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Ultraviolet Radiation in Wound Care: Sterilization and Stimulation

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Significance: Wound care is an important area of medicine considering the increasing age of the population who may have diverse comorbidities. Light-based technology comprises a varied set of modalities of increasing relevance to wound care. While low-level laser (or light) therapy and photodynamic therapy both have wide applications in wound care, this review will concentrate on the use of ultraviolet (UV) radiation.

Recent Advances: UVC (200–280 nm) is highly antimicrobial and can be directly applied to acute wound infections to kill pathogens without unacceptable damage to host tissue. UVC is already widely applied for sterilization of inanimate objects. UVB (280–315 nm) has been directly applied to the wounded tissue to stimulate wound healing, and has been widely used as extracorporeal UV irradiation of blood to stimulate the immune system. UVA (315–400 nm) has distinct effects on cell signaling, but has not yet been widely applied to wound care.

Critical Issues: Penetration of UV light into tissue is limited and optical technology may be employed to extend this limit. UVC and UVB can damage DNA in host cells and this risk must be balanced against beneficial effects. Chronic exposure to UV can be carcinogenic and this must be considered in planning treatments.

Future Directions: New high-technology UV sources, such as light-emitting diodes, lasers, and microwave-generated UV plasma are becoming available for biomedical applications. Further study of cellular signaling that occurs after UV exposure of tissue will allow the benefits in wound healing to be better defined.

Abbreviations and Acronyms

6,4-PPs = pyrimidine 6,4-pyrimidone photoproducts
8-oxodG = 8-oxo-7,8-dihydroxyguanine
AD = atopic dermatitis
ASCs = adipocyte-derived stem cells
ATM = AT-mutated
BB = broad band
BER = base excision repair
bFGF = basic fibroblast growth factor
COX-2 = cycloxygenase-2
CPDs = cyclobutane pyrimidine dimers
ERK = extracellular-regulated kinase
GaN = gallium nitride
IL = interleukin
JNK = c-Jun N-terminal kinase
(*continued*)

SCOPE AND SIGNIFICANCE

WOUND HEALING IS A COMPLEX, but well-coordinated process that involves multiple tissue types influenced by local as well as systemic components.[1] Wounds and wound-healing abnormalities cause a great deal of physical and psychological discomfort and morbidity to affected patients. Therefore, newer paradigms are required, which are non-toxic, minimally invasive, and economically feasible for improving wound healing. During the past few years, many potential therapies and approaches have been tested in wound care. Light-based technology is a set of growing modalities in wound care. While low-level laser (or light) therapy (LLLT) and photodynamic therapy (PDT) both have wide applications to wound care, this

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review will concentrate on the use of ultraviolet (UV) radiation. The UV part of the spectrum corresponds to electromagnetic radiation with a wavelength (100–400 nm) shorter compared with visible light (400–700 nm), but longer than X-rays (<100 nm). UV radiation is divided into four distinct spectral areas, including vacuum-UV (100–200 nm), UVC (200–280 nm), UVB (280–315 nm), and UVA (315–400 nm).[2] This division allows the distinction between the effects of solar and artificial UV exposure on living species. Wavelengths <290 nm are blocked by stratospheric ozone; so there is no natural exposure to UVC. UVB penetrates the ozone layer and constitutes 5%–10% of the terrestrial solar UV radiation. Radiation in the UVA range is by far the most abundant solar UV radiation (>90%) that reaches the surface of earth. UVA penetrates human skin more efficiently than UVB (Fig. 1).[3] UV radiation has both beneficial and harmful effects depending upon the type of organism, wavelength region (UVA, B, or C), and irradiation dose (intensity×duration).[4] In this review, we will discuss the effects of UV irradiation on skin cells *in vitro*, UV-induced damage and its repair, potential effects of UV irradiation for treatment of microbial infected wounds, especially those caused by antibiotic-resistant pathogens, effects of UV irradiation on wound healing, UV phototherapy for dermatological and other disorders, novel UV light sources to improve selective penetration and reduce the side effects, and future developments.

TRANSLATIONAL RELEVANCE

The effects of UV irradiation on tissue include a consecutive series of events starting with the absorption of the photons by chromophores in the skin (photoexcitation), followed by photochemical reactions, which induce molecular changes in cell and tissue biology and affect signaling networks. UV irradiation may cause both beneficial and damaging effects, which depend on wavelength, radiant exposure, and the UV source. Low-dose UVB exposure induces the production of vitamin D in the skin.[5] Recently, studies have shown that irradiation of cultured cells with UV activates genes that influence cell division and immune responses.[4,6] It is hypothesized that judicious UV exposure might be beneficial for wound healing and restoration of skin homeostasis besides its anti-inflammatory and antioxidant effects.[6,7] UV light has been investigated as a potential modulator of keratinocyte–melanocyte cross talk in promoting wound healing.[7]

CLINICAL RELEVANCE

The increasing emergence of antibiotic resistance in diverse classes of pathogens presents an inexorably growing and serious clinical challenge. UV irradiation has been investigated as an alternative approach for prophylaxis and treatment of infectious diseases, especially those caused by antibiotic-resistant pathogens.[8] UV should be used in a way whereby, the side effects are minimized and the induction of resistance of microorganisms to UV is avoided. As a result, more extensive animal studies and clinical studies are warranted to investigate and optimize the UV dose regimen for maximal beneficial biological effects.[4,8] Further, it has been proposed that moderate UV exposure should be commenced early in the healing process of cutaneous wounds.[7]

DISCUSSION OF FINDINGS AND RELEVANT LITERATURE

Effect of UV irradiation on skin cells *in vitro*

UV irradiation includes a sequential series of events starting with the

Abbreviations and Acronyms (*continued*)

KGFs = keratinocyte growth factors
LED = light emitting diode
LILT = low-intensity laser therapy
MAPKs = mitogen-activated protein kinases
MF = mycosis fungoides
MRSA = methicillin-resistant *Staphylococcus aureus*
MSH = melanotropin
NB = narrow band
NER = nucleotide excision repair
PDGF = platelet-derived growth factor
PDT = photodynamic therapy
PGE = prostaglandin
PI = phosphatidylinositol
ROS = reactive oxygen species
SOD = superoxide dismutase
TGF-α = transforming growth factor-α
TNF = tumor necrosis factor
US = ultrasound
UV = ultraviolet
VEGF = vascular endothelial growth factor
XeCl = xenon chloride

