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Features, Evaluation, and Treatment of Coronavirus (COVID-19)

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Continuing Education Activity

Coronavirus disease 2019 (COVID-19) is a highly contagious infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 has had a catastrophic effect on the world, resulting in more than 6 million deaths worldwide. It has emerged as the most consequential global health crisis since the era of the influenza pandemic of 1918. As the virus mutates, treatment guidelines are altered to reflect the most efficacious therapies. This activity is a comprehensive review of the disease presentation, complications, and current guideline-recommended treatment options for managing this disease.

Objectives:

- Screen individuals based on exposure and symptom criteria to identify potential COVID-19 cases.
- Identify the clinical features and radiological findings expected in patients with COVID-19.
- Apply the recommended treatment options for patients with COVID-19.
- Create strategies with the interprofessional team for improving care coordination to care for patients with COVID-19 to help improve clinical outcomes.

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Introduction

Coronavirus disease 2019 (COVID-19) is a highly contagious viral illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 has had a catastrophic effect on the world, resulting in more than 6 million deaths worldwide. After the first cases of this predominantly respiratory viral illness were reported in Wuhan, Hubei Province, China, in late December 2019, SARS-CoV-2 rapidly disseminated worldwide. This compelled the World Health Organization (WHO) to declare it a global pandemic on March 11, 2020.[1]

Even though substantial progress in clinical research has led to a better understanding of SARS-CoV-2, many countries continue to have outbreaks of this viral illness. These outbreaks are primarily attributed to the emergence of mutant variants of the virus. Like other RNA viruses, SARS-CoV-2 adapts with genetic evolution and developing mutations. This results in mutant variants that may have different characteristics than their ancestral strains. Several variants of SARS-CoV-2 have been described during the course of this pandemic, among which only a few are considered variants of concern (VOCs). Based on the epidemiological update by the WHO, 5 SARS-CoV-2 VOCs have been identified since the beginning of the pandemic:

- **Alpha (B.1.1.7):** First variant of concern, which was described in the United Kingdom (UK) in late December 2020[2]
- **Beta (B.1.351)**: First reported in South Africa in December 2020[2]

- **Gamma (P.1)**: First reported in Brazil in early January 2021[2]
- **Delta (B.1.617.2):** First reported in India in December 2020[2]
- **Omicron (B.1.1.529):** First reported in South Africa in November 2021[3]

Despite the unprecedented speed of vaccine development against the prevention of COVID-19 and robust global mass vaccination efforts, the emergence of new SARS-CoV-2 variants threatens to overturn the progress made in limiting the spread of this disease. This review aims to comprehensively describe the etiology, epidemiology, pathophysiology, and clinical features of COVID-19. This review also provides an overview of the different variants of SARS-CoV-2 and the guideline-recommended treatment (as of January 2023) for managing this disease.

Etiology

Coronaviruses (CoVs) are positive-sense single-stranded RNA (+ssRNA) viruses with a crown-like appearance under an electron microscope (*coronam* is the Latin term for crown) due to the presence of spike glycoproteins on the envelope.[1] The subfamily *Orthocoronavirinae* of the *Coronaviridae* family (order *Nidovirales*) classifies into 4 genera of CoVs:

- **Alphacoronavirus** (alphaCoV)
- **Betacoronavirus** (betaCoV)
- **Deltacoronavirus** (deltaCoV)
- **Gammacoronavirus** (gammaCoV)

BetaCoV genus is further divided into 5 sub-genera or lineages.[4] Genomic characterization has shown that bats and rodents are the probable gene sources of alphaCoVs and betaCoVs. Avian species seem to be the source of deltaCoVs and gammaCoVs. CoVs have become significant pathogens of emerging respiratory disease outbreaks. Members of this large family of viruses can cause respiratory, enteric, hepatic, and neurological diseases in different animal species, including camels, cattle, cats, and bats.

These viruses can cross species barriers and infect humans as well. Seven human CoVs (HCoVs) capable of infecting humans have been identified. Some HCoVs were identified in the mid-1960s, while others were only detected in the new millennium. In general, estimates suggest that 2% of the population are healthy carriers of CoVs and that these viruses are responsible for about 5% to 10% of acute respiratory infections.[5]

- **Common human CoVs**: HCoV-OC43 and HCoV-HKU1 (betaCoVs of the A lineage), HCoV-229E, and HCoV-NL63 (alphaCoVs). These viruses can cause common colds and self-limiting upper respiratory tract infections in immunocompetent individuals. However, in immunocompromised and older patients, lower respiratory tract infections can occur due to these viruses.

- **Other human CoVs**: SARS-CoV and MERS-CoV (betaCoVs of the B and C lineage, respectively). These viruses are considered more virulent and capable of causing epidemics with respiratory and extra-respiratory manifestations of variable clinical severity.[1]

SARS-CoV-2 is a novel betaCoV belonging to the same subgenus as the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), which have been previously implicated in SARS-CoV and MERS-CoV epidemics with mortality rates up to 10% and 35%, respectively.[6] It has a round or elliptic and often

pleomorphic form and a diameter of approximately 60 to 140 nm. Like other CoVs, it is sensitive to ultraviolet rays and heat.[6]

The inactivation temperature of SARS-CoV-2 is being researched. A stainless steel surface held at an air temperature of 54.5°C (130 °F) results in the inactivation of 90% of SARS-CoV-2 in approximately 36 minutes.[7] It resists lower temperatures, even those below 0°C. However, lipid solvents can effectively inactivate these viruses, including ether (75%), ethanol, chlorine-containing disinfectant, peroxyacetic acid, and chloroform (except for chlorhexidine).

