[8-10]. In addiction foam contraction during treatment reduces the perimeter of the lesion, accelerating the healing[1].

Contraindications[11] to the use of VAC® in acute wounds are presence of necrotic tissue, massive invasive infection, exposed cortical bone, untreated ostemyelitis, malignancy and active bleeding at the wound site. Necrotic tissue must be removed before VAC® therapy application with a careful debridement; infection must be treated with systemic antibiotics and the use of Granufoam Silver® which can help in the treatment of local infection, a frequent wound check with culture from wound bed must be done and VAC® therapy must be immediately stopped if the result remains poor. Sensitivity to Silver is a contraindication to the use of GranuFoam Silver®. Exposed cortical bone represents a limit to granulation tissue formation onto wound bed. Malignancy is an absolute contraindication due to the risk of cancer cells proliferation. Active bleeding from the wound site and the presence of exposed vessels or organs can led to hemorrhage during VAC® therapy. In case of small exposure a non-adherent dressing positioned between the wound bed and the foam can help to reduce this risk.

Other contraindication to VAC® therapy is the presence of non-enteric or unexplored fistulas.

VAC® device must not be placed directly in contact with exposed blood vessels, anastomotic sites, organs or nerves; in these cases the use of a non-adherent layer between deep structures and foam can be useful to prevent any damage to the underlying anatomical structures.

Complications encountered during VAC® therapy are pain and hemorrhage, as just reported.

Pain is often associated with dressing changes[12] and in this cases instillation of anesthetic agent *via* the suction tube into the foam before dressing change may be of great benefit. Pain associated with the treatment itself is often linked to intermittent regimen; in this cases a continuous TNP regimen can help to reduce pain.

Hemorrhage is linked to the suction of active bleedings at the wound. The presence of bleeding is a contraindication to TNP and in presence of a high risk for bleeding it's important to monitor continuously the canister. If active bleeding develops suddenly or in large amount during treatment, or if bright red blood is seen in the tube or in the canister, immediately stop VAC®.

An important aspect to consider is the coast load; at a first sight it is possible to think that high costs of VAC® device and dressing's materials can be a limitation when compared to other dressings. Otherwise we have to consider that dressing's costs are only a singular parameter that play a role in wound's management costs. Other important aspects we should take into consideration when evaluating from the budget perspective are costs related to nursery assistance, hospitalization and complications' management[13]. Health economy should evaluate treatment coasts also in relation to benefits achieved through it. In wound treatment costs depends on many factors such as frequency of dressing's change, time of necessary nursing assistance, rate and time of wound healing, effects on hospital stay duration and complications[1].

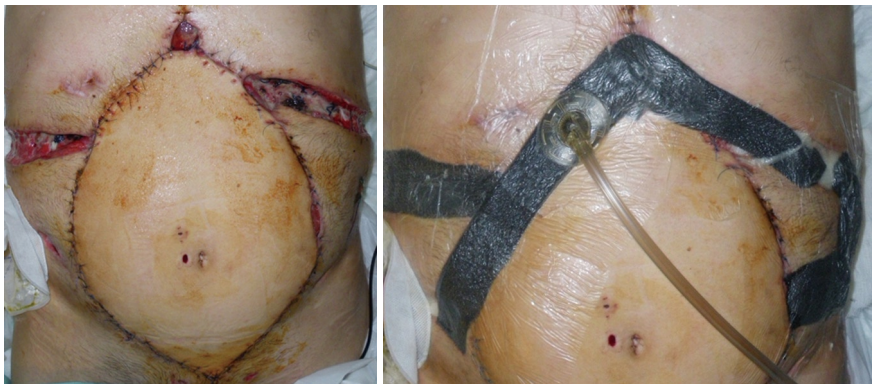

Figure 2 Vacuum Assisted Closure® application in dehiscence after abdominal wall and multivisceral transplantation.

Armstrong *et al*[14] evaluated the use of VAC® in diabetic foot after amputation. They reported an healing percentage of 56 in VAC® group and of 39 in group treated with standard dressings. The medium time of healing was 56 d in VAC® group and 77 d in the other one. Similar results were reported in pressure ulcers[15]. Schweim *et al*[16] demonstrated a significant reduction in hospitalization rate in patients treated by VAC® and several studies[14,16,17] reported lower complications rate. Hiskett *et al*[18] reported that TNP allows to reach qualitative and economic benefits in home care. Obviously comparison between all studies performed about costs and benefits of VAC® is restricted because we have different cost of nursery care, different pattern of use of TNP consumables and wound outcome. Philbeck *et al*[19] reported that the shorter healing time and downgrading of required operations in patients treated by VAC® correlates to decreased overall costs of care and, in particular, wounds can be treated in the community with minimal impact on nursing care and hospitalization. All presented considerations led to consider VAC® therapy a valuable treatment in terms of health care costs. In facts it allows to treat patients at home, reducing hospitalization time and high costs' operations.

CLINICAL APPLICATIONS

VAC® therapy is indicated in many kinds of wounds. In some cases there are clinical evidences of its application, in others there are only case reports or small series reporting good results. In our experience we used VAC® in different wounds with different goals and can occur to stop therapy after an evident failure. It is important to determine the goal before starting and to evaluate the wound after an adequate time to decide if the intermediate result is good enough to continue the therapy or if there are signs of failure guiding us to choose alternative treatments. Wound must be prepared before VAC® therapy we need to remove eschar and devitalized tissues, to treat infection and, first of all, to make a correct diagnosis. Wounds due to malignancy or ischemia are not suitable for VAC®, as just reported. We describe the principal indications for VAC® reported in literature and correlate them with our experience and level of evidence.

Open abdominal wounds

Open abdominal wounds are one of the first indication introduced for VAC® therapy.

The open abdomen is the result of decompression laparotomy and dehiscence or necrotizing fasciitis. This condition is associated with high morbidity and mortality[1].

The main goals are to achieve a primary closure or to obtain granulation tissue formation to allow a skin grafting[2]. VAC® demonstrates to improves survival, decrease surgical reconstructive complexity and reduce complication rate, such as compartment syndrome[3].

VAC® induces both skin and fascial approximation, reduces bowel oedema, bacterial counts and inflammatory substances, avoiding frequent dressing changes, maintaining intact skin and improving fluid management[4].

Dressing must be changed every 48-72 h in absence of infection and exposed bowel must be covered with a non-adherent layer to prevent fistula formation and other complications. A continuous pressure of -175 mmHg prevents fascial retraction and visceral adherence and multiple dressing sheet perforations permit intra-abdominal fluid and oedema evacuation[5]. Optimal results may take 21 d or more to show off.

We applied VAC® in many cases of open abdominal wound as a bridge tool to defintive closure with skin graft and in one case of patient treated for dehiscence after multivisceral and abdominal wall transplantation as a definitive closure method, due to the impossibility to perform surgery (Figure 2).

Sternal wounds

Dehisced sternal wounds are an optimal and well documented indication for VAC with the aim to achieve primary closure or prepare the wound for delayed reconstruction.

Mediastinitis occurs in 1%-5% of patients following sternotomy[20] with high morbidity and mortality[21].

The positive effects of VAC® consist of stabilization and salvage of the sternum, drainage of anterior mediastinum, early mobilization and reduction of mortality rate. Treatment starts after debridement. A non-adherent layer is interposed between deep structures and foam to

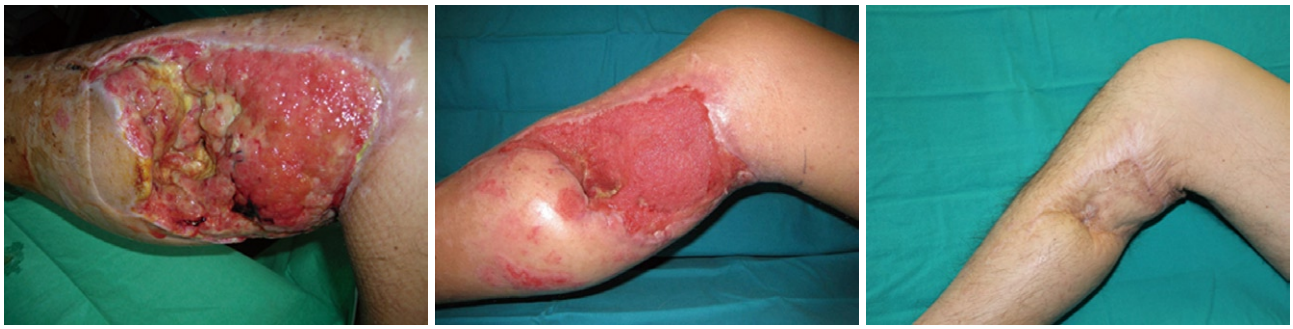

Figure 3 Complex soft tissue trauma of lower extremity with undermining in the leg posterior compartment and complete healing after 27 d of Vacuum Assisted Closure® therapy.

protect mediastinal structures against direct contact with TNP[22,23]. Full-thickness perforations allow transmission of negative pressure trough the dressing to anterior mediastinum. A double layer dressing enables optimal thoracic stabilization (sternal layer) as well as a good distribution of negative pressure over the entire wound surface (subcutaneous layer)[24]. Dressing must be changed every 48 h to evaluate the wound and perform bacterial swab at the wound bed. Also serum C-reactive protein (CRP) level can be useful to guide therapy[25]. TNP must be applied in continuous fashion at-125 mmHg. Expertise is required to treat this kind of wounds. VAC® is contraindicated in case of active bleeding or anticoagulation beyond therapeutic range.

Acute and chronic wounds

In traumatic wounds VAC® therapy can led to several benefits as stabilize soft tissue, reduce secondary damage, salvage of compromised tissue, reduce oedema, wound size and complexity (Figure 3). The goals are to promote granulation tissue formation and perfusion, to remove fluids, exudate and infected materials and to assist take of flap or skin/bioengineered tissue. The result is a reduction in complexity of reconstructive procedures, scar formation and an improved patient care and comfort due to a reduced number and frequency of dressing changes. The paramount indication is a large loss of soft tissue, but in literature several applications are described such as treatment of inflammatory wounds, open fractures management, energy trauma wounds, fasciotomy wounds, degloving injuries and burns. In all these cases VAC® therapy can help stabilization of skin graft and donor site healing[21], stabilization of energy injuries allowing safer transfer of the patient; management of open fractures reducing complexity of secondary surgery, prevent the progression of partial-thickness burns[26] and to prepare full-thickness burns to skin grafting[27].