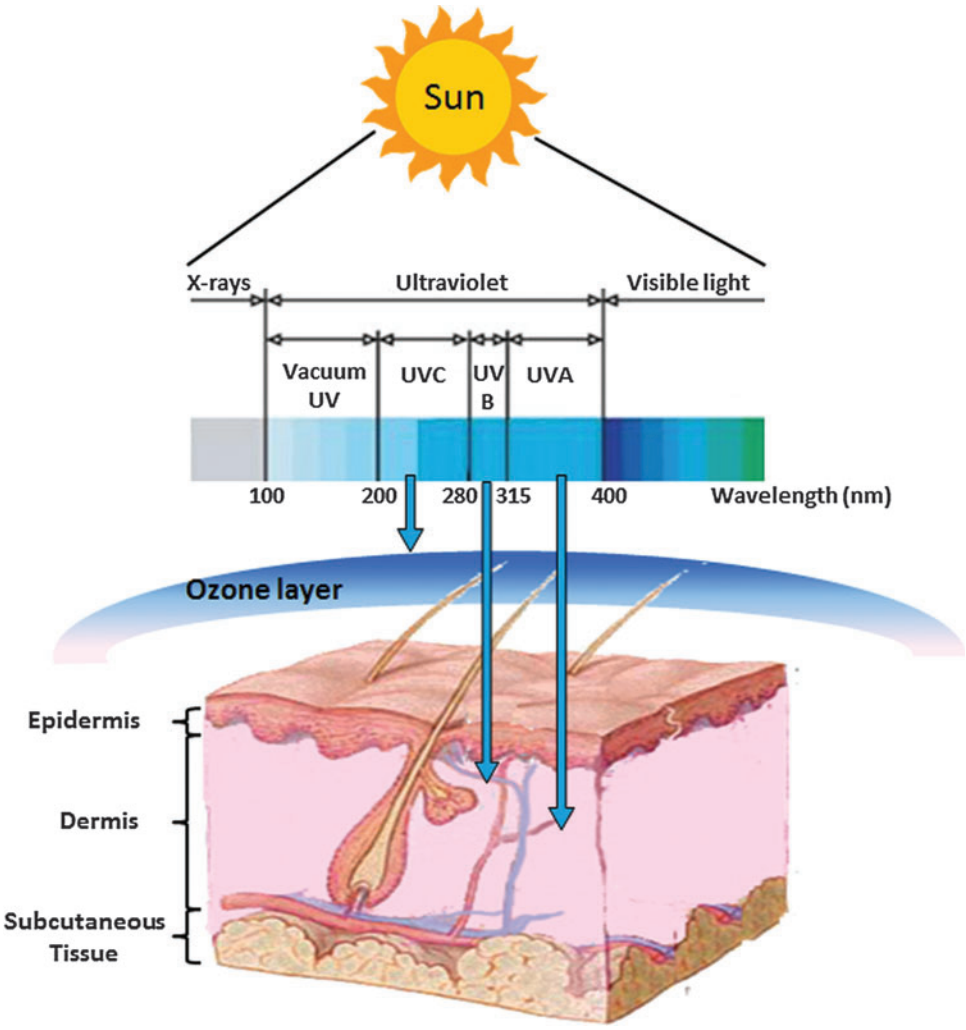

Figure 1. Spectrum of ultraviolet (UV) light and wavelength-dependent penetration of UV in the skin. Highly energetic UVC is nearly completely blocked by the ozone layer. The depth of the penetration through the epidermal layers increases with wavelength since the highly energetic shorter wavelengths are scattered and absorbed to a greater extent. Therefore, UVB mainly reaches the epidermis, while the less energetic UVA rays also affect the dermal skin layers. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

absorption of the radiation by chromophores in the skin, followed by photochemical reactions, which induce molecular changes in cell and tissue biology and affect signaling networks. The biological effect induced by UV radiation activates different signal pathways in a time-, dose-, and wavelength-specific manner.[9,10] The hypothesis is that UV wavelength-specific action spectrum is stemmed from distinct direct damages to various biomolecules.[9] The major cellular chromophores that absorb in the UVB range are nucleic acids (DNA and RNA) and proteins (mainly tryptophan and tyrosine amino acids) and other biomolecules like NADH, quinones, flavins, porphyrins, 7-dehydrocholesterol, and urocanic acid. Several molecular changes and signaling pathways are activated upon UV irradiation and the eventual fate of the UV-exposed cell will be decided by the severity of the damage. Simultaneously, intercellular communication is affected following UV irradiation producing inflammatory and proliferative responses. Keratinocytes, the main cell type in the epidermis, form a self-renewing epithelial barrier to protect the skin against environmental hazards, while melanocytes, located in the basal layer of the epidermis, are dendritic-like pigment-producing cells, which protect keratinocytes against the DNA-damaging effects of UVB irradiation through production of melanin (Fig. 2).[11] In the epidermis, melanocytes are distributed in an orderly and spatial manner and melanocyte mitosis rarely occurs. However, under certain conditions, such as wound healing, UV radiation causes proliferation of melanocytes.[12,13] Keratinocyte-derived growth factors such as basic fibroblast growth factor (bFGF), nerve growth factor, and melanocyte stimulating hormone-alpha

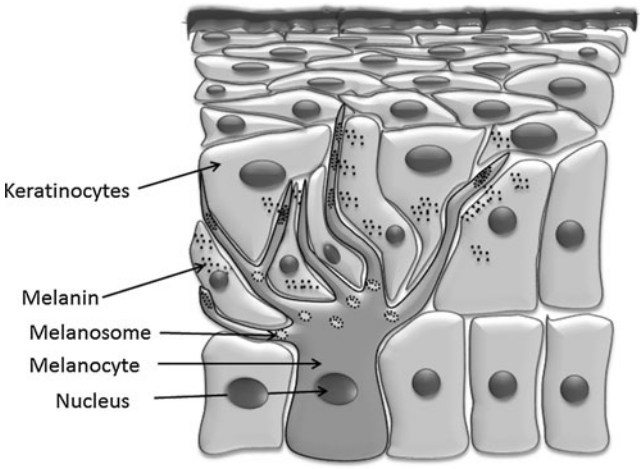

Figure 2. Keratinocyte–melanocyte cross talk, which can be stimulated by UV and facilitate wound healing. Melanocytes are known to secrete a variety of keratinocyte growth factors and cytokines like interleukin (IL)–1, IL-6, IL-8, and transforming growth factor-α following UV stimulation, all of which induce mitogenic activity in epidermal keratinocytes.

stimulate melanocyte growth, and regulate both the distribution and morphology of melanocytes, and stimulate production of melanin.[13,14] Interestingly, keratinocyte-induced melanocyte proliferation cannot be substituted by the keratinocyte-conditioned medium, but rather requires close cell-to-cell contact in which melanocytes interact via dendritic processes with adjacent keratinocytes.[7] There is some evidence that in turn, keratinocyte proliferation, which is essential for wound closure can be stimulated by melanocytes.[7] Melanocytes are known to secrete a variety of keratinocyte growth factors (KGFs) and cytokines like interleukin (IL)–1, IL-6, IL-8, and transforming growth factor alpha (TGF-α) following UV stimulation, all of which induce mitogenic activity in epidermal keratinocytes. Further, keratinocyte proliferation is stimulated by melanotropin (MSH), secreted in both autocrine as well as paracrine fashion by neighboring melanocytes and based on this fact, it can be speculated that this mitogenic effect may be enhanced by UV exposure since MSH receptors on keratinocytes are upregulated following UV irradiation.[13,15]

Evidence suggests that following UV exposure, a rapid cellular antioxidant response is induced since hemeoxygenase-1,[16] ferritin,[17] glutathione peroxidase, Cu-Zn–dependent superoxide dismutase (SOD1), mitochondrial manganese-dependent superoxide dismutase (SOD2), and catalase[18] upregulation were shown following UV irradiation in cultured human dermal fibroblast cells.[19] Exposure of human keratinocytes to physiologic doses of UVB activates epidermal growth factor receptor/extracellular-regulated kinase 1 and 2 (ERK1/2) and p38 signaling pathways via reactive oxygen species (ROS).[20,21] In cultured normal human keratinocytes, UVA irradiation was observed to trigger ceramide signaling cascade through oxidative phospholipid degradation by singlet oxygen ($^1O_2$), which resulted in AP-2 transcription factor activation and induction of intracellular adhesion molecule-1 expression.[22]