Although the origin of SARS-CoV-2 is currently unknown, it is widely postulated to have a zoonotic transmission.[1] Genomic analyses suggest that SARS-CoV-2 probably evolved from a strain found in bats. The genomic comparison between the human SARS-CoV-2 sequence and known animal coronaviruses revealed high homology (96%) between the SARS-CoV-2 and the betaCoV RaTG13 of bats (*Rhinolophus affinis*).[8] Similar to SARS and MERS, it has been hypothesized that SARS-CoV-2 advanced from bats to intermediate hosts, such as pangolins and minks, and then to humans.[9][10]

SARS-CoV-2 Variants

A globally dominant D614G variant was eventually identified and associated with increased transmissibility but without the ability to cause severe illness.[11] Another variant was attributed to transmission from infected farmed mink in Denmark but was not associated with increased transmissibility.[10] Since then, multiple variants of SARS-CoV-2 have been described, of which a few are considered variants of concern (VOCs) due to their potential to cause enhanced transmissibility or virulence. The United States Centers for Disease Control and Prevention (CDC) and the WHO have independently established a classification system for distinguishing the emerging variants of SARS-CoV-2 into variants of concern(VOCs) and variants of interest(VOIs).

SARS-CoV-2 Variants of Concern (VOCs)

- **Alpha (B.1.1.7 lineage)**
- - In late December 2020, the Alpha variant, or **GRY** (formerly GR/501Y.V1), was reported in the UK based on whole-genome sequencing of samples from patients who tested positive for SARS-CoV-2.[12][13]
  - The variant was also identified using a commercial assay characterized by the absence of the S gene (S-gene target failure, SGTF) in PCR samples. The B.1.1.7 variant includes 17 mutations in the viral genome. Of these, 8 mutations (Δ69-70 deletion, Δ144 deletion, N501Y, A570D, P681H, T716I, S982A, D1118H) are in the spike (S) protein. N501Y shows an increased affinity of the spike protein to ACE 2 receptors, enhancing the viral attachment and subsequent entry into host cells.[14][15][16]
  - This alpha variant was reportedly 43% to 82% more transmissible, surpassing preexisting variants of SARS-CoV-2 to emerge as the dominant SARS-CoV-2 variant in the UK.[15]
  - An initial matched case-control study reported no significant difference in the risk of hospitalization or associated mortality with the B.1.1.7 lineage variant compared to other existing variants. However, subsequent studies have reported that people infected with B.1.1.7 lineage variant had increased disease severity compared to those infected with other circulating variants.[17][13]

- A large matched cohort study in the UK reported that the mortality hazard ratio of patients infected with the B.1.1.7 lineage variant was 1.64 (95% confidence interval 1.32 to 2.04, P<0.0001) compared to patients with previously circulating strains.[18]
- Another study reported that the B 1.1.7 variant was associated with increased mortality compared to other SARS-CoV-2 variants (HR= 1.61, 95% CI 1.42-1.82).[19] The risk of death was reportedly greater (adjusted hazard ratio 1.67, 95% CI 1.34-2.09) among individuals with confirmed B.1.1.7 infection compared to individuals with non-B.1.1.7 SARS-CoV-2.[20]

- **Beta (B.1.351 lineage)**

- The Beta variant, or **GH501Y.V2** with multiple spike mutations, resulted in the second wave of COVID-19 infections and was first detected in South Africa in October 2020.[21]
- The B.1.351 variant includes 9 mutations (L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, and A701V) in the spike protein, of which 3 mutations (K417N, E484K, and N501Y) are located in the receptor binding domain (RBD) and increase its binding affinity for the ACE receptors.[22][14][23]
- SARS-CoV-2 501Y.V2 (B.1.351 lineage) was reported in the US at the end of January 2021.
- This variant had an increased risk of transmission and reduced neutralization by monoclonal antibody therapy, convalescent sera, and post-vaccination sera.[24]

- **Gamma (P.1 lineage)**

- The Gamma variant, or **GR/501Y.V3**, was identified in December 2020 in Brazil and was first detected in the US in January 2021.[25]
- This B.1.1.28 variant harbors ten mutations in the spike protein (L18F, T20N, P26S, D138Y, R190S, H655Y, T1027I V1176, K417T, E484K, and N501Y). Three mutations (L18F, K417N, E484K) are located in the RBD, similar to the B.1.351 variant.[25]

- **Delta (B.1.617.2 lineage)**
  - The Delta variant was initially identified in December 2020 in India and was responsible for the deadly second wave of COVID-19 infections in April 2021 in India. In the United States, this variant was first detected in March 2021.[2]
  - The B.1.617.2 variant harbors ten mutations (T19R, (G142D*), 156del, 157del, R158G, L452R, T478K, D614G, P681R, D950N) in the spike protein.