General recommended settings consist in a continuous cycle at -125 mmHg for 48 h and then, if possible, an intermittent cycle until healing is reached. Dressing must be changed every 48-72 h, only in presence of infected wound a more frequent dressing changes should be taken in consideration. Therapy should be used after debridement and vital structures must be covered with non-adherent dressing. The presence of orthopedic hardware does not represent a contraindication.

Inflammatory wounds occur in scleroderma, systemic lupus erythematosus, hypercoagulation disorders, rheumatoid arthritis and vasculitic conditions. The goal of VAC® treatment is to enhance wound bed preparation for surgical closure or delayed secondary heal. In this cases the evaluation should be done after 1-3 d.

Complex resistant ulcers often present with abundant exudates or difficult anatomical sites and poor-wound bed. In this cases VAC® could be an ideal option up to 2 wk, then you should check the result by evaluating granulation tissue formation.

In open fractures VAC® therapy could be considered when primary closure is not possible providing a temporary cover. Delayed surgical closure of open fractures is characterized by a high risk of infection and impairment of the bone synthesis[28]. VAC® therapy protects wound from infection, reduces oedema and increase the rate of viable tissue over the bone, with a simpler delayed reconstructive procedure, that has to be performed as early as possible.

Fasciotomy incisions often present oedema, skin retraction and skin edge necrosis[1] that limit primary closure after compartment syndrome resolution. VAC® reduces oedema and splint wound edges allowing primary closure in shorter time in comparison to conventional dressing[29,30].

In energy trauma, TNP is most suitable for complex soft tissue injuries in the absence of exposed bone, as loss of tissue from the foot, exposed tendons, tissue loss in gunshot wounds and degloving injuries[31-35]. Treatment should start with continuous negative pressure between -50 mmHg to -125 mmHg, although, when possible, intermittent therapy should start in the next 48 h, this may led to greater granulation tissue formation[13].

Even if coverage of exposed bone with well-vascularised tissue remains the gold standard for open fractures[11], VAC® may allow, as temporary dressing, a downstaging of the wound[36].

In burns' treatment VAC therapy aids to reduce oedema, infectious and inflammatory materials and help to improve wound perfusion. In particular it prevents burn progression in partial-thickness burns. It is well known

that in partial-thickness burns is present a zone of stasis characterized by microcirculation impairment at 12-24 h post-burn with consequent hypoxia, ischemia and cell death that led to full-thickness burn[37]. TNP applied to partial-thickness burn within 6 h after injury and for at least 48 h, helps to reduce oedema and increase blood flow, stopping the progression to full-thickness burn[38].

Skin graft and bioengineered tissue fixation require tie-over dressing for 5 d. Problems may arise when facing irregular surfaces (e.g., perineum, inguinal fold), areas prone to movement or exudative recipient beds. TNP may be used for wound bed preparation to reduce size and to assist granulation tissue formation[39]. VAC® aids to deal with serous fluid or hematoma, bolstering the graft to the bed, and increases angiogenesis and splinting of graft in difficult area[24].

The foam must be applied with an interpositional non-adherent barrier between graft and foam; TNP must be set at a range between -100 mmHg and -125 mmHg, in continuous fashion, for a period of 3-4 d[40]. Multiple holes should be performed in the graft before VAC® positioning in order to increase fluid collection. VAC® therapy is mentioned, in literature, also to improve skin graft donor site healing, showing a faster reepithelialisation with good results[41].

VAC® therapy can be applied to improve vascularization in flaps which have suffered partial necrosis after performing debridement of necrotic tissue, allowing salvage of the of the flap.

TNP improves flap survival by reducing oedema, increasing blood flow and bolstering flap placing at the wound bed. Moreover VAC® hide the flap, thus the flap monitoring is more difficult. Positive effects of TNP on venous congestion are still not well described. Morykwas *et al*[5] reported good results in animal studies in enhancing viability of random pattern flaps. Another useful application of VAC® therapy in flap surgery is the improvement of donor site healing. A particular indication is in radial forearm flap donor site management. VAC® therapy induces granulation tissue formation over exposed deep structures, improving skin grafting[42,43]. Recommended settings are a continuous cycle at -125 mmHg for 72 h.

Diabetic foot

In diabetic foot VAC® is indicated in uninfected and not ischemic deep complex ulcers with the goal to reduce the surface area. VAC® reduces the complexity of the subsequent surgical closure procedures[14,44]. In combination with systemic antibiotics, VAC® allows healing of underlying osteomyelitis avoiding ulcers recurrence[3]. VAC® therapy is used for 1-2 wk; after this time, the wound should be evaluated and to be continued if the wound has improved; if progress is poor an alternative treatment must be considered[45]. In post-surgery diabetic foot wounds, VAC® is indicated after open partial foot amputation[14], to aid skin graft or bioengineered tissue replacement fixation[46,47]. VAC is not recommended as a first line treatment in superficial wounds, but it can play a role as a second choice after advanced dressings failure[45]. Recommended settings are a continuous cycle at -125 mmHg in first 48 h, then, if possible, an intermittent cycle for rest of treatment. In absence of infection dressing can be changed every 48-72 h.

Pressure ulcers

In pressure ulcers VAC® therapy can help to reduce volume of a large cavity wound, to promote comforts for the patient and to reduce nursery management. Goals are promoting granulation tissue formation, promoting perfusion and providing a closed, moist wound healing environment. It is not indicated for stage 2 ulcers and in case of deep tissue injuries. The best indication is stages 3 and 4 wounds, in combination with pressure redistribution, good skin care and planning of an adequate nutrition[48]. In these cases VAC® could be useful both preoperatively, to allow less complex reconstruction and post-surgery to manage dehiscence, to improve perfusion of flap or grafts fixation. The effects should be evaluated continuously for a period up to 2 wk. Recommended settings are a continuous cycle at -125 mmHg in first 48 h, then, if possible, an intermittent cycle for rest of treatment. In absence of infection dressing can be changed every 48-72 h.

Venous insufficiency ulcers

In venous insufficiency[49,50] ulcers VAC® can be used to reduce oedema, to promote perfusion, to remove exudate, to promote granulation tissue formation and to provide a closed, moist wound healing environment. Recommended settings are a continuous cycle at -125 mmHg in first 48 h, then, if possible, an intermittent cycle for rest of treatment. In absence of infection dressing can be changed every 48-72 h. Wound should be adequately prepared before therapy with a correct debridement and compression garment or bandage may be placed taking care not to induce any pressure point. In presence of explored tunnels or undermining, the first choice should be VAC WhiteFoam® dressing. Foam should be placed in contact with all wound surfaces and in presence of more foam pieces a correct foam to foam contact must be ensured to achieve a better distribution of negative pressure. Superficial or retention sutures should be covered with a non-adherent material.

Enteric fistulas

VAC® may help to promote healing in wounds around enteric fistula, but cannot be considered for effluent management or containment. The goal in acute fistula should be to promote closure of the fistula. Chronic fistulas are segregated from surrounding or adjacent abdominal wound, then VAC® is applied to the wound and the effluent from fistula are deviated into another containment system. General recommendation is to start with a -125 mmHg pressure and, if effluent is noted in the tubing, pressure should be raised of 25 mmHg for 20-30 min and then check effluent. If it is still present, continue to increase the pressure and observe until there is no ef-

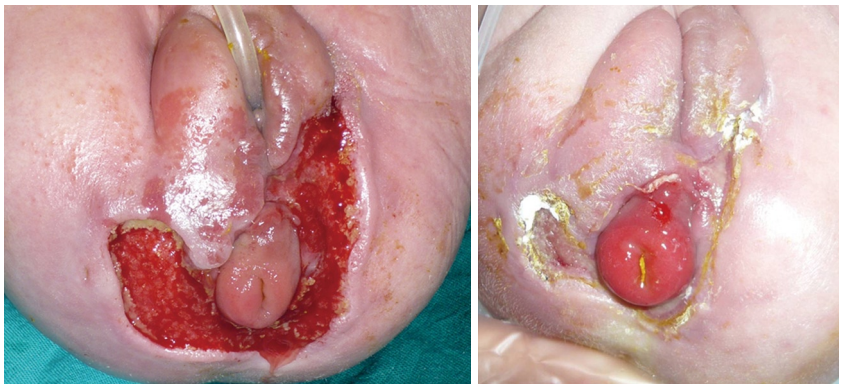

Figure 4 Newborn affected by necrotizing fasciitis of perineum and result after 13 d of Vacuum Assisted Closure® therapy.

fluent in the tubing, up to a maximum of 200 mmHg. Reduction in the amount of effluent is an early sign of initial approximation of the fistula. Otherwise, if effluent continues to flow VAC® must be stopped and other treatment should be taken into consideration.

Wounds in paediatric patients

The indications for negative pressure therapy in paediatric and neonatal wounds have been discussed by Baharestani[51]. In our experience we treated a rare case simultaneous acute myeloid leukaemia and necrotizing fasciitis due to Pseudomonas aeruginosa in a newborn (Figure 4)[52]. Our patient presented with perineal erythema and haemorrhagic pustules with a rapid progression into necrotizing fasciitis and, at 23 d, was present a lesion of approximately 18 cm^2 involving the superficial and deep fascial planes around labia majora, a greenish secretion, a black eschar with an erythematous halo. Swap culture revealed the presence of Pseudomonas aeruginosa, however, blood cultures were negative. The infant was treated with systemic administration of: broad-spectrum antibiotics, immunoglobulins, inotropic drugs and nutritional support. The initial treatment of the wound consisted of surgical debridement followed by the application of advanced dressings, such as silver PU foam and hydrofiber. Due to the reduced healing rate and the persistence of Pseudomonas colonies in the wound, we decided to apply VAC® device with GranuFoam Silver® dressing[53]. The dressing was changed every 48 h. During hospitalization at the Neonatal Intensive Care Unit, the newborn was continuously monitored: pain was assessed and opioid analgesia was used. The positioning of the VAC® dressing on the perineal area was challenging. The main problems were: preventing direct suction on the anal sphinter while maintaining normal sphinteric functions and avoiding pressure sores due to the suction tube. TNP was set at -50 mmHg according to McCord[53] for 6 d and then raised to -75 mmHg for 7 d. The rise in negative pressure was concurrant with an increase of the CRP value[54] (from 1.09 to 5.07 mg/dL), however, local signs of inflammation were reduced. After 13 d of negative pressure treatment, the wound was almost healed. Definitive closure was achieved in 5 d of application of collagen dressing (Condress®, Abiogen, Pisa). After these treatments there were no signs of necrotizing facitiis and the swab culture was negative for Pseudomonas Aeruginosa. In our experience, the use of TNP therapy for neonatal necrotizing facitiis allowed us to achieve rapid wound healing after debridement. Interestingly, after the increase of suctioning pressure from -50 to -75 mmHg, a higher CRP value was observed, although local signs of inflammation had reduced. This can be explained by the fact that TNP determines the local release of interleukin (IL)-6, IL-8 and vascular endothelial growth factor and IL-6 induces an increase in plasma CRP concentration[55].

