Steven Q. Wang · Henry W. Lim
*Editors*

# Principles and Practice of Photoprotection

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# Preface

Photoprotection captures the interest of physicians, academic researchers, industry scientists, law makers, marketers, general media, and consumers. It is a dynamic field where progresses and advancements often hinge on close collaboration of multidisciplinary teams. In the past decade, significant development has been made in the realm of sunscreens where novel UV filters and innovative formulation techniques have improved both the efficacy and aesthetic components of end products. To enhance protection from UV and even visible and infrared radiation, there has been active research exploring the application of antioxidants, nanotechnology, and DNA repair enzymes in photoprotection. Along the way, there has been a general trend towards global harmonization in guidelines for both testing and labeling claims in sunscreens. At the same time, recent clinical trials have demonstrated the benefits of sunscreen in protecting against skin cancer and photoaging. Continual research has shown the importance of photoprotection in preventing photodermatoses and photoaggravated autoimmune diseases. Despite these scientific and medical advances, there remain many myths and controversies, especially in the general media, surrounding the safety and efficacy of sunscreens and other photoprotective modalities. Continued education of the general public to practice proper photoprotective behaviors is needed.

This book aims to showcase all the rich facets and themes associated with photoprotection. Each chapter, which starts with a brief synopsis, is written by experts in their respective fields. The contributing authors have decades of clinical, research, or practical experience, and we are grateful to having enlisted this panel of experts to share their knowledge on this important topic. We sincerely hope the readers will find this book as an informative and practical guide.

Basking Ridge, NJ, USA — Steven Q. Wang
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# Acknowledgments

This book is dedicated to our families: Judy and Kevin and Mamie. We thank them for their patience and sacrifice throughout the course of this project.

# Contents

# Part I

# Chapter 1
# Clinical and Biological Relevance of Visible and Infrared Radiation

**Kelsey Lawrence, Mohammed Al-Jamal, Indermeet Kohli, and Iltefat Hamzavi**

**Key Points**

- Biologically, visible radiation has been shown to induce erythema, pigmentation, free radical production, and DNA damage, while infrared radiation has been shown to induce erythema, thermal pain, photoaging, cytotoxicity, DNA damage, and oxidative stress.
- Visible light has been shown to be an action spectrum in solar urticaria, chronic actinic dermatitis, and porphyrias; it is used for the treatment of hyperbilirubinemia. Infrared radiation can cause erythema ab igne and squamous cell carcinoma.
- Lasers with wavelengths in the visible and infrared spectrum can be used to treat vascular and pigmented lesions, keloids, etc. IPL, LLLT, and PDT are other light sources with wavelengths in the visible and infrared spectrum that are also used to treat numerous dermatologic conditions.
- New imaging techniques that use visible and infrared radiation have been recently developed. The data is promising and could greatly impact the field of dermatology in the future.
- Active research is ongoing on effective photoprotective measures against visible light and infrared radiation.

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## 1.1 Introduction

The sun emits electromagnetic radiation encompassing a wide range of wavelengths (Table 1.1). The wavelengths must be able to penetrate the ozone layer in order to reach the earth's surface. The radiation that reaches the earth is made up of 50 % visible light, 40 % infrared radiation (IR), and 9 % ultraviolet (UV) radiation [1]. It should be noted that in the UV spectrum, only UVB and UVA reach the surface of the earth; UVC is filtered out completely in the hemisphere. There has been extensive research into the effects of UV radiation on the skin, but until recently there has not been much research on the effects of visible and infrared radiation on the skin. This chapter will discuss the biological and clinical relevance of visible and infrared radiation.

Electromagnetic radiation is made up of photons, which have the properties of both waves and particles. When photons reach the surface of the skin, they can be reflected, scattered, absorbed, or transmitted. Reflection occurs at the skin surface and can be used for diagnostic purposes but is not useful therapeutically. Scattering is altering the direction of light transmission and also affects the depth of penetration. Most of the scattering of light is done by the collagen that is present in the dermis. However, scattering is also dependent on the wavelength, with shorter wavelengths undergoing more scattering compared to longer wavelengths [2].

In order for a photon to exert a clinical effect, it must be absorbed. Molecules in the skin that absorb photons are called chromophores. Absorption is dependent on the depth of penetration of the radiation and the wavelength absorbed by the chromophore. The depth of penetration into the skin varies with wavelength; the longer

**Table 1.1** Electromagnetic spectrum and corresponding wavelengths

| Light spectrum | Wavelength |
|---|---|
| Gamma ray | less than 0.01 nm |
| X-ray | 0.01–10 nm |
| Ultraviolet | 10–400 nm |
| UVC | 200–290 nm |
| UVB | 290–320 nm |
| UVA | 320–400 nm |
| Visible | 400–700 nm |
| Violet | 400–450 nm |
| Blue | 450–495 nm |
| Green | 495–570 nm |
| Yellow | 570–590 nm |
| Orange | 590–620 nm |
| Red | 620–700 nm |
| Infrared-A | 700–1400 nm |
| Infrared-B | 1400–3000 nm |
| Infrared-C | 3000 nm – 1 mm |
| Microwave | 1 mm–1 m |
| Radio | 1 mm–100 km |

wavelengths penetrate deeper than shorter wavelengths. Therefore, blue light, which is at the shorter end of the wavelength spectrum of visible light, can be used clinically for lesions contained in the epidermis, while red light, which has a longer wavelength, is useful for thick lesions or to target deeper structures [2, 3].

