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# Ultraviolet diagnostic and treatment modalities in the coronavirus disease 2019 pandemic

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**Abstract** Ultraviolet (UV) therapy is an effective and well-tolerated therapeutic method for various dermatologic conditions due to its antiproliferative and immunosuppressive effects. Contemporary phototherapy includes broadband UVB, narrowband UVB, UVA1, PUVA, and excimer laser therapy. The coronavirus disease 2019 pandemic has resulted in the closure of many patient care facilities, including phototherapy units worldwide. Home phototherapy, thalassotherapy, and other UV therapy modalities are an alternative for many patients with chronic dermatoses.

We highlighted possible interactions of UV therapy effects and the coronavirus disease 2019 pandemic, and focused on organization and measures against transmission of infections in phototherapy units. Dermatology departments have reopened their units, assessing the risks and benefits for patients, optimizing safety regulations, and adhering to the rules for disinfection.



## Introduction

Ultraviolet (UV) therapy is a uniform, highly effective, and well-tolerated treatment for various chronic dermatoses, such as alopecia areata, atopic dermatitis, cutaneous T-cell lymphomas, graft versus host disease, morphea, psoriasis, prurigo nodularis, scleredema adultorum, and vitiligo.[1] UV radiation covers three solar spectrum ranges: UVA, 320 to 400 nm; ultraviolet B rays (UVB), 290 to 320 nm; and UVC, 200 to 290 nm.

Current phototherapy (PhT) includes broadband UVB, narrowband UVB (NB-UVB), ultraviolet A1 rays (UVA1), psoralen plus ultraviolet A or psoralen & ultraviolet A rays (PUVA), and excimer laser, with traditional Goeckerman and Ingram methods having only historic value.[2]

The novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been a global health problem since December 2019. As of August 15, 2020, the World Health Organization reported 21,026,758 cases of COVID-19 and confirmed 755,786 deaths worldwide.[3] The disease fatality rate is several times higher than influenza, and the leading cause of death is due to acute respiratory distress syndrome induced by proinflammatory responses and oxidative stress.[4]

During the pandemic, it is very difficult to manage treatment options in patients with chronic dermatologic conditions. With the closing of many dermatology departments, including their phototherapy units, patients with several dermatoses are lacking suitable therapy.

## UV light, temperature, climate, and COVID-19

It is well known that ultraviolet C rays (UVC) radiation, with an intensity of 3.75 mW/cm$^2$ for 60 seconds, is capable of inactivating the SARS-CoV-2 virus and interrupting viral RNA transcription, translation, and replication.[5] This method is widely used for disinfection of respirator masks and shields, as well as other personal protective equip-

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ment.[6] Other UVC-based germicidal applications include robot-controlled surface disinfection in hospitals and microbial inactivation of food.[7] UVB light is also a promising candidate for a UV germicidal alternative. UVB therapeutic devices are available in many dermatologic offices and departments worldwide; however, not enough data for its effectiveness exists to date.[7] High dose UV radiation degrades polymer materials, which may reduce the efficacy and protection capacity of the respirators disinfected by this method.[8]

One of the pathologic effects of the SARS-CoV-2 virus is alterations of the hematopoietic system and hemostasis, causing an accumulation of iron ions in the bloodstream. Iron deposition can induce an inflammatory process corresponding with an increase of C-reactive protein, albumin, and lactate dehydrogenase.[9,10] ORF8 and other COVID-19 surface glycoproteins can bind to porphyrin, and thus, form protoporphyrin that affects hemoglobin transport ability.[11] The *in vitro* absorption of photons increases the stability of the iron ion bond with the pyrrolic ring of hemoglobin molecule, preventing the heme from losing its oxygen transport function.[12] Because porphyrins have an absorption peak at 640 nm and the peak absorption of $HbO_2$ is centered on 900 nm, the irradiation of COVID-19 patients with near-infrared region light with a spectrum between 630 and 1,000 nm has been proposed as a promising therapeutic method.[11] This method is in a clinical trial for bacterial pneumonia as well.[13]

A recent photodynamic method proposes illumination of the target lung tissue with low-power light via fiberoptic catheter, combined with systemic infusion of porphyrin-based photosensitizers.[14] Photodynamic therapy generates highly reactive oxygen singlet, capable of destroying the bonded SARS-CoV-2 viruses and decreasing the viral load in the zone of photoactivation.[14]