Wounds in patients with contraindications to surgery

An important consideration should be done about the useful application of VAC® therapy in patients with important comorbilities and contraindications to surgery, because treatment of patients with complex wound often requires surgical debridment and reconstruction with skin grafts or flaps. VAC® can be considered an alternative treatment in these patients[55].

In our experience we treated patients affected by complex wounds with conditions that contra indicates surgical procedures, as neonates, pregnant, or old patient with overall condition, such as advanced dementia or immobilization, that made difficult the management with the need for hospitalization. In all these cases the VAC® therapy has resulted in healing without the need to subject the patient to treatment achieving excellent results. The VAC® therapy is the treatment of choice when following patient at home and achieving healing quickly with satisfactory results, is needed.

RECENT APPLICATIONS

No evidences are reported for recent applications introduced by KCI: Prevena, VAC® Instill and VAC® Via.

These three devices were introduced in last few years with specific indications that must be cited in a work with the aim to resume all the possible indications of VAC® therapy and the necessity of further studies to define the level of evidence of these treatments.

Prevena®

Prevena® is a new device introduced in 2010 by KCI for the treatment of closed surgical incisions with VAC® therapy.

It consists in a preformed dressing made by a foam covered by a transparent film directly connected to the vacuum system predisposed at -125 mmHg and set for 7 d of treatment. It is generally positioned on the incision at the end of surgery, in a sterile environment. The goal is to create a favourable environment for healing processes, to approach the edges of the incision up to the closing, to stimulate perfusion, to reduce side tension, oedema and acts as a barrier against external contamination. The device is small and easy to carry.

Advantages of TNP on closed incisions were reported in several studies[56-58].

The indications of Prevena® are all surgical incisions at high risk for complications, such as in patients with poor general conditions due to diabetes, obesity or poor vascular status[59-61].

In high-energy trauma wounds the rate of complications (necrosis, infections) was reported in a range from 33% to 50%[62] and in sternal wound the mortality rate in case of infection is about 33% at 1 year[63,64].

Other conditions at high risk are orthopedic procedures[56,57], lower extremities bypass[62], abdominal[65,66] and cardiothoracic procedures[67].

Stannard *et al*[68] purposed a good system to classify the risk of wound complications high lightening cases that are best suited for TNP. Patients found to benefit from TNP are those with one or more risk factors for infection, seroma, hematoma, and dehiscence.

Contraindications to TNP are wounds with infection, dehiscence or cellulitis and incisions with ischemia or fragile skin due to radiotherapy, steroid or patient's age.

In literature there are studies reporting good results in the reduction of incidence of dehiscence and infection in high-energy trauma wounds[56], absence of complications in sternal wound patients at high risk for infection[57] and no infections in patients with foot and ankle trauma[58].

These considerations are the base of Prevena® system, it can be considered an useful and easy to use device in all surgical wounds at high risk for complications.

VAC Instill®

VAC Instill® system was introduced by KCI in 2003. it allows to add solutions to the wound bed, and it can be useful for wounds showing no response to conventional VAC® and as initial management in selected high risk wounds[69].

It is indicated in patients who would benefit from vacuum assisted drainage and controlled delivery of topical wound treatment solutions in case of chronic, acute, traumatic, subacute and dehisced wounds, partial thickness burns and ulcers.

Topical agents may be intended for extended tissue contact and compatible with VAC® dressing and disposable components (e.g., hypochlorous acid solutions applied at high concentrations for longer periods may damage VAC® system). The VAC GranuFoam Silver® is not indicated with instillation therapy.

The device is similar to traditional VAC® system with additional features. The foam is placed as usual and covered by the drape. Two different pads are connected to the dressing: one is the traditional suction drain connected to the vacuum source and the canister; the other is connected to an irrigation bag, containing the selected solution. Clinicians set automated infusion of fluids at presetted intervals without compromising the integrity of the occlusive dressing. It is important to consider patient' s position because instillation is driven by gravity. Instilled and drained fluid volumes must be monitored during treatment. In case of deep wound, a hole can be made deep in the foam in order to achieve a better action onto wound bed.

The treatment consists of repetitive cycles of TNP, instillation and holding time. Holding time allowed instilled solution to irrigate the whole wound and to perform its action, neither instillation nor TNP are applied during this period.

Instillation time must be enough to saturate the foam; holding time can range from 1 s to 1 h and continuous TNP can range from 1 min to 12 h.

Donalee[70] recommends 1-2 min of instillation time, 5 min of holding time and 5 h of TNP.

A test should be made after dress placement starting with a TNP cycle to check the seal and then with instillation to quantify the total amount of fluid necessary to saturate the foam. A wound culture may be obtained before starting in order to select the optimal fluid to instill[69].

The main goal is to reduce the bioburden within the wound; furthermore VAC Instill® may help in reduce pain in selected patient[69,71,72], even by using analgesic solutions.

In literature case reports about VAC Instill®[69,73,74] were reported. In all cases good results were achieved in terms of decrease in the main time to obtain a bioburden reduction, wound closure and hospital discharge.

In our experience we treated one patient affected by abdominal dehiscence with the presence of an exposed mesh. This condition often requires mesh removal, especially in case of infection of the device.

Our patient presented an infection of exposed mesh due to Klebsiella Pneumoniae sensible to Teicoplanin.

The continuous infusion was made using two solutions alternatively: 450 cc of physiologic saline + 50 cc of Betadine®; 500 cc of physiologic saline + 5 g of Teicoplanin (an injection of this solution is made every 45 min and then the TNP is set at 0 mmHg for 5 min then the TNP is set at -125 mmHg)

Instillation was performed every 45 min, then holding time was set at 5 min and a continuous TNP of 125 mmHg was set. The treatment was performed until the absence of infection of the wound, confirmed by microbiological examination, that was 7 d after starting. Then traditional VAC®

Table 1 Grade and level of evidence adapted from sign method of classification

Indication	Recommendation	Grade	Evidence level
Soft tissue trauma	Bridge to definitive closure when primary closure is not possible	C	L2-L3
	Stopped when delayed surgical closure is possible	C	L2-L3
	Improve the healing of fasciotomy incisions	C	L2
	Downscale the complexity of closure procedures	C	L2-L3
Open fractures wounds	Bridge to definitive closure when primary closure is not possible	B	L1-L3-L4
	Stopped when delayed surgical closure is possible	B	L1-L3
	Downscale the complexity of closure procedures	C	L2-L3
Partial thickness burns	Preventing burn wound progression	C	L2-L3
Flap procedures	For flaps which have suffered partial necrosis after debridement of necrotic tissue	D	L3-L4
	Manage donor sites which cannot be closed primarily	D	L3
Graft procedures	Improve the rate of graft success	A	L1-L2
	Case at high risk of graft loss	B	L1-L2
	Left undisturbed for 3-7 d post-grafting	B	L1-L2
	Continuous pressure level	B	L1-L2-L3

L: Level.

was continued to obtain the complete healing and coverage of prosthesis in 10 d.

VAC Via®

VAC Via® is a new device introduced by KCI for patients affected by wounds that can be treated at home. The device is relative small and set for a period of treatment of 7 d at -125 mmHg of pressure. The canister presents a capacity of 150 mL. According to our experience, we can consider that the device is simple to use and comfortable for the patient. The best indication is a relative small single wounds in a site that does not impair quotidian activities. In our experience in wide wounds or multiple ones, the device was not useful for the impossibility to regulate the pressure in relation to movements. In selected cases it can be very useful to treat patient at home, with minimal impairment in daily life.

CONCLUSION

Based on the International Expert Panel on Negative Pressure Wound Therapy[75] guidelines we found the grade and the level of evidence reported in Table 1. In the literature significant studies about other kinds of wounds are not reported.

Grade A of evidence is reported only for open abdominal wounds and graft procedures with the goal to improve the success rate. Grade D of evidence is reported in flap procedures with an evidence level 3 or 4. Other indications present an evidence grade between B and C. Considering these evidences, we think that VAC® therapy may be used in different kind of wounds with good results, reported by many studies in literature, even if an evidence based result has not even shown at this time. In our experience, VAC® therapy was useful in case of open abdomen, soft tissue trauma and paediatric patients, reporting good results. Further studies are necessary to define the evidence of VAC® therapy, especially in diabetic foot wounds, pressure ulcers, venous insufficiency ulcers and enteric fistulas. Obviously recent applications should be studied in the future to define the real utility in clinical practice, even if, also in our experience, VAC Instill® and VAC Via® reported good results. Many attempts were made to obtain an international consensus conference to define recommendation for VAC® use in different kind of wound and initial results were just obtained. We believe that further studies and definitive recommendations will underline the indications for VAC® therapy and asses the most useful regimen of treatment for each case.

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REVIEW

Dermatitis herpetiformis: Novel advances and hypotheses

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Abstract

Dermatitis herpetiformis (DH) is a gluten-sensitive autoimmune blistering disorder with a chronic-relapsing course. Very recently, several Authors reported atypical cases of patients with DH, suggesting that different clinical subsets may exist at least among different ethnicities and that the classical picture of DH probably need a significant revision. Moreover, different pathogenetic aspects of the disease are currently under investigation, including the role of epidermal transglutaminase, apoptosis and inflammatory cells in the occurrence of skin lesions, in order to explain why only a subgroup of celiac patients will develop DH. Finally, although gluten-free diet is still regarded as the only curative approach to the disease, it is very hard to comply with and even small amounts of gluten can re-activate the disease. Therefore, different therapeutical approaches for the spectrum DH/celiac disease are still under investigation. In the present paper, the most recent advances in DH will be discussed, and a novel interpretation of the disease based on the data emerging from the Literature will be proposed.