A variety of molecules can act as chromophores, some examples being amino acids, lipids, porphyrins, photosensitizing drugs, DNA, hemoglobin, bilirubin, melanin, and water. When a chromophore absorbs a photon, the chromophore transitions to an excited state, transiently. The chromophore releases energy, in the form of heat or light, when it returns to the ground state. The chromophore can then transfer this energy to another molecule or undergo chemical changes. Multiple photons are necessary to produce sufficient energy to cause cellular changes, which then leads to a clinical effect [2, 4]. The amount of absorption depends on the chromophores in the skin and the wavelength of light used. The energy absorbed is also known as the energy density, or fluence, and is measured in joules per square centimeter [5].

## 1.2 Visible Spectrum

Visible light is the portion of the electromagnetic radiation responsible for general illumination and is visible to the human eye. The wavelength of the visible radiation spectrum is from 400 to 700 nanometers (nm). Each color of light represents a different wavelength, with blue being at the shorter end of the spectrum and red at the longer end (Fig. 1.1). See Table 1.1 for more details on specific wavelengths.

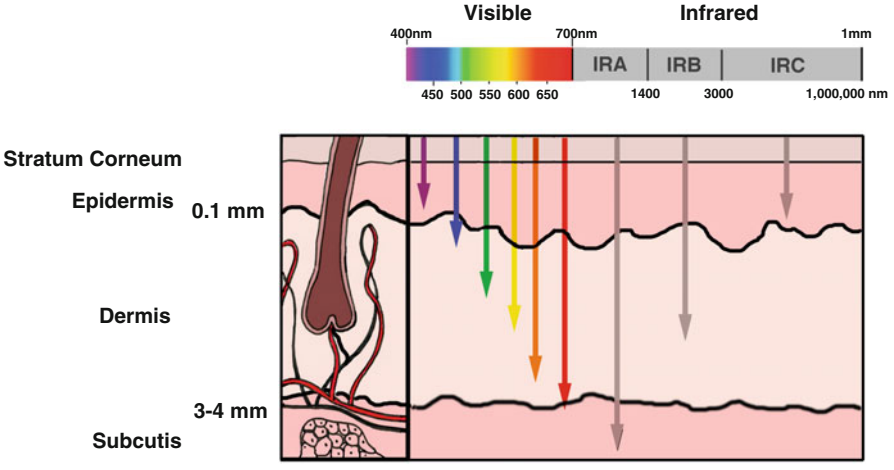


**Fig. 1.1** The wavelengths and their corresponding depth of penetration in the skin of each band within the visible and infrared spectrum

### *1.2.1 Biological Effects*

#### 1.2.1.1 Erythema

Erythema is a cutaneous inflammatory reaction and can be associated with warmth and tenderness; blisters can form if severe. Erythema during or immediately after sun exposure can occur transiently in fair skin types. Delayed erythema occurs in all skin types, with a peak occurring between 6 and 24 h after exposure [6–8].

Erythema is mostly caused by UVB radiation. However, UVA radiation, primarily UVA2 (320–340 nm), can contribute to skin erythema, and visible light has been shown to induce transient erythema [9]. The minimal erythema dose (MED) is 1000-fold more for UVA when compared to UVB [10, 11]. It is thought that the erythema caused by visible radiation is caused through a different mechanism than UVB-induced erythema, due to the differing depths of penetration. Dilatation of the vessels of the subpapillary plexus is the suggested mechanism for skin erythema from visible light, while erythema from UV radiation is thought to be from dilation of upper dermis capillaries since UV radiation does not penetrate as deeply [12].

Skin type plays a role in the timing and intensity of erythema from visible radiation. Mahmoud et al., using a light source that emits 98.3 % visible light, found that visible light can induce erythema, in individuals with Fitzpatrick skin types IV–VI, immediately after exposure, surrounding the area of immediate pigment darkening. However, the erythema started to fade 30 min later and was completely gone in 2 h. Of note, they were unable to induce any erythema in skin type II individuals even at the highest dose tested, 480 J $cm^{-2}$. The authors proposed a possible thermal effect from the reaction within the chromophores causing vasodilation and therefore erythema. They also proposed that the increased melanin concentration, one of the chromophores with absorption in the visible light spectrum, in the darker skinned individuals could account for the increased heat production and therefore the increased erythema that occurred in darker skin types [9].