- **Omicron (B.1.1.529 lineage)**
  - The Omicron variant was first identified in South Africa on 23 November 2021 after an uptick in the number of cases of COVID-19.[26]
  - Omicron was quickly recognized as a VOC due to more than 30 changes to the spike protein of the virus and the sharp rise in the number of cases observed in South Africa.[27] The reported mutations include T91 in the envelope, P13L, E31del, R32del, S33del, R203K, G204R in the nucleocapsid protein, D3G, Q19E, A63T in the matrix, N211del/L212I, Y145del, Y144del, Y143del, G142D, T95I, V70del, H69del, A67V in the N-terminal domain of the spike, Y505H, N501Y, Q498R, G496S, Q493R, E484A, T478K, S477N, G446S, N440K, K417N, S375F, S373P,

S371L, G339D in the receptor-binding domain of the spike, D796Y in the fusion peptide of the spike, L981F, N969K, Q954H in the heptad repeat 1 of the spike as well as multiple other mutations in the non-structural proteins and spike protein.[28]

- Many subvariants of Omicron, such as BA.1, BA.2, BA.3, BA.4, and BA.5, have been identified.[3]

Transmission of SARS-CoV-2

- The primary mode of transmission of SARS-CoV-2 is via exposure to respiratory droplets carrying the infectious virus from close contact or direct transmission from presymptomatic, asymptomatic, or symptomatic individuals harboring the virus.[1]
- Airborne transmission with aerosol-generating procedures has also been implicated in the spread of COVID-19. Data implicating airborne transmission of SARS-CoV-2 in the absence of aerosol-generating procedures is present; however, this mode of transmission has not been universally acknowledged.
- Fomite transmission from contamination of inanimate surfaces with SARS-CoV-2 has been well characterized based on many studies reporting the viability of SARS-CoV-2 on various porous and nonporous surfaces. Under experimental conditions, SARS-CoV-2 was stable on stainless steel and plastic surfaces compared to copper and cardboard surfaces, with the viable virus being detected up to 72 hours after inoculating the surfaces with the virus.[29] The viable virus was isolated for up to 28 days at 20°C from nonporous surfaces such as glass and stainless steel. Conversely, recovery of SARS-CoV-2 on porous materials was reduced compared with nonporous surfaces.[30] In hospital settings, the SARS-CoV-2 has been detected on floors, computer mice, trash cans, sickbed handrails, and in the air (up to 4 meters from patients).[31] The Centers for Disease Control and Prevention (CDC) has stated that individuals can be infected with SARS-CoV-2 via contact with surfaces contaminated by the virus, but the risk is low and is not the main route of transmission of this virus.
- Epidemiologic data from several case studies have reported that patients with SARS-CoV-2 infection have the live virus in feces implying possible fecal-oral transmission.[32]
- A meta-analysis that included 936 neonates from mothers with COVID-19 showed vertical transmission is possible but occurs in a minority of cases.[33]

Epidemiology

COVID-19 was the third leading cause of death in the United States (USA) in 2020 after heart disease and cancer, with approximately 375,000 deaths.[34]

Individuals of all ages are at risk of contracting this infection. However, patients aged ≥60 and patients with underlying medical comorbidities (obesity, cardiovascular disease, chronic kidney disease, diabetes, chronic lung disease, smoking, cancer, solid organ or hematopoietic stem cell transplant patients) have an increased risk of developing severe COVID-19 infection.

According to the CDC, age remains the strongest predictor of poor outcomes and severe illness in patients with COVID-19. Data from the National Vital Statistics System (NVSS) at CDC states that patients with COVID-19 aged 50 to 64 years have a 25 times higher risk of death when compared to adults infected with this illness and aged less than 30 years. In patients 65 to 74 years old, this risk increases to 60 times. In patients older than 85, the risk of death increases to 340 times. According to the CDC, these data include all deaths in the United States throughout the pandemic, from February 2020 to July 1, 2022, including deaths among unvaccinated individuals.

The percentage of COVID-19 patients requiring hospitalization was 6 times higher in those with preexisting medical conditions than those without medical conditions (45.4% vs. 7.6%) based on an analysis by Stokes et al. of confirmed cases reported to the CDC from January 22 to May 30, 2020.[35] The study also reported that the percentage of patients who succumbed to this illness was 12 times higher in those with preexisting medical conditions than those without (19.5% vs 1.6%).[35]

Data regarding the gender-based differences in COVID-19 suggests that male patients have a higher risk of severe illness and increased mortality due to COVID-19 compared to female patients.[36][37] Results from a retrospective cohort study from March 1 to November 21, 2020, evaluating the mortality rate in 209 United States of America (USA) acute care hospitals that included 42604 patients with confirmed SARS-CoV-2 infection, reported a higher mortality rate in male patients (12.5%) compared to female patients (9.6%).[38]

Racial and ethnic minority groups have been reported to have a higher percentage of COVID-19-related hospitalizations than White patients based on a recent CDC analysis of hospitalizations from an extensive administrative database that included approximately 300,000 COVID-19 patients hospitalized from March 2020 to December 2020. This high percentage of COVID-19-related hospitalizations among racial and ethnic groups was driven by a higher risk of exposure to SARS-CoV-2 and an increased risk of developing severe COVID-19 disease.[39] A meta-analysis of 50 studies from USA and UK researchers noted that people of Black, Hispanic, and Asian ethnic minority groups are at increased risk of contracting and dying from COVID-19 infection.[40]