Key words: Dermatitis herpetiformis; Celiac disease; Transglutaminase; Gluten-free diet; Direct immunofluorescence

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INTRODUCTION

Dermatitis herpetiformis (DH) is a gluten-sensitive autoimmune blistering disorder with a chronic-relapsing course. The classic cutaneous manifestations are markedly pruritic, symmetrically distributed papulovesicles that usually affect the extensor surfaces of the limbs, the sacral region and the buttocks. DH is considered the specific cutaneous manifestation of celiac disease (CD), as both diseases occur in gluten-sensitive individuals, share the same HLA haplotypes (DQ2 and DQ8) and improve following the administration of gluten-free diet (GFD)[1-5].

The diagnosis of DH is established clinically, histologically, immunopathologically [direct immunofluorescence (DIF)] and serologically [IgA anti-tissue transglutaminase antibodies (anti-tTG), IgA anti-epidermal TG (eTG) and IgA endomisial autoantibodies][1].

Histology of skin lesions in DH is characterized by a subepidermal blister with accumulation of neutrophils and very few eosinophils in the papillary dermis. DIF, that is considered the gold standard for the diagnosis, reveals granular IgA deposits along the basement membrane zone, mainly distributed at the papillary tips. Recent studies demonstrated that such IgA are mainly directed against eTG[6]. Although the features reported above have been considered the hallmarks of DH, very recently several Authors, mainly from Japan, reported atypical cases of patients with DH, suggesting that dif-

ferent clinical subsets may exist at least among different ethnicities and that the classical picture of DH probably need a significant revision.

CLINICAL MANIFESTATIONS

Although the name of the disease reflects the typical clinical presentation association with celiac disease and immunopathological features of dermatitis herpetiformis, these occur later in the disease and are often immediately excoriated, resulting in erosions, crusted papules, or areas of postinflammatory dyschromia, or there may be erythema or severe pruritus alone, making the diagnosis often challenging[7].

By contrast, as previously mentioned, an increasing number of clinical studies have recently described uncommon presentations in patients with DH. Among them, purpuric lesions on hands and feet are being reported more frequently in children with DH from their first description in 1971[8,9]. Other atypical presentation of DH include palmo-plantar keratosis, wheals of chronic urticaria and lesions mimicking prurigo pigmentosa[10-12].

Such atypical presentations are more often reported in Japanese patients with DH, who seem also to have a decreased frequency of CD[2], that is in contrast with the data regarding Caucasian patients with DH, who show typical CD alterations at the small bowel biopsy (ranging from villous atrophy to augmented presence of intraepithelial lymphocytes) almost in all the cases. It is not clear whether the decreased frequency of CD in Japanese patients with DH is due to a less aggressive and specific diagnostic approach to the potential gut involvement, decreased exposure to gluten in the Japanese patients, or a true difference in the pathogenesis of the disease[2,13].

Interestingly, according to the latter hypothesis, Japanese patients show different findings also at the DIF, where an increased incidence of fibrillar pattern of IgA deposition is seen. Whether this feature could be considered a mere morphological variant or have implications for the pathogenesis of the disease is still under debate. However, some data suggested that DH patients with fibrillar IgA deposits show atypical clinical features such as the sparing of the predilection sites, the lack of enteropathy and no HLA-DQ2/DQ8 haplotype[2,14,15].

PATHOGENESIS OF DERMATITIS HERPETIFORMIS

As in CD, the pathophysiology of DH involves a complex interplay between genetics, autoimmune factors, and environment. In fact, it is now clear that in genetic predisposed individuals with HLA-DQ2/DQ8 haplotype, the exposure to a well known environmental factor, namely gluten, is able to trigger the disease by the induction of an autoimmune response against specific autoantigens, that are tTG for CD and, probably, eTG for DH.

However, the exact mechanisms through which gluten sensitivity results into the development of the specific lesions of DH are not completely understood. As an example, it is not clear why only a small cohort of patients with CD will develop DH. A possible clue could be represented by eTG that, as previously mentioned, is currently considered the target antigen of DH. In particular, eTG has been shown to colocalize with IgA deposits in the skin and anti-eTG antibodies have been found in the sera of patients with DH[6].

Besides these data, by passive transfer of anti-eTG antibodies to SCID mice engrafted with normal human skin, very recently Zone *et al*[16] reproduced the immunopathological pattern of DH, confirming the source of IgA in DH skin and the potential role of eTG in the disease. Accordingly, they proposed that epitope spreading from tTG to eTG could determine IgA anti-eTG autoantibodies production in a subset of celiac patients who then develop DH.

Unfortunately, they failed to reproduce DH lesions with transfer of anti-eTG antibodies in their model, suggesting that other unidentified proinflammatory factors trigger the cutaneous eruption. Moreover, data from the Literature showed that not all anti-eTG positive celiac patients will develop DH, and at least a subgroup of celiac patients without DH show IgA deposits at the dermal papillae[17-19].

As a consequence, several questions arise, including the following: (1) are anti-eTG antibodies really causative or are they simply a consequence of DH? (2) Which are the additional factors involved in the inflammation found in DH skin and absent in the skin of celiac patients without DH? and (3) Why eTG deposits are found at the papillary tips in DH skin?

Regarding the latter, while tTG is ubiquitariously expressed in many tissue and, in the skin, it is found in the basal keratinocytes and dermal capillaries[20], eTG is not ubiquitary but it is primarily seen in the granular layer of the epidermis, small intestine, brain and testis[21]. Thus, it is not clear why it is found in the papillary dermis, and some potential explanations have been made. Probably, the most convincing one is linked to an accelerated apoptosis in the skin of DH patients, that has been recently demonstrated by a study of our research group[22]. Although DH should not be considered an apoptotic disease, the apoptosis of DH keratinocytes could lead to the liberation of proteins and enzymes from such cells, including eTG, that would deposit in the dermis. Accordingly, it has been shown that TRAIL, a pro-apoptotic molecule, can induce the expression of the keratinocyte differentiation markers, including transglutaminases[23]. Thus, the accumulation within the papillary dermis of the trigger antigen, i.e., eTG, might induce the development of an autoimmune response leading to the skin lesions of DH.

However, several data are in contrast with such a hypothesis. First of all, eTG deposits are found also in the skin of patients with CD that do not develop DH[19]; sec-

ondly, since apoptosis in DH skin is mainly confined in the basal layer of the keratinocytes, it could be expected a deposition in the papillary dermis even of tTG - that is present at high concentrations in such cells-, but it is not the case according to the study by Sardy *et al*[6], lastly, as previously discussed, the pathogenetic role of anti-eTG antibodies have to be determined yet and other factors are probably involved in the development of DH.

Among them, considering that DH skin lesions are predominantly distributed at sites of constant minor trauma (extensor surfaces, elbows, knee, buttocks), some Authors suggested that the latter can stimulate keratinocytes to secrete several cytokines that, in turn, are able to induce the expression of critical adhesion molecules (including E-selectin) on dermal endothelial cells and of chemokines such as interleukin (IL)-8, which would predispose these areas to the development of inflammation[24,25].

Another important factor could be represented by T cells. Accordingly, although the typical histopathological pattern of DH is characterized by neutrophilic accumulation at papillary tips, several reports showed that a predominantly lymphocytic dermal infiltrate may also be found in up to 40% of cases (and almost in all the patients in the initial phases of the disease)[26-28]. Moreover, activated CD4+ T cells with a cytokine expression pattern belonging to the Th2 phenotype have been documented in recent DH skin lesions as well as in the perilesional skin, suggesting their role in the early phases of DH skin inflammation[29,30]. In fact, the early recruitment of Th2 cells in the preferential sites of DH may allow the liberation of cytokines (such as IL-4 and IL-5) and chemotactic agents that are probably responsible for the accumulation of neutrophils and eosinophils in DH skin.

The fact that a previous study by Baker[31] failed to find gluten-specific CD4+ T cells from the skin of untreated DH patients, probably does not narrow the importance of such cells in the pathogenesis of DH, since further studies are required to confirm the absence of gluten-specific T cells in DH skin and, even in this case, some Authors suggested that CD4+ T cells in the gut could become sensitized to gluten and cause the activation of other cell types, such as neutrophils, that then migrate to the skin[3].

NEW THERAPEUTIC APPROACHES

Since DH is considered the specific cutaneous manifestation of CD, besides the symptomatic therapies often used in DH patients to control the skin flares at least in the first phases (i.e., dapsone, that should still be considered as the best option to clear DH skin lesions), GFD is still regarded as the only curative approach to the disease. However, since GFD is very hard to comply with and even small amounts of gluten can re-activate the diseases, different approaches are still under investigation.

Among them, the enzyme therapy could be considered a promising one. It is well known that gliadin peptides are highly resistant to digestive processing by pancreatic and brush border proteases[32]. Thus, the use of bacterial endopeptidases (including a supplementation to patients or pretreatment of whole gluten with them) has been proposed to promote complete digestion of cereal proteins and thus destroy gluten epitopes.

Other interesting alternatives to a GFD, although quite complicated, are represented by the use of engineered grains containing gliadin peptides able to inhibit the T cell response to gluten or different immunomodulatory strategies, including the use of tTG inhibitors, of DQ2 and DQ8 blocking peptides, as well as of inhibitors of the adaptive or the innate immunity (i.e., monoclonal antibodies against IL-15 and inhibitors of the neutrophil migration)[33,34].

Moreover, potential treatments for DH are those aimed to induce tolerance to gluten with bioengineered probiotic strains of microorganisms that could be administered orally or with intranasal administration of recombinant α-gliadin[3,35]. For example, strains of *Lactococcus lactis* that expressed a gluten-derived DQ8-restricted gliadin peptide[36] or secreted IL-10[37] were found to inhibit the activation of gluten-specific T cells or to treat mouse models of colitis, respectively.