However, in the study done by Porges et al., erythema was induced in individuals with Fitzpatrick skin types II, III, and IV only but not V and VI. Although, of note, the filter that was used did allow part of the UVA spectrum (385–400 nm) to pass through, which could account for the differing results between the two studies. Porges et al. also proposed that thermal effects may account for the erythema response [6, 9, 13].

#### 1.2.1.2 Pigmentation

Skin pigmentation is classified into immediate pigment darkening (IPD), persistent pigment darkening (PPD), and delayed tanning (DT). IPD appears immediately and fades within 20 min. PPD persists for 2–24 h. Both IPD and PPD are caused from oxidation and redistribution of preexisting melanin. DT occurs days later and is from synthesis of new melanin [7, 14]. Most research thus far regarding pigmentation is done on UV radiation.

Kollias and Baqer used a polychromatic light source with wavelength from 390 to 1700 nm, which consists of the visible spectrum and part of the spectrum of infrared radiation. They were able to induce pigmentary changes; however, they did not notice any erythema or thermal changes, even after 3 h of irradiation with a total dose of 270 W $cm^{-2}$. IPD was present, and pigmentation that lasted for 10 weeks was observed when doses greater than 720 J $cm^{-2}$ were used [15]. Rosen et al. showed that visible radiation up to 470 nm can induce an IPD response; this study was performed by using a xenon-mercury arc lamp with grating holographic monochromator to select for wavelengths of 334, 365, 405, 435, or 549 nm and spectrophotometric analysis of skin reflectance [16]. Pathak et al. identified the peak IPD response to be between 380 and 500 nm using a fixed exposure of 45 J $cm^{-2}$ [17].

Ramasubramaniam et al. used midday sunlight in Bangalore, India, with filters to determine the cutaneous effects of visible light (greater than 420 nm) and UV light (less than 400 nm) on pigmentation on Fitzpatrick skin types IV and V. They found there is not a significant difference in the IPD produced by UV and visible light. They identified similarly shaped action spectra for IPD and PPD when comparing UV and visible light. However, UV radiation is much more efficient in producing IPD, and the PPD response by visible light is much less intense. Since UV and visible light produced similar action spectra, though, they believe it is likely the same melanin precursor that UV and visible light are interacting with in order to induce these effects [18].

Mahmoud et al., using a light source that emits 98.3 % visible light, also found that visible radiation induced immediate pigmentation on volunteers with Fitzpatrick skin types IV–VI, with the lowest effective dose being 40 J $cm^{-2}$ [9]. The pigment was darker as the dose was increased. They noted that the pigment was most intense in type V skin type volunteers. The pigmentation was still present at 2 weeks, the end point of their study, even at the lower doses. However, they found that no pigmentation was induced in skin type II individuals, using the same light source and doses. The pigmentation induced in this study was more intense and lasted longer than the pigmentation described by Ramasubramaniam et al. (ref). However, the light source in Mahmoud et al. was artificial, while natural sunlight was used in the study done by Ramasubramaniam et al., and the dose used was four times higher in the study by Mahmoud et al., which could account for the differences [9, 18]. Confocal microscopy used by Mahmoud et al. showed that visible radiation induced redistribution of melanin from the basal layer to the upper epidermis. Diffuse reflectance spectroscopy also showed increased melanin content directly related to the visible radiation dose [9].

Of note, Duteil et al. showed recently that not all wavelengths of visible light have the same effect on pigmentation. Healthy volunteers of skin types III and IV were irradiated with wavelengths from both ends of the visible spectrum and the results compared. Blue-violet light (415 nm) induced pronounced and longlasting pigmentation (up to 3 months) in both skin types, while red light (630 nm) did not induce pigmentation [19].

Porges et al. used a solar stimulator to expose individuals with Fitzpatrick skin types II, III, and IV to light from 385 to 690 nm and observed IPD and DT as well as erythema. The IPD and erythema faded over 24 h. The DT remained unchanged

for 10 days. The threshold for PPD (greater than 80 J $cm^{-2}$) was slightly higher than that for IPD (between 40 and 80 J $cm^{-2}$), while the threshold for DT was higher than the threshold for IPD. Porges et al. were able to induce pigmentation in lighter skin types, while Mahmoud et al. were not. These differences could be due to the small amount of wavelengths outside the visible spectrum UV from 385 to 400 nm in the study done by Porges et al. or from the limited amount of infrared radiation in the light source in the study done by Mahmoud et al. [9, 13].

Visible light-induced pigmentation, especially in darker skin types, may be clinically relevant by potentially playing a role in pigmentation disorders. Melasma and post-inflammatory hyperpigmentation are much more prominent in darker skinned individuals. This is consistent with the clinical observation that sunscreens, which protect against UV but not visible radiation, do not fully protect the progression of these conditions [6].

