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CORONAVIRUS DISEASE (COVID-19): DERMATOLOGIST PERSPECTIVE AND REVIEW OF LITERATURE

Dermatology

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ABSTRACT

The novel corona virus (2019-nCoV) is presenting a severe global challenge to health care. The most common presenting symptoms of corona virus disease (COVID-19) are cough, fever, and shortness of breath. Diarrhea was uncommon Abnormal radiologic findings are observed. There are regional variations in the mortality rates, ranging from 1.4 - 3.4%. Dermatologists must also work with the aim to slow the spread of the virus and try to keep illness at bay so that the health care system is not overburdened. Triage, hand hygiene, N-95 masks, and coordination following local infection control policies are essential. Dermatology practices as vectors for COVID-19 transmission has been suggested and a call for an immediate cessation of non-emergent dermatology visits is made. Hand washing and social distancing are the mainstays of prevention in the absence of any targeted therapy or vaccine to stop the spread of Covid-19. Remdesivir and Hydroxychloroquine and chloroquine are presently being explored as Therapeutic Options for COVID-19 Patients. Currently, studies are underway looking at Hydroxychloroquine (HCQ) prophylaxis.

KEYWORDS

Coronavirus Disease, COVID-19, Dermatologist perspective, Biologicals.

INTRODUCTION

The novel corona virus (2019-nCoV) has devastated the global health care management affecting more than 213 countries. The most common presenting symptoms of corona virus disease (COVID-19) are cough (67.8%), fever (43.8%) and shortness of breath [1]. Diarrhea is uncommon. Abnormal radiologic findings are observed. On admission, ground-glass opacity was the most common (56.4%) radiologic finding on chest computed tomography (CT). No radiographic or CT abnormality was found in 157 of 877 patients (17.9%) with non-severe disease and in 5 of 173 patients (2.9%) with severe disease [1]. Although, a varying degrees of illness presentation is also observed including presentation without fever and without abnormal radiologic findings. Lymphocytopenia was present in 83.2% of the patients on admission [1]. The disease severity varies from mild self-limiting flu-like illness to fulminant pneumonia, respiratory failure and death. There are regional variations in the mortality rates, ranging from 1.4 - 3.4%, and these estimates are rapidly changing as more data are becoming available [1,2]. The evidence from analyses of cases in China is that the disease is mild (i.e. non-pneumonia or mild pneumonia) in about 80% of cases; most cases recover, 14% develop severe disease, and 6% experience critical illness. Recent data from EU/EEA countries indicate that 30% of cases are hospitalised, and 4% require critical care [3]. Cutaneous manifestations of COVID-19 may be uncommon. Only 0.2% had a rash [1]. COVID-19 can present with a skin rash with petechiae and be mistaken for Dengue [4]. The virus remained stable on various surfaces for several days. The virus had the ability to remain airborne for up to three hours, and it could survive on plastic for up to three days and on steel for up to two days [5].

EPIDEMIOLOGY

The March 27, 2020, Morbidity and Mortality Weekly *Report (MMWR)* early release data from Centres for Disease Control and Prevention confirm that ages 19 and younger are at lower risk, while those ages 65 years and older are at high risk if exposed to corona virus and this risk further increases if there are associated comorbidities [6]. Fallon Friedlander also noted an increased risk among older patients as 80% of deaths occurred in those >65, but she warned those 20-64 years of age ignoring social distancing protocols that the 20% of deaths occur in this age group [7]. The median incubation period was 4 days. The median age of the patients was 47 years; 41.9% of the patients were female [1]. Severe illness and death are more common among the elderly and those with associated other chronic underlying conditions [8].

In contrast with infected adults, most infected children appear to have a milder clinical course. Lymphopenia (lymphocyte count, $<1.2\times10^9$ per liter) was present in 3.5% patients [9]. Asymptomatic infections were not uncommon [10]. The mild symptoms of COVID-19 observed in children have been correlated with the relative immaturity of the presumed cell receptor for the virus (ACE2) which may make children less receptive hosts, and this knowledge may lead to therapeutic targets [10]. However, it is also important to note that children on immunosuppressive medications and with predisposing medical issues are likely at higher risk. Of those infected, there was a strikingly high proportion who developed pneumonia (65%). Between 76% and 90% had a relative with confirmed infection, highlighting the likelihood of intra-familial spread [10]. It is important to note that while kids may not get sick, they can and are actively transmitting infection that is reaching the higher risk population [9].

