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REVIEW ARTICLE

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Coronavirus disease (COVID-19): An updated review based on current knowledge and existing literature for dermatologists

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Abstract

The world entered the year 2020 with reports of the emergence of a new viral illness in Wuhan city, Hubei province, China. In January 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified to be the causative novel coronavirus for the cluster of patients suffering from pneumonia in China. The disease was later named as coronavirus disease (COVID-19) and was declared a pandemic by the World Health Organization on March 11, 2020. Several studies, since then, have tried to study and explain the origin of SARS-CoV-2, its structure and pathogenicity, epidemiology, modes of transmission, spectrum of illness and causes of mortality and morbidity. The current management strategies focus on supportive care and prevention of complications. With no definite treatment, as of now, encouraging reports of some anti-viral and anti-malarial drugs in the management of COVID-19 generate some hope. This review intends to cover the current known aspects of COVID-19 and SARS-CoV-19, based on the available literature.

KEYWORDS

coronavirus disease; COVID-19; SARS, SARS-CoV-2, MERS, acute respiratory distress syndrome (ARDS), pandemic, pneumonia

Abbreviations: 229E, Corona Virus strain 229E; 2019-nCoV, Novel Corona Virus 2019; ACE2, Angiotensin Converting Enzyme 2; ARDS, Acute Respiratory Distress Syndrome; ARI, Acute Respiratory Infection; BP, Blood Pressure; bpm, Beats per Minute; CDC, Center for Disease Control and Prevention, Atlanta, USA; CoVs, Corona Viruses; COVID-19, Corona Virus disease 2019; CPAP, Continuous Positive Airway Pressure; CRP, C Reactive Protein; DPP4, Dipeptidyl peptidase 4; ESR, Erythrocyte Sedimentation Rate; FiO_2, Fraction of Inspired Oxygen; GCSF, Granulocyte Colony Stimulating Factor; GM-CSF, Granulocyte-Macrophage Colony Stimulating Factor; HCoV, Human Corona Virus; HCQS, Hydroxycholoroquine; HCWs, Health Care Workers; HR, Heart Rate; ICTV, International Committee on Taxonomy of Viruses; $IFN\gamma$, Interferon gamma; IFN-I, Interferon Type-1; IL 1B, Interleukin 1 beta; IL 2, Interleukin 2; IL-2R, Interleukin 2 Receptor; IL 6, Interleukin 6; IL 7, Interleukin 7; IL 10, Interleukin 10 (also called Human Cytokine Synthesis Inhibitory Factor); IP 10, Interferon gamma-induced Protein 10 (also called C-X-C motif chemokine 10); MAP, Mean Arterial Pressure; MCP1, Monocyte Chemoattractant Protein 1; MERS, Middle Eastern Respiratory Syndrome; MERS-CoV, Middle East Respiratory Syndrome Corona Virus; MIP1A, Macrophage Inflammatory Protein 1 alpha (α); mRNA, Messenger RNA; Mts, Metres; NAAT, Nucleic Acid Amplification Test; NCIP, Novel Coronavirus Infected Pneumonia; NIV, Non-Invasive Ventilation; NK cells, Natural Killer cells; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; OC43, Corono Virus strain OC43; OI, Oxygenation Index; OSI, Oxygenation Index using SpO2; PaO_2, Partial Pressure of Oxygen; PEEP, Positive End-Expiratory Pressure; PPE, Personal Protective Equipment; RBD, Receptor Binding Domains; RdRP, RNA dependent RNA Polymerase; rhACE2, Recombinant Human Angiotensin Converting Enzyme 2; RNA, Ribo Nucleic Acid; rRT-PCR, real-time Reverse Transcription Polymerase Chain Reaction; SARS, Severe Acute Respiratory Syndrome; SARS-CoV, Severe Acute Respiratory Syndrome Corona Virus 1; SARS-CoV-2, Severe Acute Respiratory Syndrome Corona Virus 2; SBP, Systolic Blood Pressure; SD, Standard Deviation; Se. Ferritin, Serum Ferritin; SIRS, Systemic Inflammatory Response Syndrome; Sl no, Serial Number; SOFA score, Sequential Organ Failure Assessment Score; SpO_2, Peripheral capillary Oxygen Saturation; TMPRRS2, Trans-Membrane Protease Serine 2; TNFα, Tumor Necrosis Factor α; WHO, World Health Organization.

1 | INTRODUCTION

The world has seen three major coronavirus infections in the past two decades: Severe Acute Respiratory Syndrome (SARS) in 2003, Middle Eastern Respiratory Syndrome (MERS) in 2012 and now, coronavirus disease (COVID-19) in 2019.[1] COVID-19 has already surpassed the total number of SARS and MERS cases, combined. With the World Health Organization (WHO) declaring COVID-19 as a pandemic, it is clear that the world is facing a bigger threat, than ever before.[2] The ubiquitous nature and frequent cross-species transmission are two unique features of coronaviruses. Coronaviruses derive their name from the spike proteins that are embedded on their envelope and these proteins determine the viral host/cell type specificity.[3] The rapidity of spread, variable incubation period, unidentified modes of transmission, asymptomatic carriers, lack of herd immunity and high morbidity and mortality related to SARS-CoV-2 are some of the factors that concern clinicians, microbiologists and other research scientists all over the world.[3] At present, the information on the pathogen as well as the disease is limited.