#### 1.2.1.3 Free Radical Production

Reactive oxygen species (ROS) are chemically reactive molecules containing oxygen. Free radicals are hazardous to living organisms and have been associated with many pathological processes by damaging most cellular components. ROS are continually generated as a byproduct of metabolism, and cells have antioxidants to protect themselves from the detrimental effects of ROS. Any increase in ROS production or decrease in defense against ROS can lead to oxidative damage. Free radicals are a type of ROS with unpaired valence electrons. An oxygenation product from ascorbate, the ascorbate free radical, is a marker of oxidative stress that can be easily measured with electron spin spectroscopy [20–22].

A study by Haywood observed ascorbate free radical production in ex vivo human skin using solar-simulated light. They used sunscreen (SPF 25, containing the UVA filter butylmethoxyldibenzoyl methane) to block UV radiation and were therefore able to determine that visible light is responsible for 33 % of the free radical production in the substratum corneum, while UV accounts for the rest [23, 24]. In addition, Liebel et al. showed that commercially available sunscreens had minimal effect on reducing visible light-induced ROS, proinflammatory cytokines, and MMP-1 expression. However, when pretreatment with a photostable UVA/UVB sunscreen that contained an antioxidant was applied before visible light radiation, the production of ROS, proinflammatory cytokines, and MMP-1 expression was significantly reduced [25]. This is important because current sunscreens do not offer protection against visible light and with this information that is clearly something to look into in the future.

#### 1.2.1.4 DNA Damage

It has been well described that UVB is the predominant spectrum causing direct DNA damage, and indirect DNA damage through ROS is predominantly induced by UVA. Recently, the effects of visible light on DNA damage were studied. Edstrom

et al. irradiated normal skin with 126 J $cm^{-2}$ visible light which corresponds to about a half hour outside on a Sweden summer day. An Osram xenon arc lamp with two filters was used to block out all but the visible spectrum. This was done three times weekly for 4 weeks while taking intermittent punch biopsies. They found that visible light increased p53-positive cells as well as proliferation in the epidermis, although to a lesser extent than UVA1 (340–400 nm). p53 normally downregulates bcl-2, but interestingly they found a slight increase in bcl-2 in the epidermis, which could potentially mean the *p53* gene was mutated [26].

Kielbassa et al. used a xenon arc lamp with grid monochromator and/or cutoff filters (to make monochromatic radiation) to study the spectrum in which dimers and oxidative DNA modification occur in hamster cells. From UVA1 range into the visible light spectrum, oxidative DNA damage was observed, with a peak between 400 and 450 nm [27]. Hoffmann-Dorr et al. analyzed the effect of visible light on direct and indirect DNA damage on melanoma cells and human skin fibroblasts. Visible light induces ROS, which indirectly damages DNA. They concluded that the oxidative damage from 400 to 500 nm accounted for 10 % of the total indirect damage that occurs with sunlight exposure [28]. Liebel et al. showed that visible light radiation induced production of ROS, proinflammatory cytokines, and MMP-1 expression. However, neither thymine dimers are produced from visible light radiation nor TNF-alpha expression induced [25]. Now that visible light is being used more clinically, in lasers and photodynamic therapy (PDT), the long-term effects on DNA are becoming clinically relevant.

## *1.2.2 Clinical Effects*

### 1.2.2.1 Solar Urticaria

Solar urticaria is an uncommon photosensitivity disorder, making up 0.4 % of all urticarial cases in a 30-year retrospective study [29]. It is a type I immediate hypersensitivity response, mediated by mast cells. Urticarial lesions occur within minutes of sun exposure and resolve within 2 h if exposure is discontinued. Action spectrum can be in the UVB, UVA, and visible light ranges [30–33]. Augmentation and inhibition spectrums have also been described outside of the activating spectrum, but vary by patient; the clinical relevance of this is not yet known [31, 33–35].

### 1.2.2.2 Chronic Actinic Dermatitis

Chronic actinic dermatitis (CAD) is a chronic eczematous, photodistributed eruption that is most commonly seen in elderly males. The action spectrum for CAD is typically UVB alone or UVB and UVA; however, visible light has been reported to precipitate CAD in a few cases. Visible light can induce CAD in patients who are also affected by UVB alone or UVB and UVA [36]. However, a few rare cases were reported to only react to visible light, 600 nm [37]. Phototest results are almost always abnormal in moderate to severe cases of CAD, so can be used to confirm the diagnosis [24, 37, 38].

#### 1.2.2.3 Porphyrias

In cutaneous porphyrias, interaction of elevated levels of circulating porphyrins with sunlight (Soret band, 400–410 nm) causes cutaneous phototoxicity. Two types of cutaneous phototoxic lesions can occur, one caused by accumulation of water-soluble uroporphyrins and coproporphyrins and the other by accumulation of lipophilic protoporphyrin. The accumulation of water-soluble porphyrins leads to skin fragility and blister formation, exemplified by porphyria cutanea tarda, the most common type of cutaneous porphyria. The accumulation of lipophilic porphyrins leads to an immediate burning sensation in the skin after light exposure and can also be associated with swelling, redness, purpura, and erosions; these features are characteristics of erythropoietic protoporphyria [39].