A global variation in the severity of the disease is observed and various biological and environmental factors have been suggested to contribute significantly to this process [11]. A preliminary study on SARS-CoV2 genomes from different geographical origins—India, Italy, the US, Nepal and Wuhan in China—to identify the notable genomic features of coronavirus has come out with the finding that there may be a unique mutation in the Indian genome that needs to be studied further [12]. The microRNAs are present in all human beings. “hsa-miR-27b” is one of the six antiviral microRNAs that can potentially bind to virus genes and affect its activity. The analysis revealed that there is only a single host microRNA (miRNA) titled "hsa-miR-27b" that is uniquely targeting the India SARS-CoV2. The study revealed nine host miRNAs which can potentially target SARS-CoV2 genes. Interestingly, the nine miRNAs do not have targets in SARS and MERS genomes. Also, 'hsa-miR-27b' is the only unique miRNA which has a target gene in the Indian SARS-CoV2 genome. However, the research has so far been done in one genome sequence from India, so it is too early to predict that novel coronavirus is less virulent in the Indian context.

Dermatologic Perspective

Due to the current lack of specific treatment and the risk of transmission during the viral incubation period, infection prevention and control of 2019-nCoV are both urgent and critical to global health [1]. It is still possible to miss infected patients in the asymptomatic incubation period even after implementing a series of strict prevention and control measures. Additionally, both the awareness of protection and protective facilities are generally lacking in medical departments, including dermatology. Moreover, most patients in the dermatology department have skin lesions which makes it easier for 2019-nCoV to transmit via indirect contact. Therefore, dermatology departments could be at a relatively high-risk for COVID-19 outbreaks [13,14].

Dermatologists must work with the aim to slow the spread of the virus and try to keep illness at bay so that the health care system is not overburdened. There have been recent publications highlighting how dermatology departments have been organizing themselves in the

midst of COVID-19 [13,14]. Triage, hand hygiene, N-95 masks, and coordination following local infection control policies are essential [13]. Dermatologists must stay informed about the local COVID-19 situation through reliable resources and local health department website. An emergency plan should be kept ready to deal with staff absenteeism due to lockdown or corona virus outbreak to ensure as many of your clinic staff are available on duty as possible. **Establish** coalition, support or assistance **relationships with local public health partners in your community** and learn about plans to manage patients, accept transfers, and share supplies with them specially during emergencies. **Communicate and** share information about **COVID-19 with your hospital staff**, the potential for surge, and your facility's preparedness plans. Let your staff know your plans about providing non-urgent patient care by telephone, and visitors, and letting patients know of any changes to your appointment policies, particularly around providing non-urgent care by telephone. Consider using your facility's website or social media pages to share updates. If you are senior, or have an underlying medical condition associated with reduced immunity, cardiac or pulmonary ailments, or are pregnant, stay home and consider referring your patient to a colleague who is working.

Due protective measures should be taken for the protection of your clinic/hospital staff. Screen patients and visitors for symptoms of acute respiratory illness, such as fever, cough, or difficulty in breathing, before entering your healthcare facility to protect your workforce. Someone with any skin diseases and having fever/cough/ breathlessness should report to clinics set up for screening coronavirus cases. Sick employees should stay home. Clinical staff should be trained to know the right ways to put on, use, and take off personal protection equipment (PPE) safely. Implement mechanisms to quickly triage and separate sick patients. Hand hygiene and cough etiquette should be emphasized for everyone. Anyone who has a possibility of exposure or coming in contact with a possible COVID-19 patient should wear the appropriate PPE, including gloves, gowns, respiratory protection, and eye protection, all of which should be properly put on before making contact and removed properly with due care and discarded or cleaned and disinfected afterward.

Educate patients in waiting area and rooms by posting signs at entrances and in waiting areas about prevention actions. Keep tissues, alcohol-based hand-rub, soap at entry and sinks, and trash cans to prevent the spread of the coronavirus. Place chairs 3–6 feet apart, when possible to maintain social distancing. Use barriers (like curtains, screens), if possible. Separate patients with respiratory symptoms so they are not waiting among other patients seeking care. Provide symptomatic patients with tissues or face masks to cover mouth and nose.Limit non-patient visitors and attendants. If your office has toys, reading materials, or other time-pass objects, remove them or clean and sanitize them regularly.

Consider the methodologies to prevent patients from coming to your clinic/hospital potentially exposing themselves or others by rescheduling non-urgent appointments and procedures and using your telephone and social media in light of the presently significantly relaxed regulations on telemedicine. Dermatology practices as vectors for COVID-19 transmission has been suggested and a call for immediate cessation of non-emergent dermatology visits is made [15]. Online consultation for mild and non-emergency patients has obviously decreased the number of patients in dermatology clinics during the epidemic period, which reduces the probability of nosocomial infection of 2019-nCoV. Patients requiring emergency medical support are not subject to the restrictions on social distancing and travel. Such patients therefore may be attended in person after taking due precautions for proper treatment.

