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COVID-19 and Dermatology: A Comprehensive Guide for Dermatologists

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Introduction

As of the 11th of March, the world health organization (WHO) declared Coronavirus disease-2019 (COVID-19) as a pandemic disease caused by SARS-CoV-2 (previously known as 2019-nCoV) (1,2). By the 19th of April, 2,241,778 confirmed patients were reported worldwide with 152,552 COVID-19 related deaths (3). The COVID-19 pandemic represents the most serious health crisis facing the modern world resulting in unprecedented efforts to contain this pandemic and its consequences (1).

Virology

All the coronaviruses (CoVs) belong to the “*Coronaviridae*” family, which, consists of a group of enveloped, positive-sense, and single-stranded RNA viruses with an extended field of original roots. The CoVs are genotypically and serologically classified into four genera: α , β , γ , and δ -CoVs, of which, the α and β CoVs are capable of infecting humans (4). SARS-CoV-2 was recognized as a member of β -CoVs with a genome sequence similar to the bat CoV and SARS-CoV-1 (5,6). SARS-CoV-2 is characterized by the presence of specific spike glycoprotein that shows strong binding affinity to the Angiotensinogen Converting Enzyme 2 (ACE2) receptors; however, it is worth mentioning that SARS-CoV-2 has 10-20 folds higher binding affinity to ACE2 receptors compared to SARS-CoV-1 (6,7). Generally, ACE2 may be expressed in different parts of the human body including the lung, small intestine, colon, duodenum, kidney, testis, gallbladder, heart, esophagus, and urinary bladder, rendering these organs a potential target for the SARS-CoV-2 (6,8). Interestingly, an old report by Hamming I et al (9), demonstrated the presence of ACE2 in the basal cell layer of the epidermis continuing to the basal cell layer of the hair follicles, the smooth muscle cells that enclose the sebaceous glands, and the eccrine glands. In the same setting, Goren A et al (10), postulated a hypothesis that androgen receptors may play a role in the severity of the COVID-19 patients. This hypothesis was based on the disproportionate prevalence of severe COVID-19 among children and adult females compared to adult males. Besides, the ACE2 activity have shown to decrease with the reduction of the androgen hormones (10). However, this theory is not yet proven.

The SARS-CoV-2 is a highly contagious disease that is characterized by a basic reproductive value (R_0) of 2-3.5, reflecting the capability of one patient to transmit the disease to 2-3 other persons (11). According to the WHO, SARS-CoV-2 is transmitted through respiratory droplets of

infected person in either a direct (close contact with infected person) or indirect (fomites surrounding the infected persons or tools used during examination such as dermatoscope) (12,13). Finally, hidden transmission from asymptomatic carriers was reported (14).

There is a broad spectrum of manifestations in COVID-19 patients (fever, dry cough, dyspnea and myalgia with headache, nausea and diarrhea being less frequent manifestations) (1). The presentations are categorized into 4 categories: Asymptomatic patients (1%); mild to moderate (81%); severe (14%); and critically ill patients (5%). The overall mortality rate is 2.3% (15).

Cutaneous manifestations of COVID-19

Several viral infections are characterized by the presence of related cutaneous manifestations (16). A recent Italian study of 88 COVID-19 patients showed that 20.4% of the patients demonstrated cutaneous manifestation in the form of erythematous rash, urticaria, and chickenpox-like vesicles mainly in the trunk with little or no itching. Furthermore, the authors reported that those skin lesions were not correlated with disease severity (17). Similarly, Henry D et al (18), reported that COVID-19 patients may present with urticarial eruption without any respiratory symptoms (cough or fever). On the same hand, a COVID-19 patient was misdiagnosed as dengue in Thailand as the principal presentations were skin rash with petechiae and low platelet count (19). In these settings, dermatologists should pay particular consideration to patients presenting with viral-like skin rash so as not to miss COVID-19 cases (20).

Impact on Dermatology Practice

Potential risk of SARS-CoV-2 infection in dermatologic patients

Generally, skin is considered a part of the immune system as it acts as a shield against different environmental stimuli (21). In this setting, compromising the integrity of this barrier by lacerations, scratching, needling, pre-existing infections or diseases of skin, wounds, and burns may facilitate the invasion by micro-organisms (22). Therefore, dermatological patients may be at higher risk of SARS-CoV-2 either due the loss of the skin integrity by dermatological diseases or the immunosuppressive therapy used in the management of some diseases (23,24).