The irradiation of UV light on the skin produces vitamin D, which absorbs UVB radiation at a spectrum between 290 and 315 nm, a process essential for its activation. Vitamin D has potent antiinflammatory activities due to the inhibition of interleukin (IL)-1, IL-6, IL-17, tumor necrosis factor $\alpha$, and interferon $\gamma$ production; other proinflammatory pathways may be involved.[15] Vitamin D also increases innate cellular immunity by inducing antimicrobial peptides, including human cathelicidin LL-37 and defensins.[16] Recent investigations suggest that vitamin D can also modulate IL-6, which appears to be increased in COVID-19 infections.[17]

Statistical analysis reports a significant correlation between death rates and a country's geographic latitude, supporting the beneficial effect of sunlight.[18] In contrast, the limited sunlight exposure explains why 75% of institutional indoor populations have a marked vitamin D deficiency and have increased COVID-19 mortality.[19] Lower vitamin D levels in winter possibly facilitates viral epidemics; vitamin D supplementation could reduce the incidence, severity, and risk of them.[20] The mortality rate of COVID-19 infection is significantly reduced after peroral vitamin D supplementation.[21]

The higher incidence of sunlight is directly related to an increase in the ambient temperature on the Earth's surface. Statistical analyses of China and the United States have found a relationship between the transmissibility of COVID-19 and the temperature and humidity. An increase in 1°C in temperature reduced the effective reproductive number of COVID-19 by 2.3% in China and 2% in the United States.[22] The same correlation was found for increased humidity[20]; however, climate factors alone cannot reduce the effective reproductive number of COVID-19 below one. Even in summer, epidemiologic measures are essential to diminish the transmission of COVID-19.[20]

## UV radiation and immunity

The main effects of UV on skin include immunomodulation with a prevalence of immunosuppression, induction of apoptosis, and modification of dermal collagen metabolism. UV light-induced immunosuppression can increase a patient's susceptibility to various viral infections, including COVID-19. Both UVA and UVB radiation suppress contact hypersensitivity and delayed-type hypersensitivity to viral, bacterial, and fungal antigens in mice.[23] UV irradiation intensifies blood flow and infiltration from the blood of macrophages and neutrophils into the skin, resulting in clinically observed inflammation and increased production of nitric oxide.[24] UV-induced lipid peroxidation increases production of prostaglandins, which causes inflammation in dermal tissue.

PhT induces not only local but also systemic immune suppression, as the result of depletion of Langerhans cells in the skin and the inhibition of the CD8 T-cell response.[25] UV light induces inflammatory responses in skin; however, lower than minimal erythema doses have mainly immunosuppressive effects. *In vitro* studies indicate that UV-stimulated keratinocytes activate a cytokine cascade including prostaglandin 2, IL-4, and IL-10, resulting in suppression of interferon $\gamma$ production.[26] This concept is supported *in vivo* by a highly increased incidence of skin cancer in chronically immunosuppressed patients living in regions of intense UV exposure.[27] Using a four step analysis of the hazard, dose-response, exposure, and risk, it was calculated that approximately 100 minutes of solar exposure in southern Europe would suppress the resistance to infections by *Listeria monocytogenes*.[28]

Insufficient information concerning the effects of UV irradiation on patients with skin diseases and COVID-19 exists in the literature, substantiating the concerns about possible systemic immunosuppression. According to the San Gallicano Dermatological Institute, phototherapy is recommended only in priority cases, based on disease morbidity, severity, and the risk of erythroderma.[29]

## Phototests and photopatch tests during the COVID-19 pandemic

Phototests and photopatch tests are valuable for an evaluation of various photodermatoses. Phototesting includes determination of the minimal erythema dose (MED) toward UVA and UVB, immediate pigment darkening dose to UVA, and minimal melanogenic doses. The Fitzpatrick skin phototype classification could to be unreliable in assessing the skin response to UV, because dose ranges in phototype III, IV, and V may overlap.[30] The exact PhT course needs an initial MED test.

The diagnosis of photosensitive drug eruptions is based on the history of drug intake and the appearance of the eruption on sun-exposed areas. The diagnostic methods include phototesting, photopatch testing, and rechallenge testing.[31] Photests and photopatch tests are used to detect abnormal UV and visible light reaction to various substances, such as sunscreens, medications, and in particular nonsteroidal anti-inflammatory drugs, prescribed in the treatment of COVID-19.[32] It combines two techniques–patch testing and long-wave UVA exposure with 50 to 75% of the MED dose, and is capable of distinguishing photoallergic from phototoxic reactions. In exceptional cases, UVB irradiation is needed to prove photosensitivity, for example, systemic photosensitivity due to ambroxol.[33]

## Phototherapy recommendations in the COVID-19 pandemic

There are no uniform clinical recommendations for management of phototherapy during the COVID-19 pandemic. The British Photodermatology Group recommended a plan of action in phototherapy units[34]: all patients should be initially screened for COVID-19 and assessed for the risk of disease aggravation, so PhT could be performed in case of a marked necessity.