After patients leave, clean frequently touched surfaces like counters, beds, seating using proper disinfectants. Notify your local health authorities of patients with COVID-19 symptoms.

Hand washing and social distancing are the mainstay of prevention in the absence of any targeted therapy or vaccine to stop the spread of Covid-19. It is important to continue proper hygiene by cleaning hands with soap and water or an alcohol-based hand rub between every encounter and entrance and exit in the exam room and to practice social distancing. The WHO recommends the use of 70% ethyl alcohol to disinfect popular clinical areas between uses and sodium hypochlorite 0.5% to disinfect common surfaces [16]. Common areas including counter tops, exam beds, exam tables, door knobs, exam light buttons and handles, chairs and faucet handles should be sanitized between patients and at the end of each day.

Health officials should urge people to wash their hands at every opportunity. However, a possible side effect of frequent hand washing is dry skin that can flake, itch, crack and even bleed making person more susceptible to germs and other bacteria [17]. Dermatologists should encourage the public to moisturize after washing hand to prevent excessive dry skin and infections especially if they are prone to dry skin. Kovarik [17] recommends moisturizing immediately after washing your hands while your hands are still slightly damp helps lock in the moisture on your skin. Use moisturizers that contain mineral oil or petrolatum and make sure they are fragrance free and dye free, as these are less irritating. When soap and water aren't available, use hand sanitizer, followed by moisturizer. However, after applying hand sanitizer, make sure your hands dry completely before applying the moisturizer.

Considerations regarding immuno suppressants and biologics

There are concerns about the immunomodulatory effects of immunosuppressants and biologic therapy in the context of coronavirus (COVID-19). Indian Association of Dermatologists, Venereologists & Leprologists (IADVL) has issued guidelines on the use of immunosuppressants and biologics in patients with skin disease [18]. It says: 1. Continuing or starting immunosuppression with a patient with severe skin disease has to be done on a case to case basis. Immunosuppressed patients are at an increased risk of severe coronavirus disease 2. Instruct patients already on immuno suppressants including steroids, chemotherapeutic drugs and biologics on effective preventive strategies. International Psoriasis Council recommends discontinuation of biologics who are infected with Coronavirus. Similar measures should be considered for other immunosuppressants in other diseases 3. For other patients who are not symptomatic or have not tested positive for coronavirus infection, reduce steroids and other immunosuppressants to the lowest clinically effective dose. Consider effect of sudden reduction of dose or withdrawal of the immunosuppressant on the primary disease, and also on the patient, e.g. sudden withdrawal of long term corticosteroid and adrenal insufficiency. If the patient has been on long-term oral prednisolone, the target dose should be 7.5-10 mg/day to avoid manifest adrenal insufficiency.

Presently, there is no data on the specific risk of COVID-19 infection with biologic therapy. Specifically, we do not have direct evidence to support any preferred biologic class or mechanism-of-action with regard to COVID-19 infection risk at this moment [15,19,20]. Dermatologists must delicately balance the risk of immunosuppression with the risk of disease flare requiring urgent intervention. The American Academy of Dermatology (AAD) strongly recommends that patients should not stop biologic therapy without consulting their physicians. The AAD has put forth the following interim recommendations [20]: **1. Patients already on biologic therapy who have not tested positive or exhibited signs/symptoms of COVID-19:** There is insufficient evidence to recommend discontinuation of biologics at this time. Physicians should continue to weigh the risk vs. benefits of the use of biologic medication on a case-by-case basis. However, at the level of the individual patient, should include the original indication for the biologic, the severity of the original indication, the patient's age (whether they are >60 years old) and comorbidities. Comorbidities that may put patients at higher risk for serious illness from COVID-19 include serious chronic medical conditions such as cardiovascular disease, diabetes, severe hypertension, liver disease, kidney disease, respiratory system compromise, internal malignancies or tobacco use, among others [21,22,23]. **2. Patients on biologic therapy who have tested positive for COVID-19:** AAD recommend physicians discontinue or postpone the biologic therapy until the patient recovers from COVID-19. **3. As regards with Patients being considered for biologic therapy initiation:** AAD recommend physicians assess the risk vs. benefits in lower-risk patients before initiating biologics therapy on a case-by case basis, recognizing that anyone may develop serious complications from COVID-19 infection. For patients in a high-risk population (e.g.: individuals 60 years and older, or patients with recognized comorbidities such as cardiovascular disease, diabetes, severe hypertension, liver disease, kidney disease, respiratory system compromise, internal malignancies or tobacco use, among others) [21,22,23]. AAD recommend that physicians consider deferring

initiation of biologic therapy. Alternative therapeutic approaches can be considered to treat high-risk patients.