COVID-19-related death rates were the highest among Hispanic persons.[34] Another analysis by the CDC evaluating the risk of COVID-19 among sexual minority adults reported that underlying medical comorbidities which increase the risk of developing severe COVID-19 were more prevalent in sexual minority individuals than heterosexual individuals within the general population and within specific racial/ethnic groups.[41]

Pathophysiology

Structurally and phylogenetically, SARS-CoV-2 is similar to SARS-CoV and MERS-CoV and is composed of 4 main structural proteins: spike (S), envelope (E) glycoprotein, nucleocapsid (N), and membrane (M) protein. It also contains 16 nonstructural proteins and 5-8 accessory proteins.[42]

The surface spike (S) glycoprotein, which resembles a crown, is located on the outer surface of the virion. It undergoes cleavage into an amino (N)-terminal S1 subunit, which facilitates the incorporation of the virus into the host cell. The carboxyl (C)-terminal S2 subunit contains a fusion peptide, a transmembrane domain, and a cytoplasmic domain responsible for virus-cell membrane fusion.[43][44] The S1 subunit is further divided into a receptor-binding domain (RBD) and an N-terminal domain (NTD), which facilitates viral entry into the host cell and serves as a potential target for neutralization in response to antisera or vaccines.[45]

The RBD is a fundamental peptide in the pathogenesis of infection as it represents a binding site for the human angiotensin-converting enzyme 2 (ACE2) receptors. Inhibition of the renin-angiotensin-aldosterone system (RAAS) does not increase the risk of hospitalization for COVID-19 and severe disease.[46]

SARS-CoV-2 gains entry into the host cells by binding the SARS-CoV-2 spike or S protein (S1) to the ACE2 receptors in the respiratory epithelium. ACE2 receptors are also expressed by other organs such as the upper esophagus, enterocytes from the ileum, myocardial cells, proximal tubular cells of the kidney, and urothelial cells of the bladder.[47] The viral attachment process is

followed by priming the spike protein S2 subunit by the host transmembrane serine protease 2 (TMPRSS2) that facilitates cell entry and subsequent viral replication.[48]

In the early phase of the infection, viral replication results in direct virus-mediated tissue damage. In the late phase, the infected host cells trigger an immune response by recruiting T lymphocytes, monocytes, and neutrophils. Cytokines such as tumor necrosis factor-α (TNF α), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-1 (IL-1), interleukin-6 (IL-6),), IL-1β, IL-8, IL-12 and interferon (IFN)-γ are released. In severe COVID-19 illness, a 'cytokine storm' is seen. This is due to the over-activation of the immune system and high levels of cytokines in circulation. This results in a local and systemic inflammatory response.[49][50]

Effect of SARS-CoV-2 on the Respiratory System

Increased vascular permeability and subsequent development of pulmonary edema in patients with severe COVID-19 are explained by multiple mechanisms.[51][52][53] These mechanisms include:

- Endotheliitis as a result of direct viral injury and perivascular inflammation leading to microvascular and microthrombi deposition
- Dysregulation of RAAS due to increased binding of the virus to the ACE2 receptors
- Activation of the kallikrein-bradykinin pathway, the activation of which enhances vascular permeability
- Enhanced epithelial cell contraction causes swelling of cells and disturbance of intercellular junctions
- The binding of SARS-CoV-2 to the Toll-Like Receptor (TLR) induces the release of pro-IL-1β, which mediates lung inflammation until fibrosis.[54]

Effect of SARS-CoV-2 on Extrapulmonary Organ Systems

Although the respiratory system is the principal target for SARS-CoV-2, other major organ systems such as the gastrointestinal tract (GI), hepatobiliary, cardiovascular, renal, and central nervous systems may also be affected. SARS-CoV-2–induced organ dysfunction is likely due to a combination of mechanisms, such as direct viral toxicity, ischemic injury caused by vasculitis, thrombosis, immune dysregulation, and renin-angiotensin-aldosterone system (RAAS) dysregulation.[55]

Cardiac involvement in COVID-19 is common and likely multifactorial. ACE2 receptors exhibited by myocardial cells may cause direct cytotoxicity to the myocardium leading to myocarditis. Proinflammatory cytokines such as IL-6 can also lead to vascular inflammation, myocarditis, and cardiac arrhythmias.[56]

Acute coronary syndrome (ACS) is a well-recognized cardiac manifestation of COVID-19. It is likely due to multiple factors, including proinflammatory cytokines, worsening of preexisting severe coronary artery disease, coronary plaque destabilization, microthrombogenesis, and reduced coronary blood flow.[57]

SARS-CoV-2 has a significant effect on the hematological and hemostatic systems as well. The mechanism of leukopenia, one of the most common laboratory abnormalities encountered in COVID-19, is unknown. Several hypotheses have been postulated that include ACE 2 mediated lymphocyte destruction by direct invasion by the virus, lymphocyte apoptosis due to proinflammatory cytokines, and possible invasion of the virus in the lymphatic organs.[58]

Thrombocytopenia is common in COVID-19 and is likely due to multiple factors, including virus-mediated suppression of platelets, autoantibodies formation, and coagulation cascade activation, resulting in platelet consumption.[59]