It has been demonstrated that UV exposure results in dose-dependent increased production of immunomodulating cytokines (IL-1, IL-3, IL-6, and tumor necrosis factor [TNF]) and granulocyte-/macrophage-colony–stimulating factor by epidermal cells. The production of such immunoinhibitors might be playing an essential role during systemic UV-induced immunosuppression.[23] In a study on cultured human keratinocytes, it has been demonstrated that UVB irradiation upregulates IL-1α mRNA at a lower dose (15 mJ/cm^2), but downregulates at high doses (30–40 mJ/cm^2).[24] Further, IL-12, IL-18, and IL-23 have all been shown to reduce cutaneous DNA damage and inhibit the activity of T-regulatory cells and, hence, to inhibit the immunosuppression that follows UV most probably through activation of nucleotide excision repair (NER).[25]

It has been reported that UV irradiation produces an increase in the number of DNA-synthesizing cells about 48 h after the stimulus.[26] The same authors suggested that prostaglandin (PGE), a putative mediator of UV-induced inflammation, may be one of the chemical mediators for the UV-induced increase in DNA-synthesizing cells and the erythema.[27] Further, histamine may also contribute to the increase in DNA-synthesizing cells and the erythema.[26] When expression of cycloxygenase-2 (COX-2), the rate-limiting enzyme in the production of PGE, in UVA-irradiated human keratinocyte cells was examined, it was shown that p38 appears to play a critical role in the UVA-induced expression of COX-2. UVA irradiation was demonstrated to cause activation of transcription factors; namely, nuclear factor kappa-B[28] in human skin fibroblasts, and AP-1[29] and AP-2[30] in cultured fibroblasts, and in most cases $^1O_2$ is held responsible for UVA radiation–induced gene expression in human keratinocytes and fibroblasts.[30]

Increased blood flow changes in human skin following UV irradiation at both 250 and 300 nm have been measured.[31] However, in case of superficial vessels, following low doses of both wavelengths a slight increase in blood flow, and following higher doses, a marked reduction in blood flow was observed. This reduction was attributed to

the stasis in these superficial vessels, perhaps, secondary to vascular damage.[31] The keratinocyte-derived vascular endothelial growth factor (VEGF, also known as VPF or vascular permeability factor) provides the major cutaneous angiogenic activity in epidermal keratinocytes and its overexpression results in hyperpermeable dermal capillaries.[32] A study by Gille *et al.* on immortalized keratinocyte cell lines demonstrated that, while UVB-mediated VEGF expression are conveyed by indirect mechanisms, UVA rapidly induces VEGF mRNA expression in a fashion comparable to that seen with the TGF-α, indicating a direct and potent activator of VEGF gene transcription.[33]

A recent study worth mentioning here for the first time demonstrated that low-dose UVB (10 or 20 mJ/cm^2) preconditioning can stimulate the hair growth promoting capacity of adipocyte-derived stem cells (ASCs), which have paracrine actions on surrounding cells through secretion of multiple growth factors (VEGF, bFGF, KGF, and platelet-derived growth factor [PDGF]).[34] In a previous study, hypoxia through generation of ROS was shown to increase the survival of human ASCs, and the conditioned medium derived from hypoxia-preconditioned ASCs supported endothelial cell survival and endothelial tube formation.[35] Hypoxia preconditioning also enhanced the wound-healing capacities of ASCs.[36] Low-dose UVB pretreatment of ASCs *in vitro*, just as in hypoxia preconditioning, induced ASC survival, migration, angiogenesis, and growth factor stimulation and this was attributed to Nox4-induced ROS generation.[34] Upon absorption of UVB photons, 7-dehydrocholesterol located within keratinocytes is converted to previtamin D3, which is then isomerized to vitamin D3 and later on converted to active form of vitamin D—1,25$(OH)_2$D. 1,25$(OH)_2$D in the skin activates innate immune responses, such as the production of antimicrobial peptides, which can enhance microbial killing and the stimulation of macrophage differentiation and phagocytosis.[37]

UV-induced damage and its repair

UV radiation is one of the most important kinds of environmental stresses for skin damage. Exposure to UV is known to induce clustering of some kinds of cell surface receptors and to transduce some cell survival and proliferation signals.[9,38] Activation of intracellular signaling pathways in response to UV radiation induces various transcription factors that transactivate genes involved in DNA repair, DNA synthesis, transcription, and cell cycle regulation.[9,10] Depending on the severity of the UV radiation exposure, a cell will first try to survive by undergoing growth arrest and repairing the damage, but when the induced damage is irreparable, it will initiate the apoptotic program. Exposure to solar UV causes erythema, immunosuppression, photoaging, DNA damage, gene mutation, and serves as a major etiological factor for skin cancer and which may cause (epigenetic) disturbances in signaling pathways.[6,39] Absorption of UVB results in the direct generation of DNA photoproducts, mainly in the form of cyclobutane pyrimidine dimers (CPDs), in addition to pyrimidine 6,4-pyrimidone photoproducts (6,4-PPs),[40] leaving a typical UVB fingerprint. Moreover, methylation of cytosine has been shown to strongly enhance the formation of dimers at pyrimidine bases when cells are exposed to UVB.[41] UVA penetrates human skin more efficiently than UVB. Unlike UVB, the UVA component of solar radiation is weakly absorbed by DNA, but instead excites other endogenous chromophores, generating various ROS in cells. UVA has oxidizing properties that can cause oxidative base damage (8-oxo-7,8-dihydroxyguanine [8-oxodG]), or enhance UVB's damaging effects on skin.[3,6] UV radiation can also induce a much wider range of DNA damage, such as protein–DNA crosslinks and single-strand DNA breaks.[39,42]

To counteract mutagenic and cytotoxic DNA lesions, organisms have developed a number of highly conserved repair mechanisms, such as photoreactivation, NER, base excision repair (BER), and mismatch repair.[42] UV-induced DNA lesions are mainly repaired enzymatically through NER that efficiently identifies 6,4-PPs and more slowly takes care of CPDs. Xeroderma pigmentosum patients lack this form of repair, and run a dramatically increased risk of skin cancer.[43] The oxidative DNA damage (8-oxodG) is repaired by the BER.[44] Additionally, double-strand break repair (by homologous recombination and nonhomologous end joining), S.O.S. response, cell cycle checkpoints, and programmed cell death (apoptosis) are also operative in various organisms with the expense of specific gene products.[42]

Recent findings shed light onto the molecular mechanisms of UV-induced apoptosis.[43,45] Excessive exposure of epidermal cells to UV results in apoptosis of irreparably photodamaged cells to avoid malignant transformation.[46] UV-induced apoptosis is a complex event involving different pathways, which include: activation of the tumor suppressor gene p53; triggering of cell death receptors directly by UV or by autocrine release of death ligands; mitochondrial damage and cytochrome C release. The extrinsic pathway through death receptors such as fibroblast-associated

TNF-receptor and TNF-related apoptosis inducing ligand receptor activate caspase cascade. The intrinsic or mitochondrial pathway of apoptosis is regulated by the Bcl-2 family of proteins, anti-apoptotic (Bcl-2, Bcl-xl, and Bcl-w) and the proapoptotic (Bax, Bak, and Bid). Recently, it has been shown that the Bcl-2 family of proteins is emerging as a crucial regulator of epidermal homeostasis and cell's fate in the stressed skin.[46]