W.H.O. has issued a DRAFT landscape of COVID-19 candidate vaccines being developed on various RNA, DNA, non-replicating viral vector, prorein subunits, and inactivated and live attenuated virus [24].

Dermatologists should conserve protective equipment and vital medications. The FDA has outlined several conservation strategies based on supply levels to assist health care organizations and personnel in managing items such as surgical masks, gloves and personal protective equipment during the COVID-19 outbreak so that urgently needed medications and supplies are available for patients and health care responders on the front lines [25]. Medications should continue to be reserved for their indicated use, and for the patients who need them.

The rapeutic Options for COVID-19 Patients

Presenly, there are no US Food and Drug Administration (FDA) approved drugs specifically for the treatment of patients with COVID-19. The clinical management includes infection prevention and control measures and supportive care, including supplementary oxygen and mechanical ventilatory support when indicated. An array of drugs approved for other indications as well as several investigational drugs are being studied in several hundred clinical trials that are underway across the globe. Two of the approved drugs (chloroquine and hydroxychloroquine) and one of the investigational agents (remdesivir) currently in use in the United States are [26]: 1. **Remdesivir** is an investigational intravenous drug with broad antiviral activity that inhibits viral replication through premature termination of RNA transcription and has in-vitro activity against SARS-CoV-2 and in-vitro and in-vivo activity against related beta-corona viruses [27,28,29], **2. Hydroxychloroquine and chloroquine** are oral prescription drugs that have been used for treatment of malaria and certain inflammatory conditions. Chloroquine has been used for malaria treatment and chemoprophylaxis, and hydroxychloroquine is used for treatment of rheumatoid arthritis, systemic lupus erythematosus and porphyria cutanea tarda. Both drugs have in-vitro activity against SARS-CoV, SARS-CoV-2, and other coronaviruses, with hydroxychloroquine having relatively higher potency against SARS-CoV-2 [27,30,31]. A study in China reported that chloroquine treatment of COVID-19 patients had clinical and virologic benefit versus a comparison group, and chloroquine was added as a recommended antiviral for treatment of COVID-19 in China [32]. Based upon limited in-vitro and anecdotal data, chloroquine or hydroxychloroquine are currently recommended for treatment of hospitalized COVID-19 patients in several countries. Both chloroquine and hydroxychloroquine have known safety profiles with the main concerns being cardiotoxicity (prolonged QT syndrome) with prolonged use in patients with hepatic or renal dysfunction and immunosuppression but have been reportedly well-tolerated in COVID-19 patients [26].

There are no currently available data from Randomized Clinical Trials (RCTs) to inform clinical guidance on the use, dosing, or duration of hydroxychloroquine for prophylaxis or treatment of SARS-CoV-2 infection. Although optimal dosing and duration of hydroxychloroquine for treatment of COVID-19 are unknown, some U.S. clinicians have reported anecdotally different hydroxychloroquine dosing such as: 400mg BID on day one, then daily for 5 days; 400 mg BID on day one, then 200mg BID for 4 days; 600 mg BID on day one, then 400mg daily on days 2-5 [26].

Lopinavir-ritonavir did not show promise for treatment of hospitalized COVID-19 patients with pneumonia in a recent clinical trial in China [33].

Recently, A group of researchers in China has used mesenchymal Stem cell therapy in COVID-19 patients to effectively boost the immune system that demonstrated success at treating the condition [34]. They observed that intravenous infusion of clinical-grade human mesenchymal stem cells is a safe and efficient approach for treating patients with COVID-19 pneumonia, including in elderly patients displaying severe pneumonia.

Recently, FDA approved a new "Natural Killer" (NK) cell therapy for COVID-19 [35]. These NK cells are derived from stem cells cultivated from placental tissue, which hospitals typically treat as medical waste. "Natural Killer" (NK) cell therapy boost the immune system's disease-fighting response. NK cells typically work to support the immune system by identifying and destroying cells in the body that appear to be stressed, either from an infection or a mutation. NK cell therapy could provide a benefit to COVID-19 patients in terms of limiting SARS-CoV-2 replication and disease progression by eliminating the infected cells. However, there are some potential roadblocks and risks to pursuing the NK therapy. Chiefly, COVID-19 is deadly in part because it can push the immune system into overdrive. The "cytokine storm" that results from the infection means that the body starts attacking healthy cells in the lungs, which leads to organ failure and death. If that's the case, then boosting the immune response to COVID-19 might be dangerous for patients.