#### 1.2.2.4 Hyperbilirubinemia

Phototherapy is one of the methods used to treat hyperbilirubinemia in neonates. Blue to green light phototherapy lamps are the most effective ones in lowering serum bilirubin levels because these wavelengths penetrate the skin and are absorbed well by bilirubin [40]. Fluorescent tubes or light-emitting diodes (LEDs) can be used [41, 42]. Structural photoisomers of bilirubin are produced after phototherapy, which can then be excreted through bile and urine [43]. Two other less significant mechanisms by which phototherapy decreases serum bilirubin are through photooxidation or photooxygenation to biliverdin, maleimides, or propentdyopents and phototherapy-induced addition to protein-bound bilirubin [44, 45].

#### 1.2.2.5 Acne Vulgaris Treatment

Acne lesions have been reported to decrease after exposure to blue, red, violet, or UV light. Some individuals report an improvement in their acne after sun exposure. The exact mechanism of action has not been completely elucidated; however, it is believed that the light works through anti-inflammatory and antibacterial mechanisms. Furthermore, it is known that porphyrins are produced by *Propionibacterium acnes*; therefore, exposure to Soret band results in the destruction of the bacteria. In fact, this is the rational for the use of photodynamic therapy in the treatment of acne vulgaris [5, 46–48].

## 1.3 Infrared Radiation (IR)

The wavelength of infrared radiation ranges from 700 nm to 1 millimeter (mm). It is further divided into infrared radiation A (IR-A), which ranges from 700 to 1400 nm; infrared radiation B (IR-B), which is from 1400 to 3000 nm; and infrared

radiation C (IR-C) from 3000 nm to 1 mm (Fig. 1.1). Infrared radiation, especially IR-A, is perceived as heat. The portion of infrared radiation that reaches the Earth's surface is mostly IR-A radiation. IR-A and IR-B are able to penetrate the epidermis, dermis, and subcutaneous tissue. IR-C is almost completely absorbed by the water in the epidermis [49].

## *1.3.1 Biological Effects*

### 1.3.1.1 Physical Effects

Erythema

IR can cause erythema, typically lasting less than 1 h, and is believed to be due to vasodilation secondary to a thermal effect. By 24 h, no erythema or pigmentation is observed [6]. The erythema observed has been used to determine standardized ways to measure IR doses. The minimal response dose and minimal heating dose have been described [50, 51].

Thermal Pain

Thermal pain caused by overwarming of tissues can occur in response to IR exposures. Even single overexposures can cause skin burns, *urticarial thermalis*, or collapse of the circulatory system [49].

Photoaging

Photoaging is a term used to describe the characteristic changes that occur to the skin after chronic exposure to sunlight, originally believed to be solely due to chronic UV radiation. Some common symptoms of photoaging include wrinkles, telangiectasias, solar lentigines, laxity, and a change of the texture to leathery. IR was first found to contribute to photoaging when it was shown in albino guinea pigs that UV plus IR exposure induced more photoaging than just UV radiation alone [52].

There are multiple mechanisms by which IR, mostly IR-A (760–1400 nm), is suggested to induce photoaging. Increased expression of MMP-1 is one of these mechanisms, which leads to increased degradation of collagen [53]. It has also been proposed that IR disturbs the electron flow in the mitochondria, which results in insufficient energy production in dermal fibroblasts. Different signaling pathways are then triggered, and alterations in functional and structural aspects of the skin occur [54]. Additionally, IR has been shown to cause decreased antioxidant enzyme activity, to stimulate angiogenesis, and to increase the number of mast cells, all of which have been found associated with photoaging [55, 56].

#### 1.3.1.2 Molecular Effects

Cytotoxicity and DNA Damage

IR has not been found to induce DNA damage alone [6]. IR appears to have a protective effect on UV-induced cytotoxicity and DNA damage. Menezes et al. found a longlasting partial protection from UVA- and UVB-induced cytotoxic damage after prior radiation with IR light [57]. Jantschitsch et al. irradiated *in vivo* mouse skin with IR-A prior to UVB radiation and found decreased UVB-induced apoptosis and DNA damage compared to irradiation with UVB alone. Decreased UVB-induced DNA damage was seen in *in vitro* human skin fibroblasts after IR radiation [58].