Thrombocytopenia and neutrophilia are considered a hallmark of severe illness.[55] Although it is well known that COVID-19 is associated with a state of hypercoagulability, the exact mechanisms that lead to the activation of the coagulation system are unknown and likely attributed to the cytokine-induced inflammatory response. The pathogenesis of this associated hypercoagulability is multifactorial. The hypercoagulability is probably induced by direct viral-mediated damage or cytokine-induced injury of the vascular endothelium leading to the activation of platelets, monocytes, and macrophages, with increased expression of von Willebrand factor and Factor VIII that results in the generation of thrombin and formation of a fibrin clot.[59][60]

Other mechanisms that have been proposed include possible mononuclear phagocyte-induced prothrombotic sequelae, derangements in the renin-angiotensin system (RAS) pathways, and complement-mediated microangiopathy.[59]

History and Physical

Clinical Manifestations of COVID-19

- The median incubation period for SARS-CoV-2 is estimated to be 5.1 days, and most patients will develop symptoms within 11.5 days of infection.[61]
- The clinical spectrum of COVID-19 varies from asymptomatic or paucisymptomatic forms to clinical illness characterized by acute respiratory failure requiring mechanical ventilation, septic shock, and multiple organ failure.
- It is estimated that 17.9% to 33.3% of infected patients will remain asymptomatic.[62][63]
- Most symptomatic patients present with fever, cough, and shortness of breath. Less common symptoms include sore throat, anosmia, dysgeusia, anorexia, nausea, malaise, myalgias, and diarrhea. Stokes et al. reported that among 373,883 confirmed symptomatic COVID-19 cases in the USA, 70% experienced fever, cough, and shortness of breath, 36% reported myalgia, and 34% reported headache.[35]
- A large meta-analysis evaluating clinicopathological characteristics of 8697 patients with COVID-19 in China reported laboratory abnormalities that included lymphopenia (47.6%), elevated C-reactive protein levels (65.9%), elevated cardiac enzymes (49.4%), and abnormal liver function tests (26.4%). Other laboratory abnormalities included leukopenia (23.5%), elevated D-dimer (20.4%), elevated erythrocyte sedimentation rate (20.4%), leukocytosis (9.9%), elevated procalcitonin (16.7%), and abnormal renal function (10.9%).[64]
- A meta-analysis of 212 published studies with 281,461 individuals from 11 countries/regions reported that severe disease course was noted in about 23% of the patients, with a mortality rate of about 6% in patients infected with COVID-19.[65]
- An elevated neutrophil-to-lymphocyte ratio (NLR), an elevated derived NLR ratio (d-NLR), and an elevated platelet-to-lymphocyte ratio indicate a cytokine-induced inflammatory storm.[66]

Based on the severity of the presenting illness, which includes clinical symptoms, laboratory and radiographic abnormalities, hemodynamics, and organ function, the National Institutes of Health

(NIH) issued guidelines that classify COVID-19 into 5 distinct types.[NIH COVID-19 Treatment Guidelines]

- **Asymptomatic or Presymptomatic Infection**: Individuals with positive SARS-CoV-2 test without any clinical symptoms consistent with COVID-19.
- **Mild illness**: Individuals who have symptoms of COVID-19, such as fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, anosmia, or dysgeusia but without shortness of breath or abnormal chest imaging.
- **Moderate illness**: Individuals with clinical symptoms or radiologic evidence of lower respiratory tract disease and oxygen saturation (SpO_2) ≥94% on room air.
- **Severe illness**: Individuals who have SpO_2 less than 94% on room air, a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) of less than 300, marked tachypnea with a respiratory frequency of greater than 30 breaths/min, or lung infiltrates that are greater than 50% of total lung volume.
- **Critical illness**: Individuals with acute respiratory failure, septic shock, or multiple organ dysfunction. Patients with severe COVID-19 illness may become critically ill with the development of acute respiratory distress syndrome (ARDS). This tends to occur approximately one week after the onset of symptoms.

ARDS is characterized by a severe new-onset respiratory failure or worsening of an already identified respiratory picture. The diagnosis requires bilateral opacities (lung infiltrates >50%), not fully explained by effusions or atelectasis. The Berlin definition classifies ARDS into 3 types based on the degree of hypoxia, with the reference parameter being PaO_2/FiO_2 or P/F ratio:[67]

- **Mild ARDS**: 200 mm Hg <PaO_2/FiO_2 ≤300 mm Hg in patients not receiving mechanical ventilation or in those managed through noninvasive ventilation (NIV) by using positive end-expiratory pressure (PEEP) or a continuous positive airway pressure (CPAP) ≥5 cm H2O.
- **Moderate ARDS**: 100 mm Hg <PaO_2/FiO_2 ≤200 mm Hg
- **Severe ARDS**: PaO_2/FiO_2 ≤100 mm Hg

When PaO_2 is unavailable, a ratio of SpO_2/FiO_2 ≤315 suggests ARDS. A multicenter prospective observational study that analyzed 28-day mortality in mechanically ventilated patients with ARDS concluded that COVID-19 patients with ARDS had features similar to other ARDS cohorts, and the risk of 28-day mortality increased with ARDS severity.[68]