Eukaryotic initiation factor 2a subunit (eIF2a-Ser51) phosphorylation occurs as a cellular response to various stimuli, and is implicated in cell proliferation and apoptosis.[47] It executes a key translational control mechanism following UV irradiation.[48] UVA, UVB, and UVC all induce a dose- and time-dependent phosphorylation of eIF2a-Ser51 through distinct signaling mechanisms.[48] It was shown in a recent study that, while UVA-induced eIF2a phosphorylation occurs through mitogen-activated protein kinases (MAPKs), including ERK, c-Jun N-terminal kinase (JNK) and p38 kinase, and phosphatidylinositol (PI)-3 kinase, UVB-induced eIF2a phosphorylation through JNKs and p38 kinase, but not ERKs or PI-3 kinase, whereas UVC-stimulated response to eIF2a phosphorylation is via JNKs alone.[48] In the same study, it has also been revealed that AT-mutated (ATM) kinase, which is also located at or near the beginning of multiple signaling pathways is involved in induction of the intracellular responses to UVA and UVB, rather than UVC.[48]

Further, ROS generated by UV irradiation was shown to be critical for signal transduction cascades such as MAPK (p38, ERK, and JNK).[21,49] p38 is an important inducer of cell cycle arrest and UV-induced double-strand breaks have also been shown to activate p38 through the DNA damage sensors ATM and Rad3-related protein kinase (ATR).[9,50] It is essential to realize that cell survival or death mechanisms are often concomitantly activated after UV and share common molecular mediators. Therefore, depending on the severity of the insult (*i.e.*, the UV dose), the cellular background, and additional microenvironmental factors, the balance between cell survival and death signals will eventually decide on the fate of the irradiated cell.[43]

Effects of UV irradiation on infected wounds

It has been known for the last 100 years that UV light (particularly UVC in the range of 240–280 nm) is highly germicidal; however, its use to treat wound infections remains at an early stage of development. Most of the studies are confined to *in vitro* and *ex vivo* levels, while *in vivo* animal studies and clinical studies are much rarer.[8] UV radiation causes lethal and mutagenic effects in microorganisms.[51] The high dose of UVC or UVB, can cause direct damage to nucleic acids and proteins that can lead to genetic mutation or cell death.[4] The mechanism of UVC inactivation of microorganisms is to cause cellular damage by inducing changes in the chemical structure of DNA chains.[52] The consequence is the production of CPD causing damage and distortion of the DNA molecule, which causes malfunctions in cell replication and rapidly leads to cell death. It has been reported that with appropriate doses, UVC can selectively inactivate microorganisms, while preserving viability of mammalian host cells and, moreover, is reported to promote wound healing.[8] Further, for treatment of wound infections, it is presumed that only limited numbers of repeated UVC irradiation doses would be required, while the UV-induced carcinogenic mutation is a long-term effect of prolonged use of UVC.[8]

Animal studies. There is a growing body of literature examining the antimicrobial effects of UVC irradiation at 254 nm. Using mouse models, Dai *et al.*[53] investigated the potential of UVC light for the prophylaxis of infections developing in highly contaminated superficial cutaneous wounds. Mouse models of partial-thickness skin abrasions infected with bioluminescent *Pseudomonas aeruginosa* and *Staphylococcus aureus* were developed. Approximately, 10^7 bacterial cells were inoculated onto wounds measuring 1.2 cm × 1.2 cm on the dorsal surfaces of mice. UVC light was delivered at 30 min after bacterial inoculation. It was found that for both bacterial infections, UVC light at a single radiant exposure of 2.59 J/cm^2 significantly reduced the bacterial burden in the infected mouse wounds by 10-fold in comparison to untreated wounds (Figs. 3 and 4).[53] Further, UVC light increased the survival rate of mice infected with *P. aeruginosa* (58%) and increased the wound-healing rate in mice infected with *S. aureus* (31%).

In another study, Dai *et al.*[54] investigated the use of UVC irradiation (254 nm) for treatment of *Candida albicans* infection in mouse third-degree burns. The *C. albicans* strain was stably transformed with a version of the *Gaussia princeps* luciferase gene that allowed real-time bioluminescence imaging of the progression of *C. albicans* infection. UVC treatment with a single exposure carried out on day 0 (30 min postinfection) gave an average 2.16-log$_{10}$ (99%) loss of fungal luminescence when 2.92 J/cm^2 UVC had been delivered, while UVC at 24 h postinfection gave 1.94-log$_{10}$ (96%) reduction of fungal luminescence after

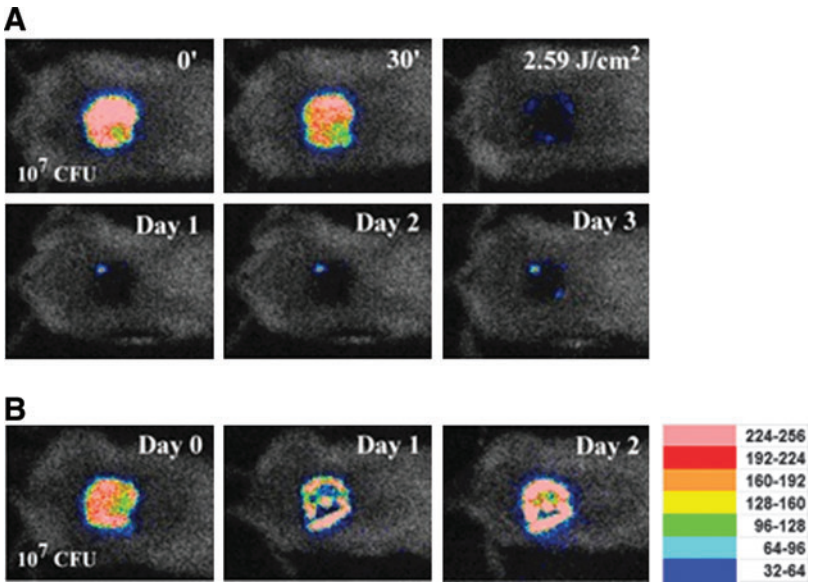

Figure 3. **(A)** Successive bacterial luminescence images of representative mouse skin abrasions infected with 10^7 colony-forming units of *Pseudomonas aeruginosa*, with UVC prophylaxis. Label 0′: the bacterial luminescence image taken immediately after the bacterial inoculation; label 30′: 30 min after bacterial inoculation and just before UVC irradiation; label 2.59 J/cm^2: after 2.59 J/cm^2 UVC light had been delivered. Labels Day 1, Day 2, and Day 3: 1 day (24 h), 2 days (48 h), and 3 days (72 h) after bacterial inoculation, respectively. **(B)** Successive bacterial luminescence images of representative mouse skin abrasion without UVC prophylaxis. Reprinted with permission from Dai *et al.*[53] To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

6.48 J/cm^2 (Fig. 5).[54] The UVC exposures were calculated at the surfaces of mouse burns. Statistical analysis demonstrated that UVC treatment carried out on both day 0 and day 1 significantly reduced the fungal burden of infected burns by 99% and 96%, respectively. UVC was found to be superior to a topical antifungal drug, nystatin cream.