Markers of Damage

Due to acute and chronic adverse effects described above that can occur from IR exposure, indicators are needed in order to better understand the tissue threshold for damage. The expression of matrix metalloproteinase (MMP)-1 has been proposed a useful marker of early IR damage at the cellular level. MMP-1 expression increases in response to over-warming of tissue, UV overexposure, or mechanical stress. Other markers that have been explored include heat shock proteins, ROS, and apoptosis-related proteins. However, results of these investigations are contradictory in many cases, so specific conclusions cannot be elucidated at this time [49].

Oxidative Stress

IR has been shown to induce oxidative stress both by increasing formation of free radicals and decreasing the antioxidant content in human skin. Zastrow et al. found that the amount of excess free radical formation was not only dependent on the dose of radiation but also on the skin temperature increase due to IR radiation (760–1600 nm). Using an *in vitro* human fibroblast model, Jung et al. showed that IR radiation at 37 °C did not induce excess free radical production, while at 39 °C or higher, production of excess free radicals was observed. Now that the detrimental effects of IR radiation have been well described, it is clear that protection from IR radiation is necessary and important and will be addressed further in the section on sunscreen [6, 53, 59, 60].

### *1.3.2 Clinical Effects*

#### 1.3.2.1 Erythema ab Igne and Squamous Cell Carcinoma

*Erythema ab igne* is an erythematous or hyperpigmented, reticulated dermatosis that is caused from chronic exposure to low levels of IR. Identified causes of *erythema ab igne* include laptop computers, heating pads, car heaters, electric space

heaters, hot water bottles, and heated reclining chairs. Treatment is withdrawal of the heat source, and if done, patients have a good prognosis [61].

#### 1.3.2.2 Acne Vulgaris Treatment

Acne vulgaris has recently been shown to be successfully treated with light in the visible range, as discussed above, but also with light sources in the infrared spectrum. Diode lasers have been used to reduce acne lesions. The 810 and 1450 nm diode lasers have been used successfully. The diode lasers work by inducing short-term thermal alteration of sebaceous glands. When the 810 nm diode laser was investigated, it was done following the administration of indocyanine green chromophore. The indocyanine green concentrated in the sebaceous glands and was subsequently targeted by the diode laser. The data for acne treatment with diode lasers is promising; however as with acne treatment with visible light sources, more research is necessary to elucidate the long-term efficacy and cost-effectiveness of these treatment options [5, 62, 63].

## 1.4 Treatment Modalities Utilizing Visible and IR Spectrum

### *1.4.1 Thermal Treatment Modalities*

#### 1.4.1.1 Lasers

Introduction to Lasers

Lasers can be classified by the wavelength they emit, as this is a very important property of the laser. Examples of lasers that emit wavelengths in the visible light spectrum are argon, KTP, copper bromide, APTD, krypton, PDL, ruby, and alexandrite lasers. Table 1.2 lists some of the common lasers with wavelength in the visible light spectrum and their respective wavelengths [5, 64].

There are many uses for lasers in dermatology. Some examples of what lasers emitting wavelengths in the visible spectrum are used for include vascular lesions, pigmented lesions, vitiligo, tattoo removal, hair removal, and keloids.

Lasers for Vascular Lesions

Common vascular lesions that have been successfully treated with lasers are port-wine stains, hemangiomas, and telangiectasia. Vascular lesions contain oxygenated hemoglobin, which is the molecule the laser targets for destruction when treating vascular lesions. Oxyhemoglobin absorbs light strongly at wavelengths of 418, 542, and 577 nm. PDL was specifically designed to treat vascular lesions based on the

**Table 1.2** Lasers in the visible and IR light spectrum and their respective wavelength peaks

| Laser | Wavelength peaks |
|---|---|
| Argon | 488 and 514 nm |
| Potassium titanyl phosphate (KTP) | 532 nm |
| Copper bromide | 510 and 578 nm |
| Argon-pumped tunable dye (APTD) | 577 and 585 nm |
| Krypton | 568 nm |
| Pulsed dye laser (PDL) | 585–595 nm |
| Helium-neon laser | 632.8 |
| Ruby | 694 nm |
| Alexandrite | 755 nm |
| Diode | 800–810 nm |
| Nd:YAG | 1064 nm |
| Nd:YAG (long pulsed) | 1320 nm |
| Diode (long pulsed) | 1450 nm |
| Erbium/glass | 1540 nm |
| Erbium:YAG (pulsed) | 2490 nm |
| Carbon dioxide | 10,600 nm |

selective photothermolysis theory and is currently the first-line treatment for vascular lesions [5, 64–66].

The Nd:YAG laser has also been used successfully for a variety of vascular lesions such as port-wine stains, hemangiomas, and facial telangiectasia. Also, the Nd:YAG and 800 nm diode lasers have been used successfully for varicose and spider veins; however, sclerotherapy remains the gold standard for these lesions [5, 67].

### Pigmented Lesion Removal

Melanin has a broad absorption spectrum, from 504 to 750 nm. The wavelengths at the shorter end of the range are more effective at removing pigmented lesions. Longer wavelength lasers are useful for lesions with deeper pigment due to the increased tissue penetration. The response of the tattoo to specific lasers is very dependent on the color, depth, and nature of the tattoo pigment [5, 64, 68].