Many patients may take advantage of the quarantine period to do some cosmetic procedures considering that the quarantine period is an appropriate opportunity for healing and downtime of the skin; however, it should be noted that fractionated ablative laser resurfacing may result in

narrow columns of dermal injuries allowing for potential infection (25). Additionally, Micro-needling especially home ones may carry high risk of infection and viral autoinoculation (26).

Impact on dermatology clinics, surgeries and education

Since the start of COVID-19 pandemic, many measures and protocols have been taken to reduce the risk of spread of infection, to flatten the peak of the epidemic curve, and to prepare the different healthcare facilities to the expected surge of COVID-19 patients (27,28). Based on the Chinese experience, only urgent dermatological surgeries should be performed, the capacity of the outpatient clinics should be reduced, all patients should be screened at the clinic entrance for fever or history of travel to endemic areas, and all patients should be wearing masks; however, it is worth mentioning that sometimes the use of masks for patients may be difficult as most of the high-risk carcinomas are located in face region. Furthermore, doctors should wear mask, goggles, protective suits, head caps and gloves (29–31). Generally, the majority of the dermatological outpatient visits are elective, thus, it is recommended to cancel all non-urgent visits and only urgent outpatient visits (including surgeries for malignancies) should be performed provided that adequate protective measures are followed (23,27,32,33). Furthermore, the authors recommended that practitioners at risk of COVID-19 (60 years or older, immunocompromised, pregnant, and comorbidities) should avoid contact with patients (32). On the same hand, hospital admission should only be preserved for patients with severe skin disease not responding to outpatient treatment (27). In conclusion, COVID-19 has dramatically affected the dermatological practice; however, dermatologists should pay careful attention not to compromise (by cancelling or deferring) urgent and high-risk cases.

One of the medical technologies that gained interest during the current pandemic is the telemedicine that allows the dermatologists to diagnose the patients remotely and prescribe proper treatment without compromising the social distancing role (34–38). There are two types of consultation in teledermatology either synchronous (which include real time interaction between the patient and the physician) or asynchronous (in which the patients data are stored and then reviewed later by the physician) (36). Interestingly, smart phone technology (especially whatsapp) has been proposed to overcome the lack of teledermatology equipment in most of healthcare facilities; however, it may be limited by the poor video and images quality, and medicolegal and privacy issues (38).

Moreover, COVID-19 pandemic has a great impact on teaching and scientific activities; however, remote teaching of medical students and residents through online lectures, seminars, and case discussion is safer compared to the classic methods during this critical time (39).

Immunomodulators / Immunosuppressants use during the COVID-19 pandemic

Immunosuppressants are mainly used in the dermatological practice for the management of autoimmune and inflammatory diseases such as psoriasis, atopic dermatitis, systemic lupus erythematosus, dermatomyositis, pemphigus vulgaris and pyoderma gangrenosum (40,41). However, their use during the current pandemic is a matter of debate as a result of lack of evidence about COVID-19 risk in immunosuppressed patients (42,43). Conforti C et al (42), suggested that these immunosuppressant drugs may be associated with higher risk of opportunistic infections as they weaken the immune response. This suggestion was based on previous reports about the increased risk of swine influenza A (H1N1) infection or death in psoriatic patients using immunosuppressant drugs (44,45). Therefore, Conforti C et al (42), proposed that the use of biologics should be weighted in endemic areas with the aim to limit and/or reduce the administration time of these drugs and to stop all immunosuppressants in patients suspected for having COVID-19. Similarly, a consensus of experts' opinion from New Zealand and Australia, advised the cessation of all immunosuppressants (except systemic corticosteroids that should not be suddenly stopped or reduced) in COVID-19 confirmed patients for at least 4 weeks, while for patients with influenza like symptoms the dose of immunomodulators should be reduced or stopped for a period of two-weeks.