A further alternative approach to a GFD is the correction of the intestinal barrier defect that, together with genetic predisposition and environmental triggers, is thought to be one of the most important factors in the development of autoimmunity. Recent evidence suggest that, in CD, the gluten-induced up-regulation of zonulin, a peptide involved in tight junction regulation, is responsible, at least in part, for the increase in gut permeability and the subsequent abnormal passage of gluten into the lamina propria[38]. Interestingly, the zonulin inhibitor AT1001, tested in recent clinical trials[39], was shown to be tolerated and to reduce gluten-induced intestinal barrier dysfunction, pro-inflammatory cytokine production, and gastrointestinal symptoms in celiac patients.

Finally, the results from recent reports lead to an interesting question: is a lifelong commitment to GFD always necessary in patients with DH? Very recently Paek *et al*[40] reported that 12% of their DH patients experienced remission, defined as absence of skin lesions and symptoms of DH for more than 2 years while not adhering to a GFD, suggesting that clinicians should continually re-evaluate the need for medical therapy and a GFD for their patients with well-controlled DH, with the idea that DH might actually be in remission in some patients. However, this approach needs confirmation in larger cohorts of patients and, in particular, an accurate histopathologic examination of the intestinal mucosa and a serologic evaluation of anti-tTG antibodies should be performed after the reintroduction of gluten-containing foods into the diet, to ensure that the remission of DH was also associated with the remission of the intestinal disease[41].

Moreover, the need for a GFD should be questioned

Table 1 Hypothetical spectrum of dermatitis herpetiformis

Classical CD-related DH	Latent/potential CD-related DH	Non CD-related DH
Histopathological features typical of CD Presence of gluten specific immunological response	Absence of villous atrophy[1] Presence of gluten specific immunological response	Absence of histopathological features of CD Absence of gluten specific immunological response[42,43]

[1]Documented by experienced gastroenterologists and pathologists after repeated bowel biopsies. CD: Celiac disease; DH: Dermatitis herpetiformis.

even in Japanese patients who, as previously discussed, seem to have a decreased frequency of CD and lack the typical HLA haplotypes associated to the development of both DH and CD[11-13].

FUTURE PERSPECTIVES

As previously mentioned, recent reports from the Literature suggest that the features as well as the diagnostic criteria of DH should be carefully revised. In particular, the sensitivity and the specificity of the DIF, that is considered the gold standard for the diagnosis of DH, should be re-evaluated. In fact, recent reports showed that skin biopsies from patients with CD but without DH can show granular deposits of IgA at the dermal-epidermal junction[19]. Accordingly, a clinical trial investigating a large series of CD patients for the findings at DIF (both on DH "predilection" and "non-predilection" sites) should be performed.

A second important point about DH is its relationship with CD and with the HLA DQ2/DQ8 haplotype, that are currently considered two of the main features of the disease. However, as reported above, Japanese DH patients seem not to show those features in all the cases[2]; moreover, patients with "paraneoplastic DH" with all the classic clinical, histopathological and immunopathological findings of DH, but without intestinal involvement and no response to a GFD were recently reported[42,43]. Do these patients really have DH? Or should CD and response to gluten be considered mandatory features and, therefore, patients without intestinal involvement should be classified as having a skin disease different from DH-although sharing common clinical, histopathological and immunopathological findings? To address these questions and understand whether both CD-associated and non CD-associated forms of DH do exist, several studies mainly focusing on HLA and non-HLA genetic background and on potential specific serologic markers of DH but not of CD should be performed.

Focusing on the CD-associated forms, according to Fry *et al*[44], a very interesting issue still remains: why do some people with CD develop DH and other do not? An answer to this interesting question is unlikely to be found only investigating the humoral immunologic response against eTG; studies analyzing the different T cell populations, including Th2 and Th17 lymphocytes specific for the several antigens involved in the CD/DH spectrum (eTG, tTG, gliadin), would be probably required. Moreover, the use of experimental models of DH would help to increase the knowledge of the disease. Recently, besides the mouse model by Zone *et al*[16] described previously, another interesting model was developed[45]. It was a gluten-sensitized non-obese diabetic DQ8+ mouse that satisfied various requirements for an animal model of DH: gluten sensitivity, Major Histocompatibility Complex II dependence for gluten sensitivity, and replication of many histopathological and immunological features of the lesional skin of DH. There were, however, three main differences between that model and the majority of DH patients (the absence of CD4+ T cells in the lesional dermis, the absence of entheropathy and the lack of colocalization of eTG with the IgA deposition on the perilesional areas), suggesting that other models closer to the disease should be developed. However, this model could also suggest the existence of a subtype of human DH overlapping its features.

Accordingly, also this model rises the problem about the presence of enteropathy in patients with DH and, therefore, the question of whether enteropathy is a crucial element of DH pathogenesis or a gluten-specific immune response without gut involvement is sufficient for the occurrence of the disease. Accordingly, as a significant minority of DH patients (10%) does not have detectable enteropathy, but do have an immune response to gluten, it might be possible that the villous destruction is an independent consequence of the inflammatory response toward gluten in the intestine of DH patients[3].

CONCLUSION

Finally, it could be hypothesised the existence of patients with non CD-associated DH, showing all the clinical features of DH but without a gluten-specific serologic immune response (Table 1). These subsets would have a great impact on patients with DH, since if a subgroup of them did not have CD, they would be managed even without a GFD that, as reported above, is difficult to comply with. However, further studies are required to confirm such hypothesis and, to date, GFD still remains the best therapeutic option for patients with DH.

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REVIEW

Impact of near-infrared radiation in dermatology

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Abstract

Sunlight that reaches the human skin contains solar energy composed of 6.8% ultraviolet (UV), 38.9% visible light and 54.3% infrared radiation. In addition to natural near-infrared (NIR), human skin is increasingly exposed to artificial NIR from medical devices and electrical appliances. Thus, we are exposed to tremendous amounts of NIR. Many studies have proven the effects of UV exposure on human skin and skin cancers but have not investigated well the effects of NIR exposure. Furthermore, many of the previous NIR studies have used NIR resources without a water filter or a contact cooling. With these resources, a substantial amount of NIR energy is absorbed in the superficial layers and only limited NIR energy can be delivered to deeper tissues. Thus, they could not sufficiently evaluate the effects of incident solar NIR. In order to simulate solar NIR that reaches the skin, a water filter is essential because solar NIR is filtered by atmospheric water. In reality, NIR increases the surface temperature and induces thermal effects so a contact cooling is needed to pursue the properties of NIR. I clarify that NIR can penetrate the skin and non-thermally affect the subcutaneous tissues, including muscle and bone marrow, using a NIR resource with a water filter and a cooling system. I would like to emphasize the biological effects of NIR which have both merits and demerits. Appropriate NIR irradiation induces dermal heating thermally and non-thermally induces collagen and elastin stimulation, which results in skin tightening. NIR also induces non-thermal DNA damage of mitotic cells, which may have the potential application for treating cancer. However, as continuous NIR exposure may induce photoaging and potentially photocarcinogenesis, we should consider the effect of, not only UV, but also NIR and the necessity for protection against solar NIR. Here, this paper introduces the new aspects of the biological effects of NIR radiation.

Key words: Near-infrared; Non-thermal; Biological effects; Photoaging; Damage; Protection; Stem cell; Cancer

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INTRODUCTION

Various kinds of ultraviolet (UV) blocking materials, such as sunblocks, sunglasses, films and fibers are often used to prevent skin damage from UV exposure. Although individuals all over the world use various types of sunscreens, unwanted biological influences, such as rosacea, erythema ab igne, long-term vasodilation[1,2], muscle thinning[3,4] and sagging still occur[5,6]. Most sunscreens can only block UV but not visible light and near-infrared (NIR)[5].

Both UV and visible light radiation are attenuated by melanin[7], whereas infrared (IR) can penetrate deep into human tissue where it can cause photochemical changes[8]. We previously reported that NIR penetrates the skin and is absorbed by sweat on the skin surface, water in the dermis[1,9-11], hemoglobin in dilated vessels[1,2], myoglobin in the superficial muscle[3,4], bone cortical mass and is scattered by adipose cells[12].

Appropriate NIR irradiation induces dermal heating thermally and non-thermally induces collagen and elastin stimulation, which results in skin laxity tightening. NIR irradiation also induces non-thermal DNA damage[13,14] and cell death by apoptosis[15], as well as the cell death of cancer cells and bone marrow cells[12]. In addition, NIR irradiation is used as a therapeutic option for the treatment of wound healing disorders[16-18] and malignant tumors[19-22].

However, the necessity to protect cells from NIR in order to prevent tissue damage has not been well investigated. Many studies have proven the effects of sun and UV exposure on the skin but have not investigated well the long-term effects of NIR exposure on human skin and skin cancers. Fair skin, with sparse melanin and a thin dermis, might allow NIR radiation to penetrate deeper into human tissue than dark skin, which has dense melanin and a thick dermis[5,6]. In addition to natural NIR, human skin is increasingly exposed to artificial NIR from medical devices and electrical appliances[23,24]. Thus, sunscreens should also protect against NIR[3,5,6,12,23-28] because we are exposed to tremendous amounts of NIR[5]. Our preliminary studies suggest that we should consider the biological effect of not only UV, but also NIR[3,5,6,12].

METHODS OF NIR RESEARCH

Previous in vitro research of NIR

In the previous studies of the NIR, lamps emitting wide wavelengths of NIR were used as a NIR source[6,29]. The temperature of the superficial layer of the culture fluid in the laboratory dish will rise immediately by the NIR irradiation because NIR is primarily absorbed by water. Then, the energy of NIR will diminish as it penetrates deeper and will not reach the target cells in the base enough (Figure 1A). Therefore, the previous studies only described thermal effects of NIR and could not find various non-thermal biological effects of NIR[6].

Previous in vivo research of NIR

NIR irradiation is known to induce dermal heating, which results in skin laxity tightening[1,9,30-34]. In previous studies[16,35,36], NIR devices without a water filter or contact cooling were used to evaluate photobiological effects on the human body.

NIR increases the skin surface temperature and induces perspiration and vasodilation because NIR is primarily absorbed by water and hemoglobin. Then, a substantial amount of energy is absorbed in the superficial layers of skin and only limited NIR energy can be delivered to deeper tissues (Figure 1B). Therefore, the previous studies only described superficial and thermal effects of NIR and could not find various non-thermal biological effects of NIR[6].