Clinical studies. In a recent clinical study, the effect of UVC for the treatment of cutaneous ulcer infections has been investigated.[55] In this study, three patients were included; the first patient suffering from a diabetic ulcer, the second from a venous ulcer, and third from a recurrent ulcer all infected with methicillin-resistant *S. aureus* (MRSA). UVC irradiation (254 nm) was applied to each wound (for 180 s, irradiance 15.54 mW/cm^2). In addition to eradication of MRSA infection upon UVC exposure, progression toward wound closure as marked by presence of epithelial buds, improved

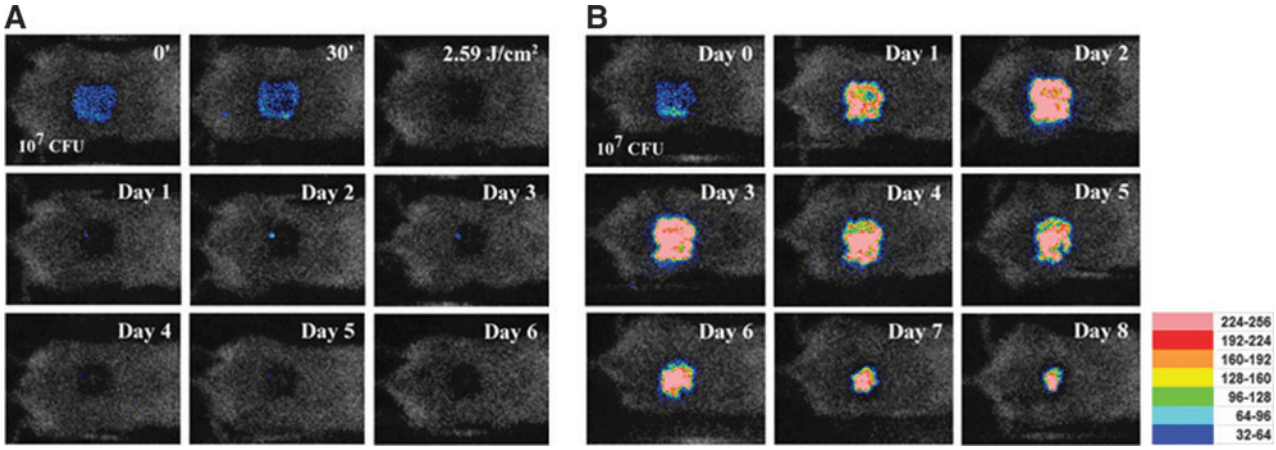

Figure 4. **(A)** Successive bacterial luminescence images of representative mouse skin abrasions infected with 10^7 colony-forming units of *Staphylococcus aureus*, with UVC prophylaxis. Label 0′: the bacterial luminescence image taken immediately after the bacterial inoculation; label 30′: 30 min after bacterial inoculation and just before UVC irradiation; label 2.59 J/cm^2: after 2.59 J/cm^2 UVC light had been delivered. Labels Day 1, Day 2, …, and Day 8: 1 day (24 h), 2 days (48 h),…, and 8 days (192 h) after bacterial inoculation, respectively. **(B)** Successive bacterial luminescence images of representative mouse skin abrasion without UVC prophylaxis. The original wound areas (borders) coincide with the areas emitting bacterial luminescence. Reprinted with permission from Dai *et al.*[53] To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

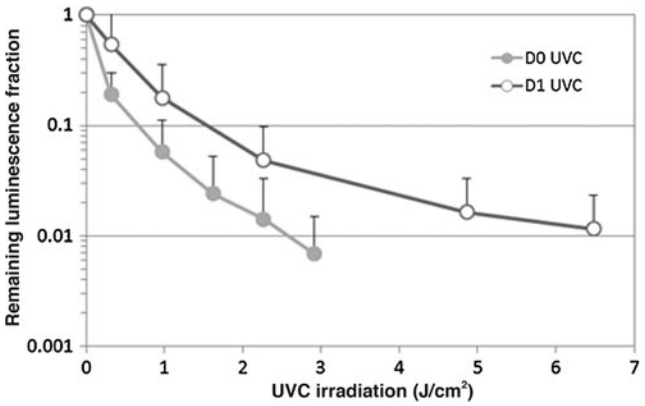

Figure 5. The correlations of mean fungal luminescence to the UVC dose. The mouse burns were infected with bioluminescent *C. albicans* and treated by use of a single UVC exposure on day 0 (30 min, $n=11$) and day 1 (24 h, $n=12$) postinfection, respectively. Reprinted with permission from Dai *et al.*[54]

epithelialization, return of normal skin color surrounding the wound, and the emergence of healthy granulation tissue was noted. Moreover, in the latter two cases, full wound closure was achieved. In a later study performed by the same group,[56] 22 patients with chronic ulcers exhibiting at least two signs of infection and critically colonized with bacteria received a single 180 s treatment of UVC. Semiquantitative swabs taken immediately before and after UVC treatment were used to assess changes in the bacterial bioburden present within the wound bed. A statistically significant reduction in the relative amount of bacteria following a single treatment of UVC was observed. The greatest reduction in semiquantitative swab scores following UVC treatment were observed for wounds colonized with *P. aeruginosa* and wounds colonized with only one species of bacteria. Significant reductions in the relative amount of bacteria also were observed in 12 ulcers in which MRSA was present.

One advantage of using UVC over antibiotics is that UVC can eradicate microorganisms much faster (a 2–3 $\log_{10}$ reduction of microorganism population *in vivo* could be achieved in < 1 h), while antibiotics usually take several days to take effect, especially in burns and other chronic wounds that frequently have impaired blood perfusion. UVC irradiation may also be much more cost effective than the commonly used antibiotics.

Effects of UV irradiation on wound healing

Wound healing is a highly dynamic, complex, but well-orchestrated physiological process that establishes the integrity of the damaged tissue. The healing involves different overlapping phases, including homeostasis, inflammation, granulation, fibrogenesis, re-epithelialization, neovascularization, and maturation/contraction.[1] The development of new and effective interventions in wound care remains an area of intense research. In the past few decades, the light-based technology is a set of growing modalities in wound care. Recently, the current opinion is shifting toward the idea that controlled UV exposure might in fact be beneficial for wound healing and skin homeostasis. The effectiveness of UV energy in producing biological changes depends on the chosen irradiation parameters, and it is important to select the maximal effective wavelength for a desired effect, which will allow the patient to benefit at the lowest irradiation level.[57] Varying biologic effects are correlated with the depth of penetration. UVA, for example, has the longest wavelength and penetrates to the levels of the upper dermis in human skin, and UVB only penetrates down to the statum basale; however, UVC only reaches the upper layer of the epidermis (Fig. 1).[58]

Exposure of the skin to UV produces erythema, epidermal hyperplasia, increased blood flow in the microcirculation, and also has a bactericidal effect.[26,59] The induced erythema initiates the first phase of healing (inflammatory phase) by creating an inflammatory response via the mechanism of vasodilatation. This may be partially explained by the effects of UV light on the arachidonic acid pathway.[60] In addition, UV light exposure induces cellular proliferation in the stratum corneum.[61] This proliferation/thickening of the skin is a protective mechanism against further sunlight damage. UV avoidance and use of sunscreens are commonly advised during the re-epithelialization process as well as after wound closure. However, it is possible that the currently accepted practice of UV protection prevents the normal cutaneous response to injury, with melanocyte redistribution and pigmentation creating hypopigmented scars.[7]

Previous studies reported that UVC light *per se* could stimulate wound healing. It was found that UVC light-induced fibronectin release led to increased healing via wound contraction.[62] Fibronectin promotes cell migration and helps regulate cell growth and gene expression. Growth factors are released from epidermal cells exposed to UV irradiation, which further augments the healing cascade.[63] UV is absorbed directly by extracellular fluid components and capillaries.[27] This absorption promotes endothelial cell proliferation,[26] and induced the expression of VEGF[64] followed by temporary epidermal hyperplasia and

increase in epidermal thickness, enhanced re-epithelialization or de-squamation of the leading edge of peri-ulcer epidermal cells, granulation tissue,[65] release of PGE, which play a role in UV-induced erythema and may mediate cell proliferation,[26] histamine release, which contributes to the increased skin blood flow,[31] increased vascular permeability, which leads to cellular elements of repair in the dermis early as 30 min following UV exposure and a delayed erythema a few hours later,[66] initial decrease and after a few days an accelerated rate of DNA, RNA, and protein synthesis, which contributes to skin thickening as a late-phase response,[26] and bacterial cell inactivation.[59,67]