Extrapulmonary Manifestations

- Acute kidney injury (AKI) is the most frequently encountered extrapulmonary manifestation of COVID-19 and is associated with an increased mortality risk.[69] A large multicenter cohort study of hospitalized patients with COVID-19 that involved 5,449 patients admitted with COVID-19 reported that 1993 (36.6%) patients developed AKI during their hospitalization, of which 14.3% of patients required renal replacement therapy (RRT).[70]
- Myocardial injury manifesting as myocardial ischemia/infarction (MI) and myocarditis are well-recognized cardiac manifestations in patients with COVID-19. Single-center retrospective study analysis of 187 patients with confirmed COVID-19 reported that 27.8% of patients exhibited myocardial injury indicated by elevated troponin levels. The study also noted that patients with elevated troponin levels had more frequent malignant

arrhythmias and a higher mechanical ventilation frequency than patients with normal troponin levels.[71] A meta-analysis of 198 published studies involving 159698 COVID-19 patients reported that acute myocardial injury and a high burden of pre-existing cardiovascular disease were significantly associated with higher mortality and ICU admission.[72]

- Lymphopenia is a common laboratory abnormality in most patients with COVID-19. Other laboratory abnormalities include thrombocytopenia, leukopenia, elevated ESR levels, C-reactive protein (CRP), lactate dehydrogenase (LDH), and leukocytosis.
- COVID-19 is also associated with a hypercoagulable state, evidenced by the high prevalence of venous thromboembolic events. COVID-19 is associated with markedly elevated D-dimer and fibrinogen levels and prolonged prothrombin time (PT) and partial thromboplastin time (aPTT).[71][55]
- GI symptoms (such as diarrhea, nausea, vomiting), anorexia, and abdominal pain are common. A meta-analysis reported that the weighted pool prevalence of diarrhea was 12.4% (95% CI, 8.2% to 17.1%), nausea or vomiting was 9% (95% CI, 5.5% to 12.9%), loss of appetite was 22.3% (95% CI, 11.2% to 34.6%) and abdominal pain was 6.2% (95% CI, 2.6% to 10.3%). The study also reported that the mortality rate among patients with GI symptoms was similar to the overall mortality rate.[73] Cases of acute mesenteric ischemia and portal vein thrombosis have also been described.[74]
- An acute increase in aspartate transaminase (AST) and alanine transaminase (ALT) is noted in 14% to 53% of patients with COVID-19 infection.[75]
- Guillain-Barré syndrome (GBS) cases from Northern Italy have also been reported.[76] [77]
- Acral lesions resembling pseudo chilblains (40.4%) are the most common cutaneous manifestation noted in patients with COVID-19.[78]
- Other cutaneous manifestations include erythematous maculopapular rash (21.3%), vesicular rashes (13%), urticarial rashes (10.9%), vascular rashes (4%) resembling livedo or purpura, and erythema multiforme-like eruptions (3.7%).[78]

Evaluation

Diagnostic Testing in COVID-19

A nasopharyngeal swab for SARS-CoV-2 nucleic acid using a real-time PCR assay is the standard diagnostic test.[NIH COVID-19 Treatment Guidelines] Commercial PCR assays have been authorized by the USA Food and Drug Administration (FDA) for the qualitative detection of SARS-CoV-2 virus using specimens obtained from nasopharyngeal swabs as well as other sites such as oropharyngeal, anterior/mid-turbinate nasal swabs, nasopharyngeal aspirates, bronchoalveolar lavage (BAL) and saliva.

The sensitivity of PCR testing depends on multiple factors, including the specimen's adequacy, time from exposure, and specimen source.[79] However, the specificity of most commercial FDA-authorized SARS-CoV-2 PCR assays is nearly 100%, provided there is no cross-contamination during specimen processing. SARS-CoV-2 antigen tests are less sensitive but have a faster turnaround time than molecular PCR testing.[80]

Despite the numerous antibody tests designed to date, serologic testing has limitations in specificity and sensitivity, and results from different tests vary. According to the NIH guidelines, diagnosing acute SARS-CoV-2 infection based on serologic testing is not recommended. They also stated that there is insufficient evidence to recommend for or against

using serologic testing to assess immunity, even if it is used to guide clinical decisions about COVID-19 vaccines/monoclonal antibodies.[NIH COVID-19 Treatment Guidelines]

Other Laboratory Assessment

- Complete blood count (CBC), a comprehensive metabolic panel (CMP) that includes renal and liver function testing, and a coagulation panel should be performed in all hospitalized patients.
- Additional tests, such as ESR, C-reactive protein (CRP), ferritin, lactate dehydrogenase, and procalcitonin, can be considered in hospitalized patients. However, their prognostic significance in COVID-19 is not clear.
- A D-dimer level is required as it guides the use of therapeutic versus prophylactic doses of anticoagulation.

Imaging ModalitiesThiss viral illness commonly manifests as pneumonia, so radiological imaging such as chest x-rays, lung ultrasounds, and chest computed tomography (CT) are often obtained. However, there are no guidelines regarding the timing and choice of pulmonary imaging in patients with COVID-19.