My research of NIR

Sunlight that reaches the human skin contains solar energy composed of 6.8% UV light, 38.9% visible light and 54.3% IR radiation[37]. The IR spectral region is arbitrarily divided according to wavelength into sub-regions of NIR (760-3000 nm), middle IR (3000-30 000nm) and far IR (30 000 nm-1 mm). NIR radiation from the sun is selectively filtered by atmospheric water[7,38]; thus, most NIR radiation that reaches the Earth's surface readily penetrates the superficial layers of the skin[3,5,6,12] (Figure 2).

In order to simulate solar NIR that reaches the skin, a water filter is essential because solar NIR is filtered by atmospheric water. I used a NIR device that emitted a spectrum of NIR irradiation from 1100 to 1800 nm with a water-filter that excludes wavelengths between 1400 and 1500 nm, which are strongly absorbed by water and hemoglobin (Figure 3).

Wavelengths below 1100 nm are preferentially absorbed by melanin in the superficial layers of the skin. Wavelengths between 1400 and 1500 nm and those above 1850 nm are absorbed heavily by water in the superficial layers of the skin, which results in heating and can lead to painful sensations and burns[20]. Filtering out the wavelengths below 1100 nm, around 1450 nm and above 1850 nm enabled the delivery of NIR irradiation to deeper tissues[39] and also simulated solar NIR radiation that reaches the skin of humans on the earth's surface. Therefore, a NIR device with a water-filter mimics the natural situation and allows the evaluation of solar NIR radiation that reaches the skin. However, the biological effects induced by near sub-region of IR radiation could not be evaluated with this NIR device. Further studies in near sub-region of IR are needed.

In reality, NIR increases the surface temperature and induces thermal effects so a contact cooling is needed to pursue the properties of NIR. Contact cooling through a temperature-controlled sapphire window was used to reduce the skin surface temperature and reduce perspiration and blood vessel dilation (Figure 4A).

These specific wavelengths and the cooling system enabled NIR to be delivered to the deeper tissues without pain or epidermal burns[39,40], which was evidenced by the ability to treat animals and humans without anesthesia and without contact burns or other adverse events.

Therefore, I found various non-thermal biological effects of NIR[1-6,9-14].

DISCUSSION

Properties of NIR

NIR is an electromagnetic wave that simultaneously exhibits both wave and particle properties and is strongly

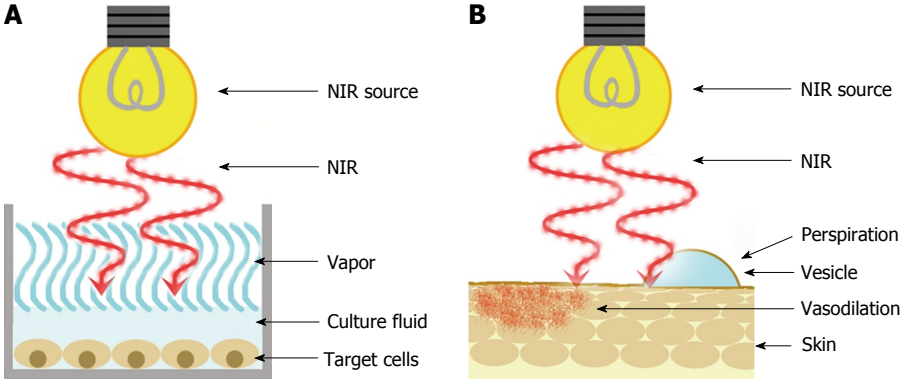

Figure 1 A schematic of the previous *in vitro* and *in vivo* research. A: *In vitro* research. B: *In vivo* research. NIR: Near-infrared.

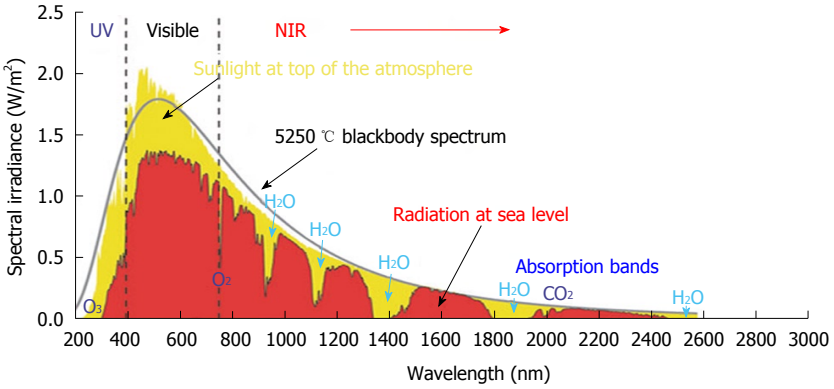

Figure 2 Solar radiation. This graph shows the radiation spectrum for direct light both at the top of the earth's atmosphere (yellow) and at sea level (red). The sun produces light with a distribution similar to that expected from a 5250 ℃ blackbody (gray), which is approximately the temperature of the sun's surface. As light passes through the atmosphere, some is absorbed by gases with specific absorption bands (blue). These curves are based on the American Society for Testing and Materials Terrestrial Reference Spectra, which are standards adopted by the photovoltaic industry to ensure consistent test conditions and are similar to the light levels expected in North America. Regions for ultraviolet, visible and near-infrared are indicated. Cited and revised from Figure 2 of reference 3.

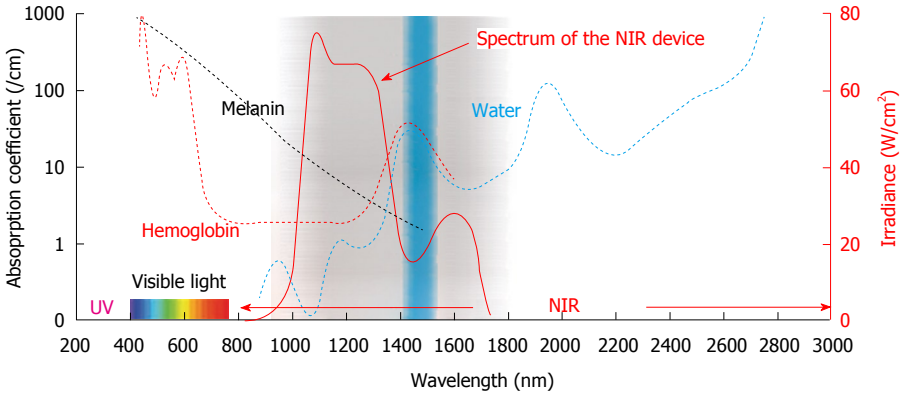

Figure 3 The absorption coefficients and wavelength of the near-infrared device. This graph shows the absorption coefficients of melanin (brown), hemoglobin (red) and water (blue). The near-infrared (NIR) device used in our study emits a spectrum of NIR from 1100 to 1800 nm (bold red), with filtering of wavelengths between 1400 and 1500 nm (blue belt) that are strongly absorbed by water and hemoglobin. Cited and revised from Figure 2 of reference 3.

absorbed by water, hemoglobin and myoglobin[2]. As a consequence, NIR irradiation can penetrate the skin and affect the subcutaneous tissues, including muscles and bone marrow, with both its wave as well as its particle properties.

The penetrating 600-1300 nm wavelength region causes photochemical changes and affects a large volume and depth of tissue[7]. Actively proliferating cells show increased sensitivity to red and NIR[41,42]. NIR irradiation induces strand breaks and apoptosis[15], as well as cell death of cancer cells and bone marrow cells[12-14]. NIR irradiation is used as a therapeutic option in the treatment of wound healing disorders[16-18] and malignant tumors[19-22]. While NIR irradiation appears to damage tumor tissue,

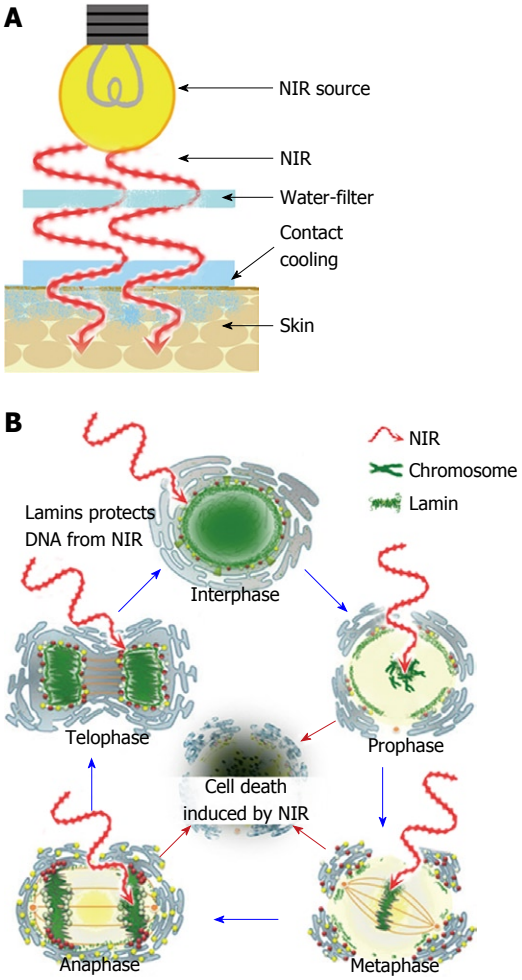

Figure 4 A schematic of my near-infrared research and cell cycle. A: A schematic of my near-infrared (NIR) research; B: A schematic of the cell cycle and effects of NIR. NIR cannot penetrate the nuclear envelope due to the protection of nuclear lamins in interphase and telophase. NIR may damage the chromosomes of mitotic cells in prophase, metaphase and anaphase due to the absence of nuclear lamin protection, which results in apoptotic cell death. Cited and revised from Figure 15 of reference 5.

it has also been shown to reduce cellular protein damage produced by biological oxidants in normal cells[43].

We also reported that NIR irradiation was shown to thermally induce the expression of collagen[9], elastin and water-binding proteins[1,9] without scar formation[10]. Furthermore, NIR irradiation non-thermally induced long-lasting muscle thinning[3], muscle relaxation[4], bone marrow damage[12], a cytocidal effect on cancer cells[13,14], stimulation of stem cells[5,12] and DNA damage[13,14] of mitotic cells[5].