Animal studies. Kaiser *et al.* used a porcine model to demonstrate that UV radiation stimulates the production and release of IL-1 by keratinocytes, which augmented the rate of healing of partial-thickness wounds.[68] IL-1 enhances wound epithelialization via keratinocyte chemotaxis and proliferation as well as the proliferation of fibroblasts. Suo *et al.* investigated the effect of UVC (254 nm) on the expression of TGF-β on full-thickness dermal wounds in rats.[69] Treatment was daily for 3 successive days with 15 or 60 mJ/cm^2 UVC irradiation. Expression of TGF-β at day 7 postwounding in the wounds treated with 15 mJ/cm^2 UVC was found to be higher than those treated with 60 mJ/cm^2. However, at day 21, expression of TGF-β in the wounds treated with 60 mJ/cm^2 UVC became much higher than 15 mJ/cm^2. The same group studied the effect of UVC irradiation on the expression of bFGF in full-thickness dermal wounds in rats. Expression of bFGF in the wounds treated with 60 mJ/cm^2 UVC was higher than 15 mJ/cm^2 and nonirradiated control wounds at day 7 postwounding.[70] On day 14, bFGF expression in the wounds treated with 60 mJ/cm^2 was significantly decreased and was lower than the wounds treated with 15 mJ/cm^2 and controls. These studies concluded that, at early stage of wounding UVC treatment, certain radiant exposure parameters promoted expression of TGF-β and bFGF in granulation tissues and was beneficial for accelerating wound healing. Further, acute and chronic effects of UVC exposure might also vary with different irradiation parameters.

When the effect of UV exposure (in range of 250–400 nm) and irradiation intensity (7.1 mW/cm^2 for UVA and 1.7 mW/cm^2 for UVB) on wound healing was studied in rat skin, a dose-dependent, significant improvement in wound contraction was observed between 4 and 15 days in wounds treated with UV as compared with untreated control wounds in the opposite side of the same animals.[71] However, wound closure did not occur earlier in treated wounds, nor did irradiation have any effect on the clinical infection rate or bacterial colonization of the wounds.[71] Basford *et al.* compared He-Ne laser (632.8 nm), UVC (254 nm, E1 level, delivered twice daily), occlusion, and air exposure in wound healing in a swine model. They demonstrated that even though wounds in all treatment groups showed a tendency to heal faster than exposed wounds, results for only occluded wounds were clinically significant.[72] Although the authors concluded that there was no advantage in using either laser or UV treatment, it is unfortunate that they did not assess the effect of each modality combined with occlusion, since optimum clinical conditions appear to be dependent on a moist wound surface.[73,74] It is important to note that in the same study, in 8 of 12 treated wounds and 12 of 24 untreated wounds of the UV-exposed pigs, clinically reduced hypertrophic healing on the same animal was observed, which is an indicator that UVC has systemic effects.[72]

Clinical studies. There have been a few human clinical trials on wound healing using UV therapy (Table 1). Unfortunately, it is difficult to draw strong conclusions or compare the articles as different wavelengths were used at various treatment times and distances from the wound surface. The first clinical study on the effect of UV on wound healing goes back to 1965. In this study, Freytes *et al.* investigated the use of UVC irradiation of 254 nm emitted from a mercury vapor lamp for the treatment of three patients who were suffering from indolent ulcers.[75] The ulcerated area was exposed to UVC for 150 s and treatments were repeated once each week. The first patient had a deep ulcer with 25.4 mm (1 inch) diameter, and following four treatments, the diameter of the ulcer reduced to 6.35 mm (0.25 inches). The second patient had an ulcer with a diameter of 63.5 mm (2.5 inches), and after four treatments, complete healing was achieved. The third patient had a decubitus ulcer, which was resistant to conventional treatments and had a diameter of 51 mm (2 inches) and was 6.35 mm (0.25 inches) in depth. At the end of the fifth treatment, the ulcer was 12.7 mm (0.5 inches) in diameter with a clean and healthy granulation tissue.

The effectiveness of UV light (combination of UVA, UVB, and UVC) has been demonstrated in a randomized placebo-controlled trial.[76] Sixteen patients suffering from superficial pressure sores (< 5 mm deep) were treated two times per week

Table 1. *Potential applications of ultraviolet phototherapy for wound care and skin disorders*

UV Phototherapy	*UV Spectrum/Dosage*	*Types of Wounds/Skin Pathologies*	*Setting*	*Study Findings*	*Ref.*
UVC	254 nm; single radiant exposure of 2.59 J/cm^2	Partial-thickness skin abrasion infected with *Pseudomonas aeruginosa* and *Staphylococcus aureus*	*In vivo*	Significantly reduced bacterial burden in the infected mouse wounds by 10-fold in comparison to untreated wounds; increased the survival rate of mice infected with highly virulent bacteria, and increased the wound-healing rate	53
UVC	254 nm; single radiant exposure either with 2.92 or 6.48 J/cm^2	Third-degree dermal burn wound infected with *Candida albicans*	*In vivo*	Significantly reduced fungal burden of infected burns by 96%–99%; superior to a topical antifungal drug, nystatin cream	54
UVC	254 nm; a single 180 s treatment of UVC lamp, irradiation 15.54 mW/cm^2, placed 1 inch from the wound bed	22 patients with chronic ulcers infected and critically colonized with bacteria	Clinical	UVC can kill bacteria such as *P. aeruginosa, S. aureus,* and methicillin-resistant *S. aureus* present in superficial layers of chronic wounds	56
UVC	254 nm; treatment daily for 3 successive days with 15 or 60 mJ/cm^2 irradiation	Full-thickness dermal wounds	*In vivo*	At early stage of healing UVC treatment, at certain radiant exposure parameters promoted expression of TGF-β and bFGF in granulation tissues; beneficial for accelerating wound healing	69,70
Combination of UVA, UVB, and UVC	UV light treatment two times per week	16 patients suffering from superficial pressure sores; a randomized placebo-controlled trial	Clinical	UV-treated group, mean time to healing was 6.3 weeks vs. 8.4 weeks for placebo group	76
UVC	UV irradiation three times per week for 6 weeks	Exudative decubitus ulcers	Clinical	Significant reduction in the amount of exudates produced by the decubitus ulcers; and improvement in their appearance and depth	77
A combination of US and UVC treatment	US (3 MHz, 0.2 W/cm^2)/UVC (95% emission at 250 nm); applied five treatments weekly	Pressure ulcers in patients with spinal cord injury	Clinical	Combined US and UVC treatment was more effective on wound healing than nursing care alone or laser light therapy	57
Multimodel phototherapy combining LILT and UVC irradiation	LILT (820 nm, 140 mW/cm^2, 2 J/cm^2 and 660 nm, 120 mW/cm^2 and 4 J/cm^2) and UVC irradiation (95% emission at 250 nm, E1 dose for 15 s; and E3 dose for 90 s	Infected postoperative diabetic foot ulcer	Clinical	Infected wound healed completely, in 3-month follow-up period, there was no recurrence of the ulcer	78
UVA1	340–400 nm; medium dose = 40–80 J/cm^2; 15 exposures	Atopic dermatitis; randomized controlled trials	Clinical	Immunomodulatory effects, including apoptosis of infiltrating T-cells, suppression of cytokine levels, and reduction in Langerhans cell numbers	79,80
UVA1	340–400 nm; medium dose = 40–80 J/cm^2 and/or high dose = 80–130 J/cm^2; 20–40 exposures	Localized scleroderma (morphea); randomized controlled trials	Clinical	Efficacy through increased production of MMP-1 and IFN-γ, and to a lesser extent by decreasing TGF-β and collagen production	79,81,83
NB UVB	308 nm XeCl excimer laser and the 308 nm XeCl excimer lamp; lesions were treated twice weekly with the same dose; 24 sessions	Vitiligo; randomized monocentric study	Clinical	Two treatments showed similar results in terms of efficacy for a repigmentation of at least 50%; lamp induced more erythema than the laser	86
PUVA (8-methoxypsoralen plus UVA) and both NB and BB UVB	medium dose = 40–80 J/cm^2 and/or high dose = 80–130 J/cm^2; 20–40 exposures	Mycosis fungoides (cutaneous T-cell lymphoma); open studies	Clinical	Safe and effective treatment options for early stages of the disease	87
308 nm XeCl laser treatment, PUVA, and combined UVA-UVB	Combined low-dose UVB, low-dose UVA, and visible light; intranasal phototherapy; randomized, double-blind study	Allergic rhinitis	Clinical	Effective in reducing symptom scores for sneezing, rhinorrhea, nasal itching, and the total nasal score in ragweed allergic patients, mechanism of action, it reduces the antigen presenting capacity of dendritic cells, induces apoptosis of immune cells, and inhibits synthesis and release of proinflammatory mediator from several cell types	85