The pulsed lasers are also successful in removing tattoo pigment. The pigment is altered by the lasers and then subsequently removed by tissue macrophages. For black pigment, the Q-switched (QS) ruby, QS alexandrite, or QS Nd:YAG lasers are most effective because black pigment absorbs throughout the red and infrared spectrum. Blue and green pigments absorb best in the 600–800 nm range and therefore are best removed with ruby or alexandrite lasers. Yellow, orange, and red pigments are removed most effectively with green light, making the 510 nm PDL or 532 nm QS Nd:YAG laser the best options for these pigments [5, 64].

The Nd:YAG laser has been found to be useful for pigmented lesions when the pigment resides deeper in the dermis. Long-pulsed diode and long-pulsed Nd:YAG lasers have been especially effective at eradicating pigmented lesions with terminal hair growth, such as congenital melanocytic nevi and Becker's nevi [5, 64].

Laser Hair Removal

Light with wavelength between 600 and 1200 nm is best for hair removal because the light can penetrate to the appropriate depth in the dermis and is able to target the melanin in the hair shaft, hair follicle epithelium, and heavily pigmented matrix. The energy is absorbed by the melanin-rich matrix and hair shaft, which then undergoes a photothermal reaction and destroys the surrounding hair follicle [5, 64, 69].

Lasers currently approved for hair reduction include the long-pulsed ruby, long-pulsed alexandrite, pulsed diode, and long-pulsed Nd:YAG [5, 64, 70]. Of note, intense pulse light (IPL) with wavelength from 590 to 1200 nm can also be used for hair removal and will be discussed in further detail below.

Lasers for Keloids

PDL has recently been used for the treatment of keloids and hypertrophic scars. PDL has been shown to decrease erythema, increase pliability, and improve texture, bulk, and dysesthesias [5, 64, 71–73].

Ablative Lasers

Ablative lasers are used primarily for cutaneous facial resurfacing for severely photodamaged skin, photoinduced facial rhytides, dyschromias, and atrophic scars. High-energy, pulsed, and scanned $CO_2$ and erbium:YAG lasers are the main ablative lasers in use today, while the $CO_2$ laser is currently the gold standard for facial rejuvenation [5].

The short-pulsed erbium:YAG laser, 2940 nm, was designed to have the beneficial effects of the $CO_2$ laser while limiting the unwanted side effects. The erbium:YAG has milder improvement than the $CO_2$ laser but with also milder side effects and faster recovery time [5].

Additionally, there are numerous other uses for the $CO_2$ laser, which includes removing a variety of epidermal and dermal lesions, treating premalignant and malignant lesions, and excisional and incisional operations [5].

#### 1.4.1.2 Intense Pulsed Light Therapy

Intense pulsed light (IPL) refers to a high-intensity polychromatic incoherent light with a wavelength range from 515 to 1200 nm; different filters can be used to obtain specific wavelengths within this range. Depending on the target structure, the right wavelength can be selected for heating and destruction [24]. The light is delivered in series of single, double, or triple pulse sequences. The filters that only allow shorter wavelengths through should only be used in fair-skinned individuals because shorter wavelength light interacts more readily with melanin in the epidermis, which

can lead to hypopigmentation or dyspigmentation. IPL has been used to successfully treat a variety of vascular lesions and benign pigmented lesions and for hair removal. Longer pulse durations make it possible to slowly heat deeper structures, making this method very useful for thick port-wine stains and hemangiomas [5, 74].

## *1.4.2 Nonthermal Treatment Modalities*

### 1.4.2.1 Low-Level Light Therapy

Low-level light therapy (LLLT) uses low-power light sources. LLLT can be performed with either coherent light sources (lasers) or noncoherent light sources (light-emitting diodes (LEDs)). LLLT is lower intensity and causes lower temperature changes and less discomfort than other types of laser, while still being effective [24].

LLLT works by absorption of red and near-infrared light by the protein components of the respiratory chain in the mitochondria, mostly cytochrome *c* oxidase. Absorption leads to dissociation of inhibitory nitric oxide from cytochrome *c* oxidase and then increased enzyme activity, electron transport, and ATP production. LLLT has also been shown to increase expression of genes related to cellular migration and proliferation and also alters expression of growth factors and cytokines [24].

Red LED LLLT has also been found to inhibit fibroblast proliferation in vitro without affecting viability. Therefore, red LED LLLT could be a possible treatment for scars or proliferative disorders in the future [75].

The helium-neon laser is a type of LLLT with wavelength of 632.8 nm. The helium-neon laser has recently been shown to be another therapeutic option for vitiligo, specifically segmental vitiligo. The mechanism by which this works is by inducing melanocyte proliferation through the interaction with type IV collagen via mitochondria-related pathways [76, 77].