2 | PATHOGEN AND PATHOGENESIS

The disease has been officially named as coronavirus disease (COVID-19) and the causative virus is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[4] The International Committee on Taxonomy of Viruses (ICTV) announced "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" as the name of the new virus on 11th February 2020. This particular nomenclature was chosen because the virus is genetically related to the coronavirus responsible for the SARS outbreak of 2003.[4]

The coronaviruses have been causing major epidemics and pandemics in the last two decades. After the SARS-CoV epidemic in 2003, a novel human CoV emerged in the Middle East in 2012, which was named as Middle East Respiratory Syndrome-CoV (MERS-CoV).[5] It was responsible for causing a series of highly pathogenic respiratory tract infections in Saudi Arabia and other countries in the Middle East.[4,6]

Coronaviruses (CoVs) were originally grouped into the family *Coronaviridae*, based on the crown like appearance given by the glycoprotein-studded envelope (visible on electron microscopy). It is now known that Coronaviruses (CoVs) are the largest group of viruses belonging to the *Nidovirales* order, which includes *Coronaviridae, Arteriviridae, and Roniviridae* families.[6,7]

The virions are spherical to pleomorphic enveloped particles, the envelope being studded with glycoproteins. The centre of the virion comprises of a matrix protein, enclosed within which is a single strand of positive-sense RNA (in association with a nucleocapsid protein).[8] The glycoproteins facilitate the attachment of the virion to the host cell surface. Additionally, the envelope also carries a number of antigenic epitopes.[7,9] **Figure 1** illustrates the virion structure and structural proteins of coronavirus.

On the basis of antigenic determinants and requirements for culturing the organism, coronaviruses fall into either of the two groups: 229E-like and OC43-like. The former can be isolated in human embryonic fibroblast cultures; however, the latter ones can be isolated and/or adapted to grow in suckling mouse brain. Minimal cross-antigenicity between the two types is noted.[8,10]

The multiplication of the virus is facilitated by aminopeptidase-N and sialic acid-containing receptors. The sites of receptor binding domains (RBD) within the S1 region of a coronavirus S protein vary depending on the virus. SARS-CoV (Severe Acute Respiratory Syndrome associated coronavirus) has the RBD at the C-terminus of S1. It is worth mentioning that the S-protein/receptor interaction is the primary determinant for a coronavirus to infect a host species. SARS-CoV uses angiotensin-converting enzyme 2 (ACE2) as their receptor, to gain entry into human cells.[6,10,11]

Following entry, the glycoprotein envelope is removed. Thereafter, the virus enters the host cell cytosol by acid-dependent proteolytic cleavage of S protein by a cathepsin, TMPRRS2 or another protease, followed by fusion of the viral and cellular membranes. The subsequent step is transcription followed by translation of the replicase gene from the virion genomic RNA. CoV messenger RNAs have a tendency to form a "nested set" with common 3′ ends; the uniqueness being the translation of only 5' ends.[8] During translation, proteins are assembled at the cell membrane and genomic RNA gets incorporated, when complete viral particle is formed as a result of budding from internal cell membranes.[7,10]

Coronaviruses cause a large variety of diseases in animals, including pigs, cows, chickens, dogs and cats. MERS-CoV had utilized Dipeptidyl peptidase 4 (DPP4) as its receptor and it was noted that the virus was only able to use the receptors from certain species such as bats, humans, camels, rabbits, and horses, to establish an infection. It is thought that SARS-CoV-2 has originated from an animal reservoir only (most likely bats, but substantial evidence is yet to be found).[10]

The virus is transmitted via inhalation of contaminated droplets (aerosol). But it should be kept in mind that the virus can also be transmitted through hands and via the nasal, oral and ocular mucosa.[7]

The virus invades the respiratory tract, portal of entry being the nose. Following an incubation period of 2-14 days, the patient

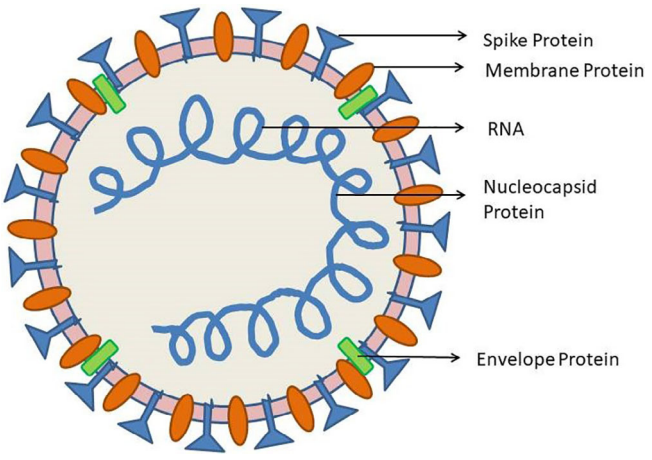

FIGURE 1 Coronavirus Virion Structure and Proteins

presents with a flu-like illness characterized by running nose, myalgia, fever, dry cough; which gradually progresses towards a more severe illness in the form of a productive cough and respiratory distress.[6,7]

3 | TRANSMISSION OF THE NOVEL SARS CoV-2

The initial four cases were reported on 29 December 2019 and were all traced back to the Huanan (Southern China) Seafood Market. The cases were identified by local hospitals using a surveillance mechanism for 'pneumonia of unknown etiology' that was established in the wake of the 2003 Severe Acute Respiratory Syndrome (SARS) outbreak, with the aim of allowing timely identification of novel pathogens such as 2019-nCoV.[12]

While the virus is zoonotic, human-to-human transmission is responsible for its rapid spread. Initial reports estimated that, on an average, one infected person would infect between two and three more.[13] A study found that cases of COVID-19 were doubling in number approximately every 7.4 days.[12] The incubation period for COVID-19 is currently estimated at between 2 and 14 days.[12,13] Coronaviruses are known to mutate effectively, which makes them highly contagious.[14,15] SARS-CoV-2 also seems to be having an easy and sustainable community spread in certain affected geographical areas.[16]