Phototherapy capacity has to be limited, with priority given to those with severe skin disease urgently requiring treatment. According to the San Gallicano Dermatological Institute protocols, all vitiligo patients should discontinue therapy and remain on local treatment with tacrolimus.[29] Patients with psoriasis maintain the NB-UVB therapy only if the psoriasis area severity index (PASI) score is $>10$, whereas those with PASI $<10$ are switched to topical corticosteroids and/or keratolytics.[29] All scleroderma patients on UVA1 are also switched to local treatment, whereas severe atopic dermatitis and cutaneous T-cell lymphoma patients may continue NB-UVB therapy.[29]

Measures should be taken to minimize the risk of patients with confirmed or suspected COVID-19 at phototherapy units. Social distancing and minimal waiting times with 30 minute intervals between appointments have to be set. The appointments should be adjusted according to operational time for cleaning of the contact parts of equipment between every patient entrance. Patients visiting the service the next day should be questioned over the phone for fever, flu-like clinical manifestations, contact with patients confirmed or in quarantine for COVID-19, or recent trips to other high-risk countries.[32]

Minimal therapeutic courses and measures to minimize treatment duration have to be done. Our experience shows that for the effective treatment of psoriasis, the shortest course has to be at least 10 procedures during a 3-week period.[35] At that time, the risk of contact and the development of unmanifested or oligosymptomatic COVID-19 infection is real. Pretreatment evaluation of MED for the most appropriate initial dose must be evaluated, as it is time-consuming. A regimen with a fixed initial dose according to patient prototype should be used instead. If doses are too low, then patients may need more sessions and a longer-lasting course.[32]

Both phototherapy staff and patients have to take all measures for self-protection. This includes wearing of protective masks, shields, gloves, and strict disinfection of machines before and after every patient. Patients must wear facial masks before entering the PhT unit and remove them when he/she is alone. Only one person should have PhT in a room at a time. If a child is treated, only one relative may accompany him/her.

Phototherapeutic units tend to be closed in seasons with high outdoor sunlight. In some counties in summer, thalassotherapy is a concurrent option. Bulgarian dermatology is a pioneer in thalassotherapy and in high mountain climate therapy for treatment of psoriasis, vitiligo, and atopic dermatitis.[36,37] In other countries, such as the United States, home phototherapy is available and should be considered as an option.[38] In regions that offer phototherapy in many locations, reintroduction of phototherapy may initially be more centralized to reduce patient traveling. Peripheral centers should plan to restart phototherapy when possible.[32] The recommendations are based on the consensus opinion of members of the dermatology expert committee of the Light Treatment Effectiveness study, a pragmatic trial of home versus office NB-UVB phototherapy to balance risks and benefits for patients and to optimize safety for staff.

Once a decision to initiate or to resume phototherapy service has been made, the following recommendations should be given for all patients[39]:

- Screened for COVID-19 clinical manifestations based on local guidelines before entering the unit.
- Attend the phototherapy appointment alone (ie, family members, friends, and caregivers should not enter the medical facility).
- Wear a face mask with the exception of during the total body phototherapy treatment.
- Apply hand sanitizer upon entering and leaving the unit.
- Be provided with individual goggles (if the face is exposed during phototherapy) that can be stored in

the unit in an individualized plastic bag. Patients should clean the goggles according to manufacturer's instructions thoroughly with disinfecting wipes before putting them into a bag.
- Be given a bag to store their clothes when they disrobe and discard the bag at the end of treatment.
- Practice social distancing.

Staff should consider:

- Scheduling patients no more than every 30 minutes.
- Arranging waiting areas with seats 6 feet apart.
- Wearing a mask.
- Applying hand sanitizer before and after each patient encounter.
- Avoiding turning on the fan of the phototherapy unit if possible; if needed, treatment can be fractionated to avoid excessive heat build-up in the unit.
- Disinfecting high-touch surfaces in the changing area after each patient.
- Disinfecting high-touch areas of the phototherapy equipment in between patients.

## Conclusions

Many dermatologic conditions may be aggravated during the COVID-19 pandemic. PhT units should make the decision to open again considering the available recommendations made for patient and staff safety. During the COVID-19 outbreak, there are discordant opinions toward the impact of classic cytostatics and biologics in psoriasis. This makes phototherapy a useful alternative.

## Declaration of Competing Interest

None.

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