On the contrary, Bashyam et al (46), reported that some biologics may even play a protective role and enhance the aberrant immune response to COVID-19. This hypothesis was supported by Bardazzi F et al (47), who reported their experience with the use of biologics for psoriatic patients in Italy during the COVID-19 pandemic. The authors demonstrated that only 24/176 psoriatic patients developed influenza like symptoms, of which, only two patients (from the highly infected regions in Italy) tested positive for SARS-CoV-2, while, the remaining 22 patients did not require testing for COVID-19. However, it is worth mentioning that those two patients were instructed to temporarily stop biologic therapy (47). Interestingly, Mihai et al (48), reported COVID-19 in a 57-years old woman with systemic sclerosis. The patient was on tocilizumab (Interleukin-6 blocker) for the management of her systemic sclerosis and had a higher risk of severe course of COVID-19 due to the associated comorbidities (insulin dependent type-2 diabetes and systemic sclerosis associated interstitial lung disease); however, the patient showed just mild symptoms for 10 days

and the tocilizumab was resumed 4 days after the negative SARS-CoV-2 test (48). Several other authors reported that a case-by-case evaluation may be more convenient as some of these biologics may not be harmful during the COVID-19 pandemic but even theoretically beneficial and their cessation may be associated with the development of anti-drug antibody (49–51).

Generally, the recommendation for the immunomodulators use should be based on the mechanism of action of each of drug and its associated risk of infection (52,53). For example, Tumor Necrosis Factor- α (TNF- α) inhibitors is associated with similar risk of infection by seasonal and H1N1 influenza as compared to normal population (54); however, it was associated with up to 7% increased rate of overall infection compared to placebo (except for etanercept) (52). Theoretically, TNF- α inhibitors may play a protective role through modulation of inflammation and decreasing alveolar damage as the pneumonia caused by COVID-19 is usually associated with cytokine storm with increased levels of TNF- α and other cytokines (55,56). Furthermore, Adalimumab (TNF- α inhibitor) is currently under trial in China for the treatment of COVID-19 patients (57). Considering interleukin-17 blockers (IL-17), it was associated with 11% increased risk of overall infection; however, major part of this infections was monilial infections. They are characterized by a paradoxical role in viral infections depending on the nature of the virus, where it may either enhance the host's aberrant immune response or it may aggravate the disease (46). Theoretically, COVID-19 patients may benefit from IL-17 blockers especially patients with higher plasma levels of interleukin-17 (58). On the other hand, corticosteroids should be used with great caution as it was associated with delayed viral clearance in SARS and MERS patients but not with increased mortality (55). Therefore, routine use of systemic steroids in the management of COVID-19 patients is not recommended by the WHO (59).

The American Academy of Dermatology recommends that patients on biologic therapy without suspicious or confirmed COVID-19 and patients considering the initiation of their biologic therapy should be evaluated on a case-by-case basis and a shared decision (between the physician and the patient) should be considered based on the risk versus the benefit of such therapy, while patients who test positive for COVID-19 should consider postponing or cessation of their biologic therapy (43). Similarly, the European Task force on Atopic Dermatitis stated that immunomodulators (including immunosuppressants) should be continued in patients with atopic dermatitis; however, patients should take care of hygienic procedures such as hand washing. Considering atopic dermatitis patients with positive tests for COVID-19, careful risk assessment should be performed before cessation of immunomodulators as the abrupt stoppage of these drugs

may be associated with exacerbations of the condition and comorbidities (including asthma, kidney disease and allergy), and topical therapy should be considered during the pause period (60).

Dermatologic malignancies

Cancer patients may be at a higher risk for the development of infectious disease with a 3.5 folds increased risk of developing COVID-19 adverse events including the need for mechanical ventilation and/or death due to their immunocompromised state that is associated to the nature and the aggressiveness of the neoplasm and the anti-cancer treatment (1). Only one report in the literature discussed the adherence of patients with advanced basal cell carcinoma to hedgehog inhibitors during the COVID-19 pandemic. The report included 37 patients, of which, only three patients interrupted the treatment as a result of severe comorbidities, while all the remaining patients either attended the outpatient clinic for the monthly prescription or used a modified treatment scheme to prolong their treatment. It is noteworthy to mention that there is no evidence against the continuation of these drugs during the current pandemic (61).