Human-to-human transmission among close contacts has occurred since the middle of December and spread out gradually within a month after that.[12] Researchers believe that the viruses transmit via fluids (mucus) in the respiratory system, produced when an infected person coughs or sneezes. Various modes of transmission of the virus are enlisted in Table 1.[13-17]

It has been observed that not only the symptomatic infected people are capable of transmitting the disease, but there is evidence suggesting that transmission can also occur from an asymptomatic infected person.[13,16] A research group analyzed the viral load in nasal and throat swabs of 17 symptomatic patients in relation to day of onset of any symptoms.18 Higher viral loads in the nose than in the throat, were detected soon after symptom onset. This study also demonstrated that the viral load detected in asymptomatic patients was similar to that in symptomatic patients; which suggests the transmission potential of minimally symptomatic or asymptomatic patients. These findings are in agreement with reports which state that the transmission may occur early in the course of infection.[1] Based on the available data, the World Health Organization has defined four transmission scenarios for COVID-19 as depicted in Table 2.[19]

4 | STABILITY OF SARS-COV-2 UNDER ENVIRONMENTAL CONDITIONS AND SUSCEPTIBILITY TO DISINFECTION

Studies suggest that the virus can survive for several hours on surfaces such as tables and door handles.[13] A comparative experiment between the SARS-CoV-1 and SARS-CoV-2, proved SARS-CoV-2 to be more stable on plastic and stainless steel than on copper and cardboard. Although the virus titre greatly reduced after application, viable virus was detected up to 72 hours on plastic and 48 hours on stainless steel, while no viable virus was measured on copper after 4 hours and on cardboard after 24 hours.[20] Another study found that SARS-CoV and human coronavirus (HCoV) strain 229E persisted up to 5 days on metals like steel, 8 hours on aluminium, 4 days on wood, 4-5 days on paper and glass, 5 days on ceramic and teflon, 5-6 days on plastic, 2 days on a disposable surgical gown but only up to 8 hours on a latex surgical glove.[21]

Comparative data obtained with SARS-CoV, demonstrated that persistence of the virus was longer with a higher inoculum. The susceptibility to temperature, humidity and other environmental factors is still not proven and it is only speculated that the SARS-CoV-2 is susceptible to higher temperatures. The range of temperature and time duration to inactivate the virus is still being studied.

Inactivation studies of coronaviruses with various biocidal agents show that ethanol (78–95%), 2-propanol (70–100%), the combination of 45% 2-propanol with 30% 1-propanol, glutardialdehyde (0.5–2.5%), formaldehyde (0.7–1%) and povidone iodine (0.23–7.5%) readily inactivate coronavirus infectivity by approximately 4 $\log_{10}$ or more. Other agents effective against coronaviruses include: sodium hypochlorite (0.21%) and hydrogen peroxide (0.5%). Data obtained with benzalkonium chloride and chlorhexidine digluconate was insufficient to prove their effectiveness. The usual contact time for these biocidal agents to disinfect the surfaces is at least 1 minute.[21]

TABLE 1 The potential routes of transmission of Coronaviruses[13-17]

Potential routes of transmission of Coronavirus

1. Aerosol/Droplet spread: Sneezing and coughing (within about 6 feet).
2. Human-to human intimacy: Shaking hands, kissing and physical contact in any form
3. Fomite-to-human: Touching the nose, eyes, or mouth after making contact with a surface or object that has the viral load on it
4. Animal-to-human
5. Oro-fecal transmission: SARS-CoV-2 has been detected in the gastrointestinal tract, saliva and urine of the infected individuals.

TABLE 2 Transmission Scenarios for COVID-19[19]

Stage	Definition
Stage 1 (No cases)	Countries with no cases.
Stage 2 (Sporadic Cases)	Countries with 1 or more cases imported or locally detected.
Stage 3 (Cluster of cases)	Countries experiencing cases clusters in time, geographic location, or common exposure.
Stage 4 (Community transmission)	Countries experiencing larger outbreaks of local transmission.

5 | CASE DEFINITION

Definitions for a confirmed, probable and a suspected case of COVID-19 have been recommended by the World Health Organization. The case definitions are based on current information and are subjected to constant revision as new information gets collected. Different countries have also modified and adapted these case definitions depending on their own epidemiological situation.[22-24]

5.1 | Suspected case

A. Patient with acute respiratory illness (that is, fever and at least one sign or symptom of respiratory disease, for example, cough or shortness of breath) AND with no other etiology that fully explains the clinical presentation AND a history of travel to or residence in a country, area or territory that has reported local transmission of COVID-19 disease during the 14 days prior to symptom onset.
   OR
B. Patient with any acute respiratory illness AND who has been a contact of a confirmed or probable case of COVID-19 disease during the 14 days prior to the onset of symptoms (see the definition of contact below); OR Surveillance for human infection with novel coronavirus: revised guidance.
   OR
C. Patient with severe acute respiratory infection (that is, fever and at least one sign or symptom of respiratory disease, for example, cough or shortness breath) AND who requires hospitalization AND who has no other etiology that fully explains the clinical presentation.

5.2 | Probable case

A. A suspect case for whom testing for COVID-19 is inconclusive (Inconclusive being the result of the test reported by the laboratory)
   OR
B. A suspected person whose testing could not be performed due to any reason.

5.3 | Confirmed case

A person with laboratory confirmation of infection with the COVID-19 virus, irrespective of clinical signs and symptoms.

5.4 | Definition of contact

A contact is a person who is involved in any of the following within 14 days after the onset of symptoms in the patient;

1. Providing direct care for patients with COVID-19 disease without using proper personal protective equipment
2. Staying in the same close environment as a COVID-19 patient (including sharing a workplace, classroom or household or being at the same gathering)
3. Travelling in close proximity with (that is, having less than 1m separation from) a COVID-19 patient in any kind of conveyance.