An anti-parasitic drug Ivermectin available throughout the world has been found to kill COVID-19 in the lab within 48 hours. This study has shown a single dose of the drug Ivermectin could stop the SARS-CoV-2 virus growing in cell culture and even a single dose could essentially remove all viral RNA by 48 hours and that even at 24 hours there was a really significant reduction in it [36].

Prophylaxis

Currently studies are underway looking at Hydroxychloroquine (HCQ) prophylaxis. HCQ may be useful as both post-exposure prophylaxis to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, as well as in the treatment of COVID-19. At EC50 values of 6.25 and 5.85 micromolar at 24 and 48 hours, HCQ may be a promising drug for prevention of SARS-CoV-19 if it is ingested days before the virus is introduced to the body [37]. The drug can accumulate at high concentrations in lung tissue. Physiologically-based pharmacokinetic models (PBPK) implemented by integrating in vitro data and simulating the concentration of hydroxychloroquine in lung fluid suggests that a single dose of hydroxychloroquine at 800 mg may provide a lung tissue concentration that is more than twenty times higher than EC50 values necessary to inhibit SARS-CoV-2 in the lung on day 1. It is plausable that a single dose of 400 mg or even 200 mg can provide adequate lung tissue concentration to inhibit SAR-CoV-2. Since the half life after a single dose of 200 mg is 22 days (FDA data), a single dose every three weeks should be sufficient for prevention of SARS-CoV-2 induced lung damage [38]. Data published online March 17, 2020, in the *International Journal of Antimicrobial Agents*, shows that patients who were given 200mg HCQ, three times/day for 10 days, had significant clearance of the SARS-CoV-2 viral load in the nasopharynx compared with non-treated controls, and that effect was enhanced when azithromycin was added [39].

In India, Indian Council of Medical Research (ICMR) recommends use of hydroxy-chloroquine for critical COVID-19 cases [40]. Hydroxy-chloroquine is recommended only for preventive treatment of healthcare workers and individuals in close contact of coronavirus patients. The National Task Force for COVID-19, constituted by Indian Council of Medical Research (ICMR), recommended the use of hydroxy-chloroquine for preventive treatment of healthcare workers and individuals in close contact of coronavirus patients. The task force has recommended the use of hydroxy-chloroquine for prophylaxis of SARS-CoV-2 infection for selected individuals, such as asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19. The drug may be also used in case of asymptomatic household contacts of confirmed COVID-19 patients [40]. For healthcare workers, a dose of 400 mg twice a day on day 1, followed by 400 mg once weekly for next 7 weeks, has been prescribed. The medicine has to be taken with meals, as per the report. The task force has recommended a dose of 400 mg twice a day on day 1, followed by 400 mg once weekly for next 3 weeks for household contacts of laboratory confirmed cases. This has to be taken with meals.

The Bacillus Calmette-Guerin (BCG) vaccine

Recently, US scientists linked Bacillus Calmette-Guerin (BCG) vaccination with fewer Covid-19 cases [41]. The severity of coronavirus impact may be linked to national policies on BCG childhood vaccination. They found that countries without universal policies of BCG vaccination, such as Italy, the Netherlands, and the United States, have been more severely affected compared to countries with universal and long-standing BCG policies. According to the study, a combination of reduced morbidity and mortality could make the BCG vaccination a game-changer in the fight against coronavirus in countries like India. BCG had in the past been found in children to

demonstrate a non-specific protective effect against infections, particularly respiratory infections. Live vaccines, such the BCG, measles and oral polio vaccines, are thought to have non-specific beneficial effects on some infections. Therefore it is possible that BCG could reduce the intensity of SARS-CoV-2 infection by stimulating the memory of innate immunity, the first line of immunity in the face of infection, and thereby inducing "trained innate immunity" [42]. Epidemiological studies have shown a correlation between rates of BCG vaccination and rates of COVID-19 morbidity and mortality. While most of these studies point in the same direction, a causal relationship cannot be concluded because major biases remain, particularly in terms of differences in living standards and healthcare policies between countries with high and low vaccination rates.

Conclusion / Key Message

Due to the current lack of specific treatment and the risk of transmission during the viral incubation period, infection prevention and control of 2019-nCoV are both urgent and critical to global health. It is still possible to miss infected patients in the asymptomatic incubation period even after implementing a series of strict prevention and control measures. At this point of time, hand sanitation and social distancing are the two most effective way we can combat the spread of COVID-19. Minimize OPD attendance, postpone elective procedures, delay return visits for stable established patients, and practice teledermatology in any way and as often you can to reduce the number of patients coming for face to face office visits. Due measures to protect yourself, your staff, and your patients should be taken.

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