Biological effects of NIR on human skin

The biological effects of NIR have both merits and demerits. The dermis tends to increase the amount of fluid by inducing an increase in collagen, elastin and water-binding protein in order to protect subcutaneous tissues from NIR[1,9]. Pre-exposure of NIR prevents UV-induced toxicity[29,44,45] and this effect is independent of heat shock protein induction and cell division[45]. These findings suggest that NIR irradiation prepares skin to better resist the subsequent damage of UV or NIR.

In contrast, similar to UV, NIR seems to exert biological effects on human skin[23]. NIR irradiation was shown to cause skin changes similar to those observed in solar elastosis and enhanced UV-induced dermal damage[35]. NIR irradiation is able to activate mitogen-activated protein kinases and induce gene transcription and is likely to increase collagen degradation[23,24,46]. Epidemiological data and clinical reports point to the ability of NIR to cause and enhance actinic skin damage, implying that NIR is not innocuous to human skin[23,47,48].

The mean facial surface area that is covered with wrinkles is significantly smaller in African Americans than in Caucasians and characteristics of age-related periorbital changes seem to occur at a more accelerated rate in Caucasians[49]. In addition, fair skin is more sensitive to skin aging[50,51]. These findings support the observation that fair skin tends to wrinkle and sag earlier in life[52,53] because fair skin is thinner and is more susceptible to NIR damage to the underlying frontalis, orbicularis oculi and platysma muscles than dark skin[5,6]. NIR is attenuated by thick water-containing dermis. Thus, skin with sparse melanin and a thin dermis might allow NIR radiation to penetrate deeper into human tissue than skin with dense melanin and a thick dermis[5,6].

Repeated exposure to sources of heat and NIR, such as fires and stoves, results in a skin lesion described as erythema ab igne[54], which is clinically characterized by a reticular hyperpigmentation and teleangiectasia accompanied histologically by epidermal atrophy, vasodilation and dermal melanin and hemosiderin deposits. After many years, these lesions may develop thermal keratoses, such as hyperkeratosis, keratinocyte dysplasia and dermal elastosis, which are similar to the changes that occur in actinically damaged skin[55]. Similar to actinic keratoses, thermal keratoses are precancerous lesions that exhibit epidermal dysplasia, which may develop into invasive squamous cell carcinoma. There are several reports of carcinomas arising from heat induced erythema ab igne[47,56,57]. NIR radiation, similar to UV radiation, induces photoaging and potentially photocarcinogenesis[23]. In addition, skin tumors in mice appeared faster after irradiation with the full lamp spectrum containing UV, visible and NIR compared to irradiation with UV alone[58].

Biological effects of NIR on cancer cells

Wavelength of NIR anticancer therapy: Photodynamic therapy (PDT) is the most common antitumor therapy using IR for select forms of cancer[59]. PDT is based on the accumulation of a photosensitizing agent in tumors and uses wavelengths near 800 nm as a photoactivating wavelength to achieve maximum penetration depth[19,22,60]. This wavelength, however, also has high melanin absorption, which limits the ability to deliver light to highly pigmented tumors[61].

Although wavelengths near 800 nm are the standard activators for PDT, other wavelengths have also shown treatment promise. Santana-Blank *et al*[62] reported that NIR at 904 nm may have antitumor activity, as shown

by an increase in cytomorphological changes, as well as apoptosis in neoplastic cells. Unlike wavelengths beyond 1100 nm where melanin absorption is negligible[7], absorption at 904 nm was significant. This may limit the possible uses of the 904 nm wavelength for certain body areas in races with skin that is rich in melanin.

Although many studies have shown the thermal effects of NIR irradiation on cancer cells in the field of hyperthermia, non-thermal effects of NIR irradiation were not investigated in detail. We first reported on the non-thermal effects of NIR using a specialized broad spectrum light source emitting light between 1100-1800 nm (with a filter to exclude wavelengths between 1400 and 1500 nm) on cancer cells and suggested the possibility of beneficial uses for cancer treatment[13,14]. However, further studies are needed to evaluate variations in treatment parameters and conditions, which will enable development of procedures that achieve maximum results while providing the greatest margin of safety.

Biological effects of NIR on *in vivo* cancer studies: The histological findings showed tumor shrinkage and dying cells in the center of the tumor mass, which supports that NIR electromagnetic properties induce these biological effects non-thermally. If the cytocidal effect of NIR was induced thermally, the histology would show a gradient cytocidal effect from the superficial layer to the center of the tumor and the thermal effect would be reduced by the contact cooling (20 ℃) of the NIR device. Due to surface cooling, NIR can penetrate deeper tissue and induce a drastic non-thermal cytocidal effect in the center of the tumor mass[13].

A significant reduction in tumor volume and a high level of TUNEL-positive cells in the irradiated group indicated that NIR irradiation induces apoptosis in cancer cells. However, the mechanism of NIR-mediated tumor cell death appeared to be different than standard apoptosis because high levels of activated caspase-3 expression and ssDNA-positive cells appeared gradually after NIR irradiation, although tumor shrinkage happened rapidly.

On the other hand, NIR irradiation induced the stimulation of CD34-positive bone marrow stem cells in our previous study[12] and the frequency of Ki67-positive cells on day 45 was significantly higher than the irradiated group on day 9. These results suggest that NIR irradiation may stimulate stem cells.

The immunohistological staining results suggested that NIR may induce cell death of highly proliferative tumor cells, stimulate stem cells and then induce apoptosis of the cells which are unnecessary to promote the development of melanoma. These steps appeared to be a part of the mechanism driving the effects of NIR on cancer cells.

Biological effect of NIR on molecular structure

NIR is absorbed by water, hemoglobin and myoglobin. The NIR spectrum of biological materials is a result of the overtones and combination of O-H, C-H and N-H groups' bond stretching vibrations[63]. Water is a polar molecule with an electrical dipole moment and possesses hydrogen bonds. A water molecule will be resonated by NIR and absorb NIR due to the O-H intramolecular hydrogen bonds and electrical dipole moment[64]. Since T2 weighted MRI enhances water as well as active proliferating cancer cells, active proliferating cells may have a rich water content, which strongly absorbs NIR[5].

Hemoglobin has four heme-binding subunits, each largely made of α helices, and myoglobin consists of eight α helices that are connected through turns with an oxygen binding site. The similarity between hemoglobin and myoglobin resides in the heme binding sites and α helices. Heme is a prosthetic group that consists of an iron atom located in the center of a large heterocyclic organic ring called porphyrin. Our results of long-lasting muscle thinning and vasodilation induced by NIR suggest that NIR might resonate and damage heme. However, our collagen, elastin and cancer studies suggest that NIR may mainly resonate helical structures, α helices and DNA. α helices are thought to be resonated by NIR and have strong amide bands in the IR spectra, which have characteristic frequencies and intensities[65]. Both hemoglobin and myoglobin are the oxygen-carrying proteins and have many α helices. It is possible that NIR induces resonance of α helices in the oxygen-carrying proteins and degenerates proteins containing α helices, which results in damage to the storage and transport of oxygen. This could be one of the mechanisms of apoptosis. In our previous study, we evaluated the effect of NIR on myoglobin; however, similar effects may also be found for hemoglobin[2].

NIR increases the amount of water retained in the dermis by inducing vasodilation and the expression of collagen and elastin[1]. Both collagen and elastin possess helical structures and hydrogen bonds. Elastin has higher absorption properties than that of water[64]. These findings suggest that we have acquired biological defense mechanisms in which induced helical structures and hydrogen bonds are resonated by NIR and absorb NIR to protect the subcutaneous tissues against NIR.

Similarly, DNA consists of two long strands in the shape of a double helix, which is stabilized by two forces: hydrogen bonds between nucleotides and base-stacking interactions among the aromatic bases. Many studies regarding DNA and cancer imaging have been performed using a NIR spectroscopy since biological molecules such as proteins, lipids and nucleic acids provide a unique absorption spectral pattern and NIR induces the vibration of DNA. IR irradiation alone appears to induce DNA strand breaks and apoptosis[15]. DNA will be also resonated and absorb NIR, which is most likely due to its helical structures and hydrogen bonds.

Biological effects of NIR on lamin

The nuclear lamina is a proteinaceous structure located underneath the inner nuclear membrane that forms a stress-resistant elastic network where it associates with the

peripheral chromatin[66]. It contains lamins and lamin-associated proteins, including many integral proteins of the inner nuclear membrane, chromatin modifying proteins, transcriptional repressors and structural proteins[67-70].

Lamins are type-V intermediate filament proteins located in the nucleus, primarily in the periphery, and underlie the nuclear envelope[71]. Lamins have a conserved α helical central rod domain and variable head and tail domains[66,72,73]. α helical structures are surmised to absorb NIR and protect the nucleus and DNA from NIR.

Lamins play important roles in DNA replication, chromatin organization, adult stem cell differentiation, aging and tumorigenesis. In addition, mutations in lamin lead to laminopathic diseases[66]. Nuclei assembled *in vitro* in the absence of lamins are more prone to breakage than nuclei assembled in the presence of a full complement of lamins[74,75]. Disruption of the lamins results in abnormal mitosis, chromosomal segregation and cell death[76].

During mitosis, lamin molecules are transiently disassembled into monomers[77,78] through phosphorylation[79] by the protein kinase p34cdc2[80]. In addition, actively proliferating cells show increased sensitivity to NIR[41,42] and IR irradiation induces DNA strand breaks and apoptosis[15]. Therefore, these findings suggest that NIR exposure appears to damage nuclear lamins and DNA in the mitotic phase due to absence of nuclear lamins protection, which results in apoptotic cell death[5]. Thus, NIR induces non-thermal DNA damage of mitotic cells in prophase, metaphase and anaphase due to the absence of nuclear lamin protection, which may have the potential application for treating various forms of cancer[13,14] (Figure 4B).

Biological effect of NIR on stem cells

NIR irradiation abruptly induced subcutaneous adipocytes on the panniculus carnosus and CD34-positive cells around the subcutaneous adipocytes[12]. Adipose-derived stem cells express CD34 in higher percentages than bone marrow-derived mesenchymal stem cells[81]. CD34-positive human adipose-derived stem cells have a greater replicative capacity compared to CD34-negative cells[82]. These results suggest that NIR irradiation may enrich and stimulate CD34-positive adipose-derived stem cells to increase subcutaneous adipocytes on the panniculus carnosus.