UV, ultraviolet; TGF, transforming growth factor; bFGF, basic fibroblast growth factor; LILT, low-intensity laser therapy; MMP-1, matrix metalloproteinase 1; IFN-γ, interferon gamma; NB, narrow band; XeCl, xenon chloride; BB, broad band.

compared to control patients who received the same light; however, a mica cap was left over the quartz window, effectively blocking all UV radiation. In the UV-treated group, mean time to healing was 6.3 weeks, whereas mean time to healing was 8.4 weeks for the placebo group. In this study, it is worth mentioning that the difference persisted unchanged when each patient's age and the initial size of the sore were taken into account by an analysis of covariance.[76] Onigbinde *et al.* examined the effect of UVB radiation on exudative decubitus ulcers.[77] Decubitus ulcers on the left lower extremities were the experimental limbs and were exposed to UV radiation three times per week for 6 weeks as adjunct, while the right lower limbs served as control and received only the saline wet-to-moist wound dressing. Not only was there a significant reduction in the amount of exudates produced by the decubitus ulcers, but there was also significant improvement in their appearance and depth.[77]

Standard wound care was compared to ultrasound (3 MHz, 0.2 W/cm^2)/UVC (95% emission at 250 nm) combination and red/near infrared laser treatment (820 nm laser diode and 30 superluminous diodes 10 each at 660, 880, and 950 nm, 4 J/cm^2) in treatment of pressure ulcers, where ultrasound/UVC combination was applied five treatments weekly, alternating the treatment modality daily, and laser was applied three treatments weekly. The results indicated that a combination of ultrasound and UVC treatment was more effective on wound healing than nursing care alone or laser light therapy.[57]

UV irradiation has also been shown to be effective in other types of ulcers, such as diabetic ulcers,[55,78] arterial and venous insufficiency related ulcers.[55] A recent case report on an infected postoperative diabetic foot ulcer showed that after 23 sessions of multimodel phototherapy combining low-intensity laser therapy (820 nm, 140 mW/cm^2, 2 J/cm^2 and 660 nm, 120 mW/cm^2 and 4 J/cm^2) and UVC irradiation (95% emission at 250 nm, E1 dose for 15 s at a lamp distance of 2.5 cm for granulation tissue; and E3 dose for 90 s at a lamp distance of 2.5 cm for infected tissue), not only infected wound healed completely, but also during the 3-month follow-up period, there was no recurrence of the ulcer.[78]

UV phototherapy for skin and other disorders

Broad-band (BB) UVB was one of the first phototherapy modalities used in the treatment of psoriasis. Today, however, narrow-band (NB) UVB (310–315 nm) has become a first-line therapy in the treatment of psoriasis and many therapeutically challenging dermatologic disorders of its many advantages. Unlike UVB radiation, UVA has the ability to penetrate to the deep dermis and tissues. Moreover, UVA1 (340–400 nm) does not induce erythema effectively. Psoralen UV, also known as PUVA, is the use of psoralen combined with BB UVA irradiation. PUVA was first used to treat vitiligo in 1947. The most common PUVA regimen in the United States uses 8-methoxypsoralen, which is administered orally 2 h before UVA irradiation. Bath PUVA is application of a topical psoralen before UVA irradiation, either to the entire body or limited areas (hands and feet). Compared to oral psoralen, bath PUVA has some advantages, including shorter irradiation times and lack of gastrointestinal side effects, but its use is limited by the need for special facilities, patient inconvenience, and results unpredictability. Consequently, PUVA is usually administered via the use of oral psoralen.

UVA1 phototherapy has been reported to have efficacy in a growing number of dermatological disorders.[79] The therapeutic effect of UVA1 is related to the fact that its long wavelength penetrates the dermis more deeply than UVB. UVA1 radiation induces collagenase (matrix metalloproteinase-1) expression, T-cell apoptosis, and depletes Langerhans and mast cells in the dermis. UVA1 exposure stimulates endothelial cells to undergo neovascularization. UVA1 exerts significant therapeutic effects in atopic dermatitis (AD) and morphea (localized scleroderma); there is also evidence for its use in other skin diseases, including cutaneous T-cell lymphoma and mastocytosis.[79]

The therapeutic potential of UVA1 first administrated in 1992 in the treatment of AD, and then in 1995 for the treatment of localized scleroderma. Multiple phototherapeutic modalities have been credited with exerting a beneficial effect in AD.[79,80] Skin disease associated with scleroderma is disabling and highly symptomatic (including significant pruritus). Phototherapy, particularly UVA1, has showed benefit in scleroderma in largely uncontrolled trials.[81] Kerscher *et al.*[82] was among the first to report the benefit of low-dose UVA1 for patients with morphea. In terms of demonstration of efficacy, the use of UVA1 phototherapy for morphea is second only to methotrexate. Moreover, studies indicate that low-dose UVA1 might be of some efficacy or similar to NB UVB, but medium- and high-dose UVA1 are likely more efficacious. This finding is similar to reports in AD. The efficacy of low-dose UVA phototherapy in the treatment of morphea is mainly obtained by the increased

production of matrix metalloproteinase 1 and interferon gamma, and to a lesser extent by decreasing TGF-β and collagen production.[83] UVA1 potentially exerts its therapeutic effect through modulation of the three predominant pathogenic mechanisms in sclerosis: immune dysregulation, imbalance of collage deposition, and endothelial dysfunction.[84] Treatment advantages of UVA1 phototherapy include the ability to penetrate into the deep layers of the skin to affect changes on disease-causing T-cells, as well as activation of endothelial cells to promote neovascularization. This beneficial effect is predominantly reported in morphea, systemic sclerosis (scleroderma), lichen sclerosus, dyshidrosis, systemic lupus erythematosus, and chronic graft versus host disease.[84]