On the other hand, immune checkpoint inhibitors (ICIs) are considered one of the promising treatment options for patients with advanced melanoma (62). Noteworthy, the susceptibility of patients taking ICIs to infectious diseases has not been thoroughly discussed in the literature. The use of ICIs during the current pandemic may represent a matter of concern as a result of the potential overlap between the SARS-CoV-2 related pneumonia and the pulmonary toxicity of the ICIs (however, it should be mentioned that this pneumological toxicity is a rare event ranging from 2.5-5% in case of ICIs monotherapy to 7-10% in case of combination therapy). Furthermore, the synergism between the ICIs mechanism of action and the SARS-CoV-2 pathogenesis may potentiate the pathological effect of COVID-19. In this setting, the use of ICIs should be carefully weighted according to a case-by-case scenario (63). Considering squamous cell carcinoma of the skin, the same precautions (discussed before) should be followed if immunomodulators is considered for treatment.

Other diseases

Arora G et al (64), raised the concern that patients with rheumatologic skin disease may be at higher risk for COVID-19 either due to the disease itself or its medications. Furthermore, some rheumatological diseases such as rheumatoid arthritis may be associated with new-onset or reactivation of arthritis during the remission following some viral infections (including coronavirus) (64).

Considering sexually transmitted diseases (STDs), the quarantine and social distancing measures may not only affect physical and psychosocial health of the individuals but also the sexual health, where, these measures may lower the opportunity for casual sex that in turn might reduce the incidence of STDs such as syphilis, gonorrhoea and chlamydia in the future (65). Furthermore, it is also recommended not to cancel the visits of STD patients (it can be performed using teledermatology or virtual clinics) to avoid the consequences including the further spread of the disease.

Occupational skin problems among healthcare workers during COVID-19

Several skin complications may result from the prolonged use of personal protective equipment as a result of hyperhydration effect, friction, and allergic contact reactions (24). The prevalence of skin damage resulting from wearing protective equipment was 97.0% among healthcare workers including lesions of the nasal bridge (83.1%), hands, cheek and forehead (66). Furthermore, excessive hand washing with detergents and/or disinfectants may cause contact dermatitis (24). In these settings, a consensus of Chinese experts on the protection of the skin and mucous membranes was released recommending that hand washing or gloves decontamination should be limited to the following moments; before touching the patients or any aseptic procedure and after exposure to body fluids, touching the patient or any of the patients' items. Furthermore, they recommended the use of ethanol for hand hygiene and applying hand cream following each time of hand hygiene if possible. However, in case of latex gloves it is recommended to wear a cotton gloves below and to use moisturizers with topical glucocorticoid cream. Similarly, it is recommended to use a properly fitting mask and goggles and apply moisturizers or gel at contact areas (67). Furthermore, Yin Z et al (68), suggested the use of double protection (benzalkonium chloride paste on the nasal bridge followed by hydrocolloid dressing) before wearing the N95 masks.

Potential use of dermatological drugs for management of COVID-19

Many vaccines had been injected intralesionally to treat warts, as BCG, which, results in IL-12 increase and IL-4 decrease and MMR vaccine, which, is capable of stimulating the cell-mediated and humoral immune response (69). Children are characterized by significantly lower risks for developing severe form of COVID-19 with lower mortality rates compared to adult population and this may be due to the global active viral immunization of children (70,71). Based on these observations, the vaccines that have been used to treat viral skin lesions can theoretically be a

potential treatment option of COVID-19; however, further studies are required to confirm the role of vaccines in COVID 19 prophylaxis and/or treatment.

There is a strong rationale for the use of antimalarial drugs (chloroquine [CQ] and hydroxychloroquine) to treat infections. These drugs are considered to be immunomodulators as they reduce T cell activation, suppress the toll-like receptors (TLR) signaling, and inhibit pro-inflammatory cytokines production by T cells and B cells (72). In animal studies, CQ was capable of Inhibiting SARS-CoV spread either prior to or after infection, suggesting that CQ might have both prophylactic and therapeutic advantages (73). In this setting, Chinese experts recommend that patients with COVID-19 (mild, moderate or severe) and without contraindications to chloroquine should be treated with 500 mg chloroquine twice daily for ten days (74). However, these drugs should be used with caution and under medical supervision to avoid macular retinopathy and cardiovascular disorders that may be life-threatening (75).