When obtained, the chest X-ray usually shows bilateral multifocal alveolar opacities. Pleural effusions can also be demonstrated. The most common CT chest findings in COVID-19 are multifocal bilateral ground glass opacities with consolidation changes, usually in a patchy peripheral distribution.[81]

Radiologic imaging is not a sensitive method for detecting this disease. A retrospective study of 64 patients with documented COVID-19 reported that 20% had no abnormalities on chest radiographs during the illness.[82] A chest CT is more sensitive than a radiograph but is not specific. No finding on radiographic imaging can completely rule in or rule out COVID-19 illness. Therefore the American College of Radiology (ACR) advises against the routine use of chest CT for screening or diagnosis of COVID-19.[ACR Position Statement for Diagnosis of COVID-19]

Treatment / Management

According to the National Institutes of Health (NIH), the 2 main processes driving the pathogenesis of COVID-19 include replication of the virus in the early phase of the illness and dysregulated immune/inflammatory response to SARS-CoV-2 that leads to systemic tissue damage in the later phase of the disease.[NIH COVID-19 Treatment Guidelines] The guidelines, therefore, advise antiviral medications to halt viral replication in the early phase of the illness and immunomodulators in the later phase.

Remdesivir is the only antiviral drug approved by the USA Food and Drug Administration (FDA) to treat COVID-19. Ritonavir-boosted nirmatrelvir, molnupiravir, and high-titer COVID-19 convalescent plasma have Emergency Use Authorizations (EUAs) for treating COVID-19. Tixagevimab 300 mg plus cilgavimab 300 mg monoclonal antibodies have received EUAs that allow them to be used as SARS-CoV-2 preexposure prophylaxis (PrEP) in certain patients.

Many other monoclonal antibodies had EUAs; however, as Omicron subvariants emerged, their EUAs were revoked as they were no longer effective.

The most recent NIH treatment guidelines for the management of COVID-19 illness (accessed on January 3rd, 2023) are outlined below:[NIH COVID-19 Treatment Guidelines]

Nonhospitalized Adults With Mild-to-Moderate COVID-19 Illness Who Do Not Require Supplemental Oxygen

- The NIH recommends against using dexamethasone or any other systemic corticosteroids in patients who are not hypoxic.[83]
- In patients who are at high risk for progression to severe disease, they recommend the following therapies (in order of preference):
    - Ritonavir-boosted nirmatrelvir
        - Ritonavir-boosted nirmatrelvir is a combination of oral protease inhibitors. It has been shown to reduce hospitalization and death when given to high-risk, unvaccinated, nonhospitalized patients. It must be given within 5 days of symptoms onset.[84]
        - It is a strong cytochrome P450 inhibitor with many drug-drug interactions that must be carefully assessed.
        - Some interactions can be managed by temporarily holding the medication, some may be managed with dose adjustment, but some may warrant the use of alternate COVID-19 therapy.
        - Ritonavir-boosted nirmatrelvir is not recommended in patients with an estimated glomerular filtration rate (eGFR) of less than 30 mL/min.
        - The recommended dose is nirmatrelvir 300 mg with ritonavir 100 mg orally twice daily for 5 days.
    - Remdesivir
        - This is a nucleotide analog that inhibits the SARS-CoV-2 RNA polymerase
        - The recommended duration of therapy in this setting is 3 days.
        - The recommended dose is 200 mg IV on day 1, followed by 100 mg IV for 2 more days.
    - Molnupiravir
        - It is a mutagenic ribonucleoside antiviral agent.
        - Fetal toxicity has been reported in animal studies with this agent. Due to the risk of genotoxicity with this agent, it is not recommended in pregnant patients.
        - This agent should only be used if both therapies are unavailable or cannot be given.
- The NIH guidelines recommend against using anti-SARS-CoV-2 monoclonal antibodies (mAbs) for treating COVID-19 in this cohort because the Omicron subvariants are not susceptible to these agents.
- Adequate and close medical follow-up is recommended; however, the frequency and duration of follow-up depend on individual risk factors and the severity of their symptoms.
- Risk factors for progression to severe disease include advanced age and underlying medical conditions. The CDC maintains an updated list of medical conditions associated with a high risk of progression.
- According to the CDC, conditions with conclusive evidence demonstrating higher risk include:

- Asthma
- Cancer
- Cerebrovascular disease
- Chronic kidney disease
- Bronchiectasis
- COPD (Chronic obstructive pulmonary disease)
- Interstitial lung disease
- Pulmonary embolism
- Pulmonary hypertension
- Cirrhosis
- Nonalcoholic fatty liver disease
- Alcoholic liver disease
- Autoimmune hepatitis
- Cystic fibrosis
- Diabetes, type 1 and 2
- Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)
- HIV (Human immunodeficiency virus)
- Mental health conditions such as mood disorders and Schizophrenia spectrum disorders
- Obesity (defined as body mass index (BMI) of greater than 30 kg/m^2 or greater than 95th percentile in children)
- Pregnancy and recent pregnancy
- Smoking, current and former
- Solid organ or blood stem cell transplantation
- Tuberculosis
- Use of corticosteroids or other immunosuppressive medications (CDC: Underlying Medical Conditions Associated with Higher Risk)

Therapeutic Management of Hospitalized Adults With COVID-19 Who Do Not Require Oxygen

- If patients are hospitalized for reasons other than COVID-19 illness and are not on oxygen, their management is similar to nonhospitalized patients.
- If they are hospitalized for COVID-19 illness but do not require oxygen, the NIH advises against the use of dexamethasone or any other systemic corticosteroid.
- A prophylactic dose of anticoagulation should be given if there is no contraindication.
- If they are hospitalized for COVID-19 illness, do not require oxygen, but are at high risk of progression to severe disease, they should be treated with remdesivir.

- The benefit of remdesivir is greatest when given early, ideally within ten days of symptom onset.
- Remdesivir should be given for 5 days or until hospital discharge.