6 | CLINICAL PRESENTATION

The clinical manifestations due to COVID-19 greatly resemble that of a viral pneumonia. Therefore, the illness caused by this virus was named “novel coronavirus-infected pneumonia” (NCIP). The infection shows a male predominance and is more commonly seen in individuals in their 40s.[25-28]

The clinical spectrum may range from an asymptomatic infection to a mild-moderate infection, acute respiratory distress syndrome, septic shock and multi-organ failure and death.[22,25-29] The most common initial symptoms being reported are fever (>90%), malaise/fatigue (upto 70%), cough or chest tightness (around 75%), and dyspnea (around 50%).[25-29] Cough is usually dry or non-productive. However few cases have shown productive cough with white sputum. Most cases are reported to experience a mild illness course. Small subsets of patients have also been reported to have hemoptysis, gastrointestinal symptoms such as anorexia, abdominal pain, nausea, vomiting and diarrhea.[28--29] In a study by Huang et al, out of a total of 41 infected patients, 73% were male with average age of 49 years. Fever was seen in 40 patients (98%), cough [76%], and myalgia or fatigue in 44%. Less common symptoms observed were sputum production (28%), headache (8%), haemoptysis (5%), and diarrhoea (3%). Dyspnoea developed in 22 (55%).[29]

There are few asymptomatic cases reported in the literature, where the patient may present with respiratory symptoms without any fever or cough. Asymptomatic carriers or close contacts have tested positive without presentation of any signs or symptoms.[28-30] WHO has provided guidelines and definitions of various clinical syndromes associated with COVID-19 infection (Table 3).[23]

In pediatric population, fever and cough are again the most common symptoms. Most of the cases show a consolidation with a surrounding halo sign on CT scan of the lungs. This finding has been observed to be different from adults. It is suggested that underlying co-infection may be more common in pediatrics, and the consolidation with a surrounding halo sign is considered as a typical sign in pediatric patients.[32]

In pregnant females, the clinical manifestations have been observed to be similar to those reported for non-pregnant adult patients.[33] Although, it may have adverse effects on newborns like fetal distress, premature labor, respiratory distress, thrombocytopenia along with abnormal liver function, and even death. there is currently no concrete evidence for intrauterine infection caused by vertical transmission in women who develop COVID-19 pneumonia

TABLE 3 Clinical Syndromes associated with COVID-19.[23]

Mild pneumonia	Patient with pneumonia and no signs of severe pneumonia. Child with non-severe pneumonia has cough or difficulty breathing + fast breathing: fast breathing (in breaths/min)
Severe pneumonia	Adolescent or adult: fever or suspected respiratory infection, plus one of respiratory rate >30 breaths/min, severe respiratory distress, or SpO2 <90% on room air. Child with cough or difficulty in breathing, plus at least one of the following: central cyanosis or SpO2<90%. severe respiratory distress (e.g. grunting, very severe chest indrawing); signs of pneumonia with a general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions. Other signs of pneumonia may be present: chest indrawing, fast breathing (in breaths/min):
Acute Respiratory Distress Syndrome	**Onset**: new or worsening respiratory symptoms within one week of known clinical insult. **Chest imaging** (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by effusions, lobar or lung collapse, or nodules. **Origin of oedema**: respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of oedema if no risk factor present. Oxygenation (adults): • Mild ARDS: 200 mmHg < PaO2/FiO2 ≤ 300 mmHg (with PEEP or CPAP ≥5 cmH2O, 7 or non-ventilated8) • Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤200 mmHg with PEEP ≥5 cmH2O, 7 or non-ventilated8) • Severe ARDS: PaO2/FiO2 ≤ 100 mmHg with PEEP ≥5 cmH2O, 7 or non-ventilated8) • When PaO2 is not available, SpO2/FiO2 ≤315 suggests ARDS (including in non-ventilated patients) Oxygenation (children; note OI = Oxygenation Index and OSI = Oxygenation Index using SpO2): • Bilevel NIV or CPAP ≥5 cmH2O via full face mask: PaO2/FiO2 ≤ 300 mmHg or SpO2/FiO2 ≤264 • Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5 • Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3 • Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥ 12.3
Sepsis	Adults: life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection, with organ dysfunction*. Signs of organ dysfunction include: altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, or laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate or hyperbilirubinemia. Children: suspected or proven infection and ≥2 SIRS criteria, of which one must be abnormal temperature or white blood cell count.
Septic Shock	Adults: persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥65 mmHg and serum lactate level >2 mmol/L. Children (based on [12]): any hypotension (SBP 2 SD below normal for age) or 2-3 of the following: altered mental state; tachycardia or bradycardia (HR 160 bpm in infants and HR 150 bpm in children); prolonged capillary refill (>2 sec) or warm vasodilation with bounding pulses; tachypnea; mottled skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia

Abbreviations: ARI, acute respiratory infection; BP, blood pressure; bpm, beats/minute; CPAP, continuous positive airway pressure; FiO2, fraction of inspired oxygen; MAP, mean arterial pressure; NIV, noninvasive ventilation; OI, Oxygenation Index; OSI, Oxygenation Index using SpO2; PaO2, partial pressure of oxygen; PEEP, positive end-expiratory pressure; SBP, systolic blood pressure; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SpO2, oxygen saturation. *If altitude is higher than 1000m, then correction factor should be calculated as follows: PaO2/FiO2 x Barometric pressure/760. * The SOFA score ranges from 0 to 24 and includes points related to 6 organ systems: respiratory (hypoxemia defined by low PaO2/FiO2), coagulation (low platelets), liver (high bilirubin), cardiovascular (hypotension), central nervous system (low level of consciousness defined by Glasgow Coma Scale), and renal (low urine output or high creatinine). Sepsis is defined by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score13 of ≥2 points. Assume the baseline score is zero if data are not available.