Ivermectin is an FDA-approved antiparasitic drug that is characterized by anti-viral activity. An ex-vivo study demonstrated that ivermectin is able to produce approximately 5000 folds reduction in the viral RNA in the treated cells compared to the control samples. These promising results should promote in-vivo studies (76).

Summary of recommendations for infection control in dermatology clinics

These recommendations are based on the findings of the current review, the protocols in the dermatology department in our universities, and the measures recommended by CDC (center for disease control and prevention). **Table 1** shows a summary of recommendations based on the findings of the current review.

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Table 1:

Summary of recommendations

Topic	Recommendations
<i>Cutaneous manifestations of COVID-19 (17-19)</i>	Dermatologists should pay particular consideration to patients with Viral-like skin rash (with or without infection) as some COVID-19 patients presented with skin rash and petechiae. Generally, they should be aware of the clinical features of COVID-19.
<i>Dermatological clinics and surgery (27, 29-38)</i>	<ul style="list-style-type: none">- Non-urgent outpatient visits should be deferred- Fever screening at the clinic entrance in endemic areas using a contact-free forehead thermometer (if feverish, refer to specialized fever clinic).- Patients should stick to wearing masks (if possible)- Physicians should stick to personal protective equipment- Dermatological surgeries should be restricted to urgent cases (including malignancies)- All cosmetic complaints should be postponed- Hospital admission should be limited to patients with severe skin disease not responding to outpatient treatments- Consider telemedicine and virtual clinics for follow up and consultation of non-emergency patients
<i>Teaching (39)</i>	<ul style="list-style-type: none">- Consider remote teaching through online lectures and seminars
<i>Immunomodulators/ immunosuppressants (49-51)</i>	<ul style="list-style-type: none">- It is recommended to perform a case-by-case evaluation considering the risk and benefit for each patient before stopping biologics during the current pandemic- In patients with confirmed COVID-19, immunomodulators should be stopped until the patient tests negative.- The recommendations should be based on the mechanism of action and the risk of infection for each drug.- Corticosteroids may be associated with delayed viral clearance but not increased risk of mortality so they should be used with caution
<i>Rheumatologic skin</i>	<ul style="list-style-type: none">- Dermatologists should be careful that COVID-19 may be

<i>disease (64)</i>	associated with new-onset or reactivation of arthritis during the remission period of rheumatoid arthritis.
<i>Sexual transmitted disease (65)</i>	<ul style="list-style-type: none"> - It is recommended to use teledermatology to continue the consultations of sexually transmitted diseases to avoid the further spread of these disease
<i>Dermatologic malignancies (62, 63)</i>	<ul style="list-style-type: none"> - Cancer patient may be at higher risk for development of infectious disease - Immune checkpoint inhibitors should be used with caution in patients with advanced melanoma (due to the lack of evidence regarding the susceptibility of patients using immune checkpoint inhibitors to SARS-CoV-2 infections)
<i>Occupational skin problems among healthcare workers (67, 68)</i>	<ul style="list-style-type: none"> - Avoid excessive hand washing (just limit it to the moments before and after contact with the patient or patients' items) - Use ethanol for hand hygiene and apply hand cream to avoid dermatitis - Wear cotton gloves below latex gloves and use moisturizers with topical glucocorticoid cream. - Use properly fitting masks and goggles and apply moisturizers or gel at contact and pressure areas - For N95 masks, use double protection of the nasal bridge (Benzalkonium chloride and hydrocolloid dressing).
<i>Dermoscopy (13)</i>	<ul style="list-style-type: none"> - Avoid dermoscopy for all COVID-19 confirmed patients (except if urgently indicated) - Avoid dermoscopy for highly dangerous sites for infection spread as hands, nails, face, eyes and mucous membranes - Sterilize the dermoscope before and after use using 70% alcohol - Consider using disposable dermatoscopic lense or transparent adhesive tape.
<i>Precautions for dermatologists working in endemic areas</i>	<ul style="list-style-type: none"> - All patients should be asked about respiratory symptoms, travel history to endemic areas or dealing with a confirmed COVID-19 patient. - All physicians should be wearing proper personal protective

	<p>equipment and keep the distance with the patient as much as possible</p> <ul style="list-style-type: none">- Special care of hand hygiene
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