Optically, fatty tissue can scatter NIR[83] and fatty acids are the major NIR absorbing materials in soft tissues[64]. The oil in the liquid phase is transparent, whereas the oil in the solid phase is highly scattering to NIR[84]. The long-lasting induction of subcutaneous adipocytes may protect the underlying tissues, including the panniculus carnosus, against NIR damage.

NIR irradiation that simulated solar radiation non-thermally affected the subcutaneous tissues, cortical bone and bone marrow[12]. The apoptotic damage to bone marrow cells might be minimized by a biological defense against NIR irradiation by means of an increase in subcutaneous and bone marrow adipocytes, as well as cortical bone mass through the enrichment of CD34-positive stem cells at the inner surface of the bone cortex.

Lamin A and pre-lamin A regulate stem cell maintenance and differentiation by influencing key signaling pathways in stem cells[66]. Lamin A/C expression seems to be reduced or absent in undifferentiated or proliferative cells but is observed in differentiated or non-proliferative cells, such as quiescent adult stem cells[85]. Lamin A regulates stem cell maintenance through a range of regenerative signaling pathways, which suggests that the regulation of adult stem cell aging may occur at a number of different pathway steps that intersect with lamin A, including adult stem cells, their progenitors and/or stem cell niches[85]. These results suggest that NIR radiation may stimulate stem cells, including cancer stem cells[5].

CONCLUSION

In order to simulate solar NIR that reaches the skin and to pursue the properties of NIR, a water filter and contact cooling are essential for a NIR source.

Appropriate NIR irradiation induces dermal heating thermally and non-thermally induces collagen and elastin stimulation, which results in skin laxity tightening. NIR also induces non-thermal DNA damages of mitotic cells in prophase, metaphase and anaphase due to the absence of nuclear lamin protection. NIR irradiation might have a potential application for treating various forms of cancer, including highly proliferative cells, since the schedule reduces discomfort and side effects, reaches the deep subcutaneous tissues and facilitates repeated irradiations.

In contrast, solar NIR radiation may also cause unexpected muscle thinning and stimulation of stem cells, including cancer stem cells, in areas of the body that are exposed to the sun. Although various kinds of sunscreen materials are often used to prevent skin damage from UV exposure, these materials cannot block visible light or NIR.

Therefore, exposed skin should be protected with sunscreens that block not only UV, but also NIR radiation, in order to prevent overlying skin ptosis, photoaging and oncogenicity. Additional non-thermal studies are required to decipher the biological effects of NIR in humans.

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CASE REPORT

Primary cutaneous anaplastic large cell lymphoma with subsequent leg involvement

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Abstract

Primary cutaneous anaplastic large cell lymphoma (C-ALCL) is regarded as an indolent type of cutaneous T-cell lymphoma. However, a few recent publications revealed that C-ALCL patients with initial leg involvement had significantly worse survival than those without initial leg involvement. Herein, we report a case of C-ALCL with subsequent leg involvement, which led to death after chemoradiation therapy. A 75 years old Japanese man presented with multiple erythematous nodules in his left arm and the side of his left chest. Histopathological and immunohistochemical studies led to the diagnosis of primary C-ALCL. At the initial diagnosis, no leg lesion was found. One year after the initial diagnosis, C-ALCL appeared in his right lower thigh and left hip. Radiation therapy, low-dose etoposide and CHOP therapy were performed; however, the patient died of malignant lymphoma 4 years after the initial diagnosis. We speculated that the occurrence of subsequent leg involvement may also be indicative of a worse prognosis, as in the case with initial leg involvement in C-ALCL. Therefore, we propose that C-ALCL patients with initial or subsequent leg involvement should be classified as a distinct clinicopathological variant of C-ALCL ("*leg-type*" involvement) and that they may require intense therapy.

Key words: Cutaneous lymphoma; Cutaneous CD30-positive T-cell lymphoproliferative lesion; Primary cutaneous anaplastic large cell lymphoma; Leg involvement; Prognosis; Chemotherapy

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INTRODUCTION

Primary cutaneous anaplastic large cell lymphoma (C-ALCL) is a member of the primary cutaneous CD30-positive T-cell lymphoproliferative disorders group, which is the second most common type of cutaneous T-cell lymphoma[1]. The prognosis of C-ALCL is usually favorable, with a 10 year disease-related survival of approximately 90%[1]. However, a few recent publications revealed that C-ALCL patients with leg involvement had worse survival than those without leg involvement[2,3].

Herein, we report a case of C-ALCL with subsequent leg involvement, which led to death after chemoradiation therapy.

CASE REPORT

A 75 years old Japanese man, with no evidence of im-

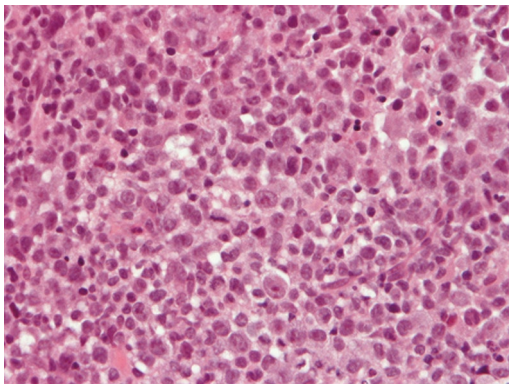

Figure 1 Histopathological finding of the erythematous nodule from the left arm. Diffuse infiltrate of large atypical lymphocytes containing large nuclei with prominent nucleoli in the dermis (original magnification, × 400).

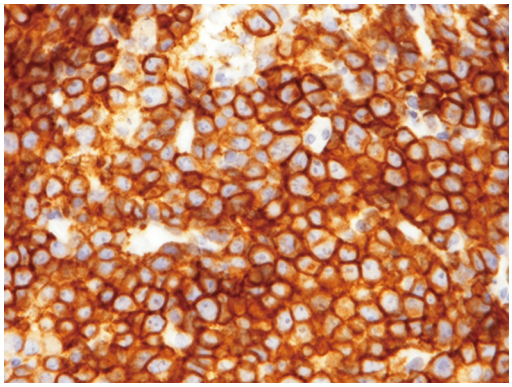

Figure 2 Immunohistochemical findings. CD30 is expressed in the large atypical lymphocytes (original magnification, × 400).

munosuppression, presented with multiple erythematous nodules in his left arm and the side of his left chest. The biopsy specimen from his left arm nodule revealed diffuse infiltrate with cohesive sheets of large atypical lymphocytes without epidermotropism in the dermis. These atypical lymphocytes had large round to oval nuclei with prominent nucleoli and rich eosinophilic cytoplasm (Figure 1). Immunohistochemically, the atypical lymphocytes expressed CD3, CD4, CD30 and epithelial membrane antigen (Figure 2). Granzyme B and T cell intracellular antigen-1 were also expressed in some of the atypical lymphocytes but they were negative for CD15, CD56 and anaplastic lymphoma kinase protein. These histopathological and immunohistochemical findings were typical for C-ALCL. In addition, gene analysis revealed clonal rearrangement of the T cell receptor C β gene. Physical examination and systemic computed tomography did not reveal any lymph node and visceral lesions. All these findings led to the diagnosis of primary C-ALCL. At the initial diagnosis, no leg lesion was found.

After the diagnosis, resection of the nodules and radiation therapy were performed. During the medical follow-up, some nodules showed spontaneous remission.

One year after the initial diagnosis, erythematous nodules appeared in his right lower thigh and left hip, although the erythematous nodules in his arm and chest had mostly disappeared. The histopathological and immunohistochemical features of his right lower thigh specimen were the same as those of the first biopsy specimen. Radiation therapy and administration of low-dose etoposide were performed; however, the nodules continued to enlarge and increase in number. CHOP therapy was added but the patient died of malignant lymphoma 4 years after the initial diagnosis.

DISCUSSION

Primary C-ALCL is regarded as an indolent type of cutaneous T-cell lymphoma[1]. Risk factors that predict an unfavorable course in patients with C-ALCL are largely unknown. However, previous studies suggested that patients who are older than 60 years of age and have multifocal skin lesions and the absence of spontaneous remission show correlation with unfavorable prognosis. Recently, Benner and Willemze[2] analyzed the clinical outcome of 18 cases of C-ALCL with generalized skin lesions. Three of 11 cases with leg involvement at initial presentation died of malignant lymphoma, compared with none of the 7 cases without any initial leg involvement. In addition, in the patients with a regional skin lesion, initial leg involvement was associated with reduced 5 years disease-specific survival[2]. These results indicate that C-ALCL patients with initial leg involvement have significantly worse survival than those without initial leg involvement. However, they did not present any data regarding whether subsequent leg involvement, as seen in the present case, shows a poor prognosis or not. We speculate that the occurrence of subsequent leg involvement may also be indicative of a worse prognosis, as in the case with initial leg involvement in C-ALCL.

Moreover, Benner and Willemze emphasized that C-ALCL patients with regional and generalized skin lesions that involve the leg should be monitored very closely and may require systemic chemotherapy at an earlier phase of disease progression[2], although the therapeutic guideline created by Bekkenk *et al*[4] indicates that in patients with regional skin lesions, excision and radiotherapy are the first choice of treatment, whereas in patients with multiple lesions, low-dose oral methotrexate and/or radiotherapy are preferred.

In conclusion, if dermatologists encounter a patient with subsequent leg involvement, as seen in the present case, careful observation is expected to determine whether the patient will show an aggressive clinical course or not. Further clinicopathological studies are needed to clarify the therapeutic strategies for C-ALCL with subsequent leg involvement.

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New York, NY 10017, United States

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León, Spain

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Australasian College of Dermatologists 45th Annual Scientific Meeting 2012
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Alabama Dermatology Society Seminar in the City
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"Preliminary Program" - 13th Congress of the German Society for Veterinary Dermatology
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Cosmetic Bootcamp 8th Annual Didactic and Live Technique Symposium 2012
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GENERAL INFORMATION

World Journal of Dermatology (*World J Dermatol*, *WJD*, online ISSN 2218-6190, DOI: 10.5314) is a bimonthly peer-reviewed, online, open-access (OA), journal supported by an editorial board consisting of 110 experts in dermatology from 34 countries.

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Maximization of personal benefits

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)
16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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