in late pregnancy.[33,34] Recently, a second trimester miscarriage in a female infected with SARS-CoV-2 was reported without any identifiable cause. During labor, amniotic fluid and vaginal swabs tested negative for the virus. Immediately, after the miscarriage, swabs from umbilical cord blood, fetus and placenta were also tested. While all the samples tested negative, the placental swabs (from both periphery and near umbilical cord) tested positive. This could imply the risk of placental transfer and risk of miscarriage in pregnant females with COVID-19.[35]

Data regarding the relative frequency of severe illness is likely to be skewed at present by detection bias towards these cases, with sicker patients more likely to present for clinical assessment; these cases may therefore be over-represented in recent data.[28,31]

7 | DERMATOLOGICAL MANIFESTATIONS

Dermatological manifestation in COVID-19 can occur either as a direct implication of coronavirus infection or due to PPE. Joob et al reported a patient who presented with petechiea, later developed respiratory symptoms and turned out to be positive for COVID-19.[36] Recalcati et al studied cutaneous manifestations in 148 patients with COVID-19. Skin involvement was seen in 18 patients in the form of erythematous rash (14 patients), urticaria (3 patients) and one patient also developed chicken pox like vesicles. Eight of these patients developed lesions at the onset of the disease, while rest developed after hospitalization. Trunk was the most common site of involvement. Itching was either mild or absent. No correlation was found with these lesions and the disease's severity.[37]

A large scale study by Casas et al studied the dermatological manifestation in 375 patients with COVID-19 and classified the lesions into acral areas of erythema (Pseudochilblain) (19%), other vesicular eruptions (9%), urticarial (19%), maculopapular lesions (47%) and livedo or necrosis (6%). The vesicular eruptions were monomorphic in nature, unlike varicella and manifested during the early stage of infection. The pseudo-chilblain pattern was seen predominantly in younger age group and manifested during the late stage. Unlike all other dermatological manifestations, the acral erythema was seen in less severe form of infection.[38] Acral erythema or chilblain like lesions have been increasingly been reported in COVID-19[38-40] and a state of hypercoagulability has been proposed behind this manifestation.[41,42] Such patients tend to show elevated levels of D-dimer, fibrinogen and fibrinogen degradation product (FDP) and prolonged prothrombin time (PT).[43]

Kolivras et al demonstrated histopathological finding in a 23 year old COVID-19 patient with chilblain like lesion, which showed papillary dermal edema and perivascular and perieccrine lymphocytic infiltration along with scatter necrotic keratinocytes in the superficial layers of epidermis.[44] They also correlated the this chilblain like presentation in young individual as a good prognostic factor, occurring as a consequence of immune response generating Type-1 interferons (IFN-I). However, in older age group, the presentation is due to acral ischemia due to a delayed or insufficient IFN-I response (muted response) which indicate poor prognosis and increases the risk of morbiditiy and mortality.[44]

Gianotti et al studied histopathological findings in COVID-19 patients presenting with different cutaneous lesions in varying stage and degree of severity. Maculopapular rash in its early stage revealed only telengiectatic small blood veseels in upper dermis. As it progressed, presence of langerhan cells was observed. In purpuric maculopapular rash, increased Langerhans cells, perivascular lymphocytic infiltration with eosinophils and extravasated erythrocytes was seen. Intravascular microthrombi in upper dermal vessels was appreciated in a patient with severe macular hemorrhagic rash while lesions mimicking Grover disease revealed dykeratosis, multinucleated giant cells and necrotic keratinocytes.[45]

Exacerbation of pre-existing skin condition such as rosacea, eczema, atopic dermatitis and neurodermatitis have also been observed in one report.[46] Drug reactions such as acute urticaria and urticarial vasculitis have been reported by Zheng et al owing to the increased use of potential anti-coronavirus drugs, chinese herbs and other antibiotics.[46] The spectrum of dermatological manifestations would become clear as new studies become available.

The signs and symptoms pertaining to skin also occur as a consequence of the preventive measures taken by the healthcare workers (HCWs) and the general population to avoid the spread of infection. A high incidence of cutaneous complications related to prolonged wearing of personal protective equipment (PPE) like face mask, face shield, eye goggles, double gloves has been observed among healthcare workers treating patients with the Coronavirus (COVID-19) infection.[47,48]

In a study by Lan et al, 97.0% (526/542) of frontline healthcare workers showed some sign of skin damage secondary to the preventive health measures taken. Most common sites affected were the nasal bridge, hands, cheek and forehead. The nasal bridge was the most commonly affected site (83.1%). The dermatological signs and symptoms in the health workers following preventive measures include dryness, redness, tenderness, itching, desquamation, tightness and less commonly maceration, fissures, papules, vesicles, ulcers and wheals on the skin. Frequent hand hygiene and wearing of double gloves was associated with a higher incidence of hand dermatitis. Both the N95 mask and goggles were implicated in most of the facial injuries. The symptoms on the corresponding sites were observed in healthcare workers wearing PPE for more than 6 hours. Table 4 summarizes the dermatological manifestations of COVID-19 secondary to PPE.[47]

TABLE 4 Dermatological manifestations due to preventive measures of COVID-19[46]

Common	Less Common	Sites Affected
Dryness	Erosions/ulcer	Nasal bridge
Tightness	Papule	Cheeks
Desquamation	Fissure	Forehead
Burning/itching	Maceration	Hands
Redness	Wheal	