Vitiligo is a common skin disease characterized by loss of normal melanin pigments in the skin, and its pathogenesis is still unclear. Potent topical steroids remain the first-line treatment for limited areas of vitiligo, but phototherapy should be considered when more than 20% of the body surface area is involved. PUVA was a mainstay of treatment for vitiligo until 1997 another recommendation was supported by a single randomized double-blind trial comparing PUVA with NB UVB, which showed that NB UVB was superior to PUVA. Today, NB UVB irradiation is now considered as the gold standard for the treatment of diffuse vitiligo, and treatment with the 308 nm xenon chloride (XeCl) excimer laser and the 308 nm XeCl excimer light, defined as "targeted phototherapy," has also been reported to be effective.[85,86]

Mycosis fungoides (MF) is the most common form of the cutaneous T-cell lymphomas, characterized by an epidermotropic infiltrate of T-lymphocytes with the phenotypic display of mature memory T-cells. Today, the most common forms of phototherapy used in the treatment of MF are PUVA and both NB and BB UVB.[87] It is now commonly accepted that early stage MF should be treated with skin-directed therapies, while systemic and aggressive treatments should be reserved. Allergic rhinitis is an allergen-induced immunoglobulin E–mediated inflammatory disease of the nasal mucosa. The disease shares several common pathogenetic features with AD. 308 nm XeCl laser treatment, PUVA, and combined UVA–UVB phototherapy are successfully used in the treatment of allergic rhinitis.[85]

Another clinical application of UV phototherapy is UV irradiation of the blood. In the early 1940s, UV blood irradiation was being used in several American hospitals. By the late 1940s, numerous reports were made about the high efficacy for infection and complete safety of UV blood irradiation. As antibiotics were developed and grew in popularity, infection therapy with UV blood irradiation became far less common. UV blood irradiation resulted in the prompt healing of chronic very long-term, nonhealing wounds.[88] However, with the increased drug resistance of antibiotic therapy, UV blood irradiation and other traditional antimicrobial therapies are becoming alternative treatments for infection.

Novel UV light sources

UV lasers. UV lasers generate invisible wavelengths in the range of 150–400 nm. Medical industries that benefit from UV lasers include dentistry and sterilization, and they can be used in outpatient therapy by allowing professionals new methodologies and tools to perform procedures and operations that require microknife precision surgery.

There are various kinds of lasers, which can directly generate UV radiation:

- Laser diodes can emit in the near-UV region.[89] These UV lasers are normally based on gallium nitride (GaN). Power levels of UV diodes laser are usually limited.
- Some fiber lasers can produce UV radiation. For example, some neodymium-doped fluoride fibers can be used for lasers emitting UV radiation at 380 nm, but only at low power levels.
- Some laser dyes are also suitable for UV emission. Jiang *et al*.[90] used a β-BaB_2O_4 crystal to frequency double the dye laser into UV, with a tuning range from 279 to 305 nm demonstrated from a single-doped pyrromethene 597 dye.
- Excimer lasers are very powerful UV sources.[91] They can also emit nanosecond pulses, with average output powers between a few watts and hundreds of watts. Typical wavelengths of excimer lasers are between 157 and 351 nm. The 308-nm excimer laser and a related 308-nm excimer lamp have been approved to treat psoriasis and vitiligo.[86]
- Argon-ion lasers can emit UV radiation at wavelengths of 334 and 351 nm. An argon-ion laser operates in the UV spectral region by utilizing an ionized species of the noble gas argon. Argon-ion lasers function in a continuous wave mode when plasma electrons within the gaseous discharge collide with the excited laser species to produce light.
- Free electron lasers can emit UV radiation of essentially any wavelength and with high-

average powers.[92] However, they are very expensive and bulky sources, and are therefore not very widely used.

UV LED. A device based on light emitting diode (LED) emitting UV radiation (wavelength 365 nm, full width half maximum 7 nm, output power 250 mW) was developed by Inada *et al*.[93] This is a type of single-chip GaN-based UV LED, which is relatively small (350 μm $\times$ 350 μm). This UV LED can be operated with a dry battery and can be used to irradiate only the diseased skin. Moreover, the lifetime of the LED is three times longer compared with normal fluorescent light bulbs, and the LED contains no toxic substances. In addition, the UV LED has a narrower spectrum range than the fluorescent light bulb.

Microwave-assisted plasma UV. A recently developed technology uses microwaves to generate plasma, an ionized gas mixture that emits UV light and also contains oxidizing species, such as ozone.[94] The main applications at present are related to sterilization in the food processing industries,[95] but applications to human tissue are also possible.

FUTURE DEVELOPMENTS OF INTEREST

UV irradiation may cause both beneficial and damaging effects, which depend on wavelength, radiation exposure, and UV sources. In this review, the potential beneficial effects of judicious UV exposure to augment wound healing, restoration of skin homeostasis, and selectively inactivate microorganisms over the host cells were briefly summarized. UVC should be investigated as an alternative approach for prophylaxis and treatment of localized infectious diseases, especially those caused by antibiotic-resistant pathogens. As a result, more extensive *in vivo* and clinical studies need to be carried out to investigate and optimize antimicrobial UVC treatment. Further study of cellular signaling that occurs after low doses of UVA exposure of tissue will allow the benefits as antioxidant, anti-inflammatory as well as wound-healing effects to be better defined. Technologies that help reduce the side effects (*e.g.*, enhanced repair of UV-induced DNA damage to human cells, selective protection of human tissue, and cells from UV irradiation) of UV treatment are also worthy of being further investigated. New high-efficient light delivery technologies, for example, optical fibers, and optical clearing techniques, should be investigated to improve the penetration of UV irradiation in human skin and tissue. With the development of novel high-technology UV sources, using an NB wavelength range or a mono wavelength, such as LED, lasers, and microwave-generated UV plasma

TAKE-HOME MESSAGES

Basic science advances

- UV irradiation causes both beneficial and damaging effects, which depend on wavelength, exposure dose, and UV sources.
- The UVA, UVB, and UVC spectral bands differ in their biological effects and in their depth of penetration through the skin layers.
- Short-term UVB exposure induces the production of vitamin D in the skin. UVA has distinct effects on cell signaling. Judicious UV exposure might be beneficial for wound healing and skin homeostasis.
- Exposure to solar UV radiation is a major risk in the occurrence of nonmelanoma skin cancer. High doses of either UVC, UVB, or UVA radiation are harmful to all living organisms in the following order: UVC > UVB > UVA.
- The mechanism of UVC inactivation of microorganisms is to damage the genetic material in the nucleus of the cell or nucleic acids in the microbial cell.

Clinical science advances

- The potential of UVC irradiation as an alternative approach for prophylaxis and treatment of localized infectious diseases has been reported, especially those caused by multidrug resistance pathogens.
- With appropriate doses, UVC can selectively inactivate microorganisms, while preserving viability of mammalian cells and promote wound healing.
- UVB has been directly applied to wounded tissue to stimulate wound healing, and irradiation of blood to stimulate the immune system.

Relevance to clinical care

- As striking increase in the average age of the population and the incidence of diabetes continues to rise, new and more efficient strategies to manage chronic wounds are needed. Light-based technology is a set of growing minimally invasive modalities in wound care.
- UV phototherapy has been associated with both beneficial and deleterious effects to patients with localized and systemic skin disorders.
- UVC is less damaging to human tissue than UVB, which is an accepted option for a large number of cutaneous disorders in humans with excellent safety profile. UVC irradiation offers fast and cost-effective antimicrobial therapy compared to commonly used antibiotics.
- Under excessive repeated UVC irradiation, resistance of microorganisms to UVC inactivation may develop.
- UV should be used in a manner such that the side effects would be minimized, while the wound-healing process is augmented.

for UV phototherapy, will become as efficient biomedical modalities for the treatment of different localized and systemic dermatological disorders.

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