The current uses of LLLT within the IR spectrum are to stimulate wound healing and hair growth and for the treatment of herpes simplex. It has been shown that LLLT stimulates wound healing by promoting contraction through the induction of fibroblast to myofibroblast transition [78]. Recently, LLLT using a 1072 nm LED light source has been found to be a potential treatment for herpes simplex labialis. Significantly reduced healing times were experienced in patients treated with LLLT [79].

### 1.4.2.2 Photodynamic Therapy

Photodynamic therapy (PDT) is a common way visible light is used clinically. PDT is approved for the treatment of actinic keratosis in the United States; however, there are many off-label uses which continue to expand [80]. PDT requires a photosensitizer, a light source, and oxygen [81, 82].

Light Source

Any light source can be used for PDT, as long as the wavelength of light coincides with the absorption spectrum of the photosensitizer, and the penetration depth of the light is equal to the depth of the target cells or target tissue. Protoporphyrin IX has important absorption peaks in the red and blue wavelength regions, from 404 to 420 nm and at 635 nm. Therefore, continuous red and blue light are very commonly used in PDT [81].

Clinical Uses of PDT

Aminolevulinic acid (ALA) is only approved in North America for the treatment of hypertrophic actinic keratosis on the face and scalp in combination with blue light. Methyl aminolevulinate (MAL) is approved for non-hyperkeratotic actinic keratosis of the face and scalp in the United States [81].

There are numerous off-label uses of PDT. PDT has been used to treat noninvasive, nonmelanoma skin cancers (NMSCs), mycosis fungoides, Kaposi's sarcoma, extramammary Paget's disease, cutaneous B-cell lymphoma, vascular malformations, acne vulgaris, rosacea, hidradenitis suppurativa, morphea, actinic cheilitis, cutaneous warts, condyloma acuminata, epidermodysplasia verruciformis, molluscum contagiosum, herpes simplex virus, onychomycosis, cutaneous leishmaniasis, erythrasma (*Corynebacterium minutissimum* infection), keloids, and hypertrophic scars [81]. PDT has also been used for photorejuvenation.

## 1.5 Photoprotection Against Visible and IR Spectrum

Currently available sunscreens protect against UV radiation but do not protect against the visible spectrum of light. Up to 50 % of free radicals formed during solar radiation are generated following exposure to visible and infrared spectra; therefore, it would be necessary to provide photoprotection in these spectra as well. Meinke et al. showed that antioxidants and inorganic, i.e., physical filters, along with organic UV filters, are necessary to provide protection from the entire solar spectrum [83].

Visible light photoprotection is relevant in several clinical situations. Some photodermatoses have action spectrum in the visible light range. Photofrin, used in systemic PDT, has an action spectrum in the visible light range [24]. Furthermore, visible light can induced persistent pigmentation in dark-skinned individuals, as described before [12].

At this time there is no organic filter for visible light. The only filters that are able to reflect and scattered visible light are optically opaque filters. Zinc oxide (ZnO) and titanium dioxide ($TiO_2$) are two inorganic sunscreen agents that protect against visible light in some forms. When visible light photons encounter non-micronized ZnO or $TiO_2$ particles, the light gets reflected into the direction of our eyes, therefore

causing the ZnO and $TiO_2$ to appear white. The particle size determines the absorption range. ZnO and $TiO_2$ used in sunscreens are micronized (particle size of less than 100 nm in diameter) because they are then less visible on the skin and more cosmetically acceptable. Ferrous oxide, which is pigmented and opaque, has recently been used and found to be effective in offering sun protection in the visible light spectrum [84].

## 1.6 Diagnostic Imaging

Noninvasive, diagnostic imaging is a rapidly expanding field. Confocal scanning laser microscopy and optical coherence tomography are two ways noninvasive imaging is being used to image the skin. Confocal scanning microscopy uses a near-infrared light source and allows for imaging of tissue in vivo, in real time, with the same resolution as conventional histology. The epidermis, microvascular blood flow, and inflammatory cells can be identified. Possible uses of this imaging technique include potentially diagnosing lesions without biopsy and detecting tumor margins [5, 85–87].

Optical coherence tomography uses low-coherence interferometry and provides two-dimensional images up to 1.5 mm deep. The architecture of the epidermis and papillary dermis can be visualized. However, individual cells cannot be visualized. This imaging technique can potentially be used to diagnose skin tumors and bullous diseases without biopsies [5, 88, 89].

There are numerous other, new imaging applications using the infrared spectrum. Near-infrared fluorescence has been shown to accurately assist in sentinel lymph node mapping intraoperatively [90]. Recently, infrared images of individuals' faces have been used to determine acne severity and monitor acne treatment efficacy [91]. Most of these imaging techniques are still in the early stages of development. However, the data is promising and could greatly impact the field of dermatology in the future.

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