Due to the skin lesions associated with symptoms such as itching/burning on the central face, the HCW may be forced to touch his/her face or adjust the mask in an unconscious effort to relieve a source of itching. This may expose the HCW to further spread of infection.[49] Therefore, it is important to take measures to avoid or treat such lesions at an earliest. All the HCWs must be educated about the possible skin lesions secondary to PPE. To avoid cutaneous lesions, the points of pressure of the PPE should be regularly changed, and they should be advised regarding frequent application of moisturizers and emollients. HCWS with history of contact dermatitis may experience worsening of the lesions. For such cases, use of full-face respirator or using a full-face shield rather than mask or goggles would be advisable. Prophylactic dressing may also be utilized as a preventive measure. Further, application of any topical ointment to the skin should be done with great precaution with help of a sterile cotton-tipped applicator.[47,49,50]

8 | SEVERITY AND COMPLICATIONS

SARS-CoV2 caused clusters of fatal pneumonia with a clinical presentation greatly resembling SARS-CoV. Patients infected with 2019-nCoV may develop acute respiratory distress syndrome, with a higher risk of ICU admission and death. Table 5 enlists the risk factors that increases the risk of severe infection and mortality.[27,30,31] The predictors of the severe complications and risk of mortality includes older age, the presence of underlying diseases, the presence of secondary infection and elevated inflammatory indicators in the blood. Patients admitted in ICU have shown to have higher plasma levels of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNFα.[29,31,51]

TABLE 5 Risk factors associated with increased mortality in COVID-19.[27,30,31]

Age > 60 years
Coronary heart disease
Diabetes
Hypertension
Respiratory rate>24 breaths/min
Higher SOFA score
D-dimer >1 μg/ml
Elevated levels of IL-6
Elevated Cardiac troponin I
High lactate dehydrogenase
Lymphopenia

In a study by Zhou et al, out of 191 patients with COVID-19, 137 were discharged and 54 died in the hospital. The median time from illness onset (i.e. before admission) to discharge was 22 days, whereas the median time to death was 18.5 days. 91 (48%) patients had comorbidity, the most common being hypertension (30%) followed by diabetes (19%) and coronary heart disease (8%). An increased risk of mortality was found in patients with old age, high SOFA (Sequential Organ Failure Assessment Score) score, D-dimer > 1 μg/mL. Common causes of death in patients with COVID-19 include respiratory failure, acute kidney injury, myocardial injury, or a combination of any of them. Some cases have shown fulminant myocarditis as the cause of death.[31]

9 | IMMUNE STATUS AND DYSREGULATION

COVID-19 has been observed to be more severe in older populations with higher incidence of comorbidities and with weaker immune functions.[25,29,52] Serum cytokines were found to be associated with lung damage and pulmonary inflammation in SARS, MERS-CoV and COVID-19 infections.[29,53,54] A study by Chuan Qin et al, retrospectively analysed 452 patients with COVID-19, reported that most of the patients had a low lymphocyte count, high procalcitonin, ESR, Serum Ferritin and CRP along with raised inflammatory cytokines (IL-2R, IL-6, TNF -α) whereas immunoglobulins (IgA, IgG and IgM) and complement proteins (C3 and C4) were within normal range. Amongst the lymphocyte subsets, total number of B cells, T cells and NK cells were significantly decreased in patients. All the lab changes were more evident in severe cases as compared to the non-severe cases.[55]

In another study of 41 patients admitted in a hospital, high amounts of IL1B, IP10, IFNγ, and MCP1 were noted. GCSF, MIP-1A, MCO1 and TNFα were present in much higher concentrations in patients admitted to the ICU suggesting the possibility of cytokine storm associated with disease severity[29].

According to yet another study, CD4+ T lymphocytes get activated following the infection to convert to Th-1 cells and start producing GM-CSF. The excess cytokines released induce inflammatory monocytes with increased IL-6 production which accelerates the inflammation. Severe COVID-19 patients were found to have abundant inflammatory cells in the lungs.[56,57] The aberrant monocytes and the Th1 cells may flood the pulmonary circulation and disable lung function to increase morbidity and mortality.[58]

10 | LABORATORY TESTS

10.1.1 | Specimen Collection

According to CDC (Centers for Disease Control and Prevention) guidelines, a nasopharyngeal swab should be collected for upper respiratory tract infection and a broncho-alveolar lavage/tracheal aspirate for a lower respiratory tract infection. Specimen should be stored at 2-8°C and tested within 72 hours of collection.[59]

10.1.2 | Nucleic acid amplification tests (NAAT) for COVID-19 virus

Cases are detected using NAAT such as real-time reverse transcription polymerase chain reaction (rRT-PCR) and further confirmed by nucleic acid sequencing if required. These techniques target unique sequences of viral RNA like N, E, S and RdRP genes.[60] To reduce the false negative rates of PCR, specimen collection from multiple body sites is preferred. For example, in Guangzhou city, China, nasal swabs were found out to be positive while throat and/or anal swabs were negative in patients after discharge.[61]

10.1.3 | Serological testing

Serological tests are useful in epidemiological studies to determine the attack rate and the extent of spread. Paired samples can be assessed in suspicious cases with persistent negative NAAT.[60] One challenge with serological testing is the presence of cross reactivity to other coronaviruses.[62]

10.1.4 | Viral sequencing

Viral sequencing has an additional benefit of detecting viral genome mutations. It also aids in molecular epidemiology studies.[60]

10.1.5 | Viral culture

Viral culture is not advised as a routine procedure at present.[60]

10.1 | Laboratory findings in Proven cases:

10.1.1 | Hematological Investigations

A study of 1099 patients in China showed lymphocytopenia in 83.2% of the patients, thrombocytopenia in 36.2%, and leukopenia in 33.7%. Acute phase reactants such as C-reactive protein, alanine aminotransferase, aspartate aminotransferase, creatine kinase, and d-dimer were also elevated although less commonly.[28] In another study by Wang et al comprising of 138 patients, severe cases had more pronounced lab findings especially lymphocytopenia, presence of d-dimer and fibrin degradation products in the serum.[26]

10.1.2 | Radiography

In the same study by Wang et al, chest radiography abnormalities were found in a majority of patients in the form of ground glass opacities.[26] Huang et al reported chest CT changes in 41 patients out of which, 98% had bilateral involvement. While patients in ICU had multiple segmental and lobular areas of consolidation, non-severe cases showed ground glass opacities and sub-segmental consolidations.[29] In a retrospective study of 112 patients by Inui et al, changes of pneumonia on CT were observed even in 54% of asymptomatic patients.[63]

10.1.3 | Pathology

The autopsy findings of lungs showed desquamated pneumocytes, interstitial lymphocyte infiltration and hyaline membrane formation indicating ARDS. Viral cytopathic changes such as syncytial cells with atypical pneumocytes and large nuclei and prominent nucleoli were also observed.[56]

11 | MANAGEMENT

At the time this article was being written, the new case detection rate had taken a steep curve, with more than 4 million cases (as on May 13, 2020).[64] The coronavirus disease (COVID-19) exemplifies Benjamin Franklin's famous words – "An ounce of prevention is worth a pound of cure." Given the highly contagious nature of the SARS-Cov-2, and the relatively rapid escalation of the disease outbreak to a pandemic, preventive public health measures have been recommended by the World Health Organization (WHO).[65] These are multi-pronged in approach to facilitate prevention, infection containment and disease control at various levels – global, community and personal. The aim of containment at each echelon is to contain the COVID-19 outbreak in a particular region to a particular stage, be it imported case, local transmission, community transmission, epidemic or pandemic.

11.1 | Global preventive measures

While no formal restrictions have been imposed by the WHO on travel, it does recommend the conduction of exit and entry interviews which comprise a cursory clinical examination and recording of temperature, from countries that have reported the incidence and community transmission of COVID-19.[66] While not as foolproof as genetic testing, this may still identify a major subset of potentially infected individuals. Global summits, international conferences and meetings have been discouraged by the WHO, the Centre for Disease Control and Prevention (CDC, Atlanta, USA) and many other nations as part of a complete or partial lockdown.[67-69]

11.2 | Community prevention measures

The mainstay of preventing community transmission is social distancing – 1m between 2 individuals, and an overall avoidance of closed spaces and large gatherings. These include, and are not limited to, public transport by land (road, rail), air and sea, schools, colleges and educational institutions, retirement communities, convenience stores, workplaces and places of worship. Law enforcement agencies, the armed forces and healthcare professionals and workers, unfortunately, have to continue their duties, albeit with personal protective measures, which is covered in the following section.[70] Another element of community protection is environmental disinfection. Since the SARS-Cov-2 is transmitted via respiratory droplets / aerosols, this faction has not been given due importance as it eliminates fomite infectivity. Although sufficient data on surface RNA detection, persistence and infectivity of SARS-Cov-2 is not available, the other members of the Coronaviridae family have shown persistence on inanimate objects with detectable infectivity for 5-10 days after exposure.[71] Fortunately, routine disinfectants can easily combat the colonization of this novel Coronavirus as well.[21]

11.3 | Personal preventive measures

These are the measures which must be implemented at the grassroot level, and are the most rate limiting factors in the transmission of COVID-19. Standard WHO and CDC guidelines include hand hygiene, respiratory etiquette and facial hygiene. Other measures like social distancing, avoiding large gatherings, and disinfection have to be followed, as for community prevention. Hand hygiene involves frequent washing of hands for at least 20 seconds if soiled, usage of medical grade alcohol routinely, and avoiding shaking hands as a social gesture.[72] Respiratory etiquette involves covering one's mouth and nose while sneezing to maintain droplet precautions, followed by diligent hand hygiene, and avoiding touching the face unnecessarily.[73]

The utility of protective masks has been a bone of contention and a topic of mass debate, as far as COVID-19 transmission is concerned. However, the current consensus states that even in a COVID-19 transmissible zone, for people not caring for an infected person

directly, a mask offers no additional benefit, and may cause an economical and logistical burden.[74,75]

11.4 | Specific considerations for Health care workers (HCWs)

On an outpatient basis, HCWs in direct contact with infected or potentially infected individuals, a mask becomes necessary. However, a simple procedural mask with loops, or a surgical mask with ties is sufficient to prevent airborne transmission of SARS-Cov-2. Particulate masks such as N95 and N99 offer no seemingly additional benefit, as per the current consensus.[75] HCWs at quarantine centres need Personal Protective Equipment (PPE) suits, as mandated by WHO.[76] Containment of non-emergent health services and elective surgeries has been recommended, in COVID-19 transmission area, even though no formal statement exists at the time.

11.5 | General management

Management measures vary for the presenting symptomatology and history of travel, and can be divided by attending HCWs into the following groups:

1. **Patients who are symptomatic but have no history of travel:** Initial screening is done for individuals who are symptomatic, as mentioned previously. These individuals are treated empirically, given protective masks and monitored on an outpatient basis. If the patient has respiratory symptoms, additional droplet and eye precautions are advised. Follow-up visits may entail genetic testing on collected nasopharyngeal swabs, on a case-to-case basis. Special co-existing conditions like pregnancy, lactation, immunocompromised state, old age, chronic illnesses, long-term medications, immunomodulator medication usage and other debilitating diseases must be dealt with, as per existing guidelines. [34,77-79]
2. **Patients who are asymptomatic but have a history of travel:** Algorithmically, patients who have a positive history of travel to a COVID-19 transmissible area in the past 14 days, but have not exhibited symptoms of fever, cough or dyspnea, are tested via molecular assay conducted on collected nasopharyngeal swabs. If found negative, then are monitored on an outpatient basis, as discussed under Sl no 1. Individuals who test positive are placed under self-quarantine and monitored for clinical features of COVID-19, till they test negative. Contact tracing is of paramount importance in these individuals, from an epidemiological and pathological point of view. [77,78,80]
3. **Patients who are asymptomatic but have been in contact with an infected individual:** Same guidelines as mentioned under Sl no 2.
4. **Patients who are asymptomatic but have tested positive via RT-PCR on consecutive nasopharyngeal swabs:** Same guidelines as mentioned under Sl no 2.
5. **Patients who are symptomatic and have a history of travel and/ or contact or have tested positive:** Clinical and laboratory testing is performed, as mentioned previously, and the patient is classified on the basis of severity and progression of the disease. Patients with a mild form of the disease are put on self-quarantine or home isolation, which may be revoked on full symptomatic recovery if testing facilities are scarce, and two negative nasopharyngeal swabs in addition to an afebrile state for over 72 hours.[77,78,81] Needless to say, all patient groups mentioned here must be given reassurance, proper guidance to allay their anxiety and fears.[79,82] Patients who develop severe disease are admitted in a hospital setting for specific care.

12 | SPECIFIC TREATMENT

Extensive lung involvement, persistent dyspnea and/ or fever and non-resolution of mild disease, are few of the factors that mandate hospital admission for disease control, auxiliary, ancillary care and specific treatment.[83] This must not be confused with a hospital quarantine, which serves an additional epidemiological role. Severe viral pneumonia warrants high-flow oxygenation, and the use of breathing apparati, wherever necessary. A few of these cases, and all cases of Critical COVID-19 that progress to Acute Respiratory Distress Syndrome (ARDS) require prone positioning, ventilatory support and therapy targeted at the neuromuscular blockade, failing which patients progress to Multiple Organ Dysfunction System and subsequent death.[84] Targeted management of COVID-19 has been reported in a spate of publications with varying levels of evidence. Several drugs continue to be under investigation or trial to treat COVID-19. They range from immune boosting composite probiotic powders, recombinant angiotensin-converting enzyme (rhACE2), sildenafil, biologics, antimalarials, glucocorticoids, NSAIDs, antiretrovirals and mesenchymal stem cells to pirfenidone (for fibrotic sequalae), immunomodulators, thalidomide, bromhexine and washed microbiota transplantation.[85] The ever-increasing list of pharmacological therapies continue to be repositioned and investigated for use in COVID-19. Most of these drugs have in vitro evidence but lack sufficient clinical evidence. Of these, the highest levels of evidence are in favor of the following drugs:

1. **Tocilizumab** – This disease-modifying anti-rheumatic drug (DMARD) targets the viral cytokine storm by selectively inhibiting IL-6. It has recently entered a Phase III trial.[86,87] Sarelumab is another drug in the same class that is being repurposed for use in the ongoing pandemic.[88]
2. **Antimalarials** – Hydroxychloroquine and chloroquine phosphate have shown antiviral effects by lysosomal inhibition, as monotherapy and combination therapy, in various in vitro studies and ongoing trials. The dosage of hydroxycholoroquine (HCQS) ranges from 400-800mg in daily and weekly regimes. Combinations with macrolide antibiotic azithromycin have also been documented to have a therapeutic effect on COVID-19, albeit amongst concerns of the combination having the potential to cause QT interval prolongation. There are anecdotal reports of the utility of HCQS as a prophylactic agent, especially in HCWs.[89,91] Even when used

standalone, antimalarials have the potential to cause cardiovascular toxicity, hypoglycemia and retinopathy.[88]

3. **Antivirals** – The protease inhibitor combination Ritonavir/Lopinavir showed in vitro efficacy against other coronaviridae SARS-Cov and MERS-Cov, but has failed to translate into clinical efficacy against SARS-Cov2. Reportedly, protease inhibitors induce transaminitis, which is also a feature of COVID-19. Other antivirals like ribavirin, remdesivir, interferons that inhibit viral RNA replication have met a similar therapeutic fate.[92,93] A similar drug called Favilavir (Favipiravir) inhibits RNA-dependent-RNA-polymerase and has been approved in areas with the highest COVID-19 transmission – Italy and China, and is purported to be effective for treating the disease in the Wuhan and Shenzen provinces.[94-97] Though well tolerated in comparison to other antivirals, it is currently unavailable in most parts of the world

12.1 | Vaccination against SARS-Cov2

Amidst erroneous reports and media hype, WHO states that there are 2 vaccines under Phase I clinical trials – an adenoviral vector and an encapsulated mRNA vaccine, and 42 other vaccines under pre-clinical trials.[97-99]

13 | CONCLUSION

COVID-19 is an ongoing pandemic which has affected over half a million people worldwide, with an overall case fatality rate of 4.4%, making it the largest public health emergency of this millennium. The causative organism is ubiquitous and physicians across the globe must have a high index of suspicion to diagnose this condition early. The control prevention methods are multipronged, and no definitive treatment or vaccination exists as of now. The disease per se, the psychological after-effects, the economic shutdown and social disruption emerging from this would take significant time, resources and efforts to be rescinded.

CONFLICT OF INTEREST DISCLOSURES

None

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