Therapeutic Management of Hospitalized Adults With COVID-19 Who Require Conventional Oxygen

- Conventional oxygen is defined as oxygen that is NOT high-flow nasal cannula, noninvasive mechanical ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)
- For most patients in this cohort, the recommended treatment is dexamethasone plus remdesivir.
- Dexamethasone dose is 6 mg IV or oral (PO) once daily for up to 10 days or until hospital discharge (dexamethasone should not be continued at discharge).[83]
- If the patient is on minimal oxygen, remdesivir monotherapy (without dexamethasone) should be used.
- If remdesivir cannot be obtained or given, dexamethasone monotherapy is recommended.
- If dexamethasone is unavailable, corticosteroids such as prednisone, methylprednisolone, or hydrocortisone may be used.
- If the patient is already receiving dexamethasone but has rapidly increasing oxygen needs and/or signs of systemic inflammation, oral baricitinib or intravenous (IV) tocilizumab should be added to the treatment regimen as these agents have been shown to improve outcomes in rapidly decompensating patients.[85]
- Alternate immunomodulatory agents for this cohort include oral tofacitinib and IV sarilumab. These agents should only be used if baricitinib and tocilizumab are not available.
- If the D-dimer level is above normal in this cohort of patients, they recommend therapeutic anticoagulation if the patient is not pregnant and has no increased risk of bleeding. Contraindications for therapeutic anticoagulation in these patients include a platelet count of less than 50 x10^9 /L, hemoglobin less than 8 g/dL, use of dual antiplatelet therapy, any significant bleeding within the past 30 days, a history of a bleeding disorder or an inherited or active acquired bleeding disorder.
- For pregnant patients, a prophylactic dose of anticoagulation is recommended.

Therapeutic Management of Hospitalized Adults With COVID-19 who Require High-flow Nasal Cannula (HFNC) or Noninvasive Mechanical Ventilation (NIV)

- A meta-analysis study evaluating the effectiveness of HFNC compared to conventional oxygen therapy and NIV before mechanical ventilation reported that HFNC, when used before mechanical ventilation, could improve the prognosis of patients compared to conventional oxygen therapy and NIV.[86] HFNC or NIV is associated with decreased dispersion of exhaled air, especially when used with good interface fitting, thus creating a low risk of nosocomial transmission of the infection.[87] However, these treatment modalities are associated with a greater risk of aerosolization and should be used in negative-pressure rooms.[88]
- According to the NIH, dexamethasone plus oral baricitinib or dexamethasone plus IV tocilizumab are the preferred treatment regimens in these patients.

- Alternate immunomodulatory agents for this cohort include oral tofacitinib and IV sarilumab.
- Dexamethasone monotherapy is recommended if baricitinib, tocilizumab, or sarilumab cannot be obtained/given.
- Clinicians may consider adding remdesivir to corticosteroid and immunomodulator combination regimens in immunocompromised patients who require HFNC or NIV ventilation; however, using remdesivir without immunomodulators is not recommended.
- A prophylactic dose of anticoagulation is recommended in these patients.
- If patients were started on a therapeutic dose of heparin while on conventional oxygen therapy, they should be switched to prophylactic dosing at this time unless they have another indication for full anticoagulation.

Therapeutic Management of Hospitalized Adults With COVID-19 who Require Mechanical Ventilation (MV)

- The management of this cohort is the same as those requiring HFNC or NIV, except that remdesivir is not recommended.
- Remdesivir is most effective earlier in the course of the disease and in patients not on mechanical ventilation or ECMO.
- According to the NIH, one study showed a slight trend toward an increase in mortality in patients who received remdesivir while on mechanical ventilation or ECMO.[89]
- With this data in mind, the NIH recommends against using remdesivir in patients receiving MV or ECMO; however, if the patient was started on remdesivir and progressed to requiring mechanical ventilation or ECMO, they recommended continuing remdesivir to complete the treatment course.

High-Titer COVID-19 Convalescent Plasma (CCP)

- The United States Food and Drug Administration (FDA) approved convalescent plasma therapy under a EUA for patients with severe life-threatening COVID-19.[90][91] Data from multiple studies evaluating the use of convalescent plasma in life-threatening COVID-19 has generated mixed results. Data from 3 small randomized control trials showed no significant differences in clinical improvement or overall mortality in patients treated with convalescent plasma versus standard therapy.[92][93][94]
- According to the NIH, high-titer CCP is not recommended in immunocompetent individuals.
- However, the NIH states that some experts consider it appropriate for use in immunocompromised individuals. Therefore, the current NIH guidelines state that there is insufficient evidence for or against the use of high-titer CCP for treating COVID-19 in hospitalized or nonhospitalized patients who are immunocompromised.

Medications/Treatments That Should NOT Be Used for the Treatment of COVID-19 According to the Latest NIH Guidelines [NIH COVID-19 Treatment Guidelines]

- Chloroquine or hydroxychloroquine with or without azithromycin
- Lopinavir/ritonavir
- Azithromycin

- Doxycycline
- Colchicine
- Fluvoxamine
- Ivermectin
- Inhaled corticosteroids
- Metformin
- Excess supplementation of vitamin C, vitamin D, and zinc
- Interferons alfa, beta, or lambda
- Nitazoxanide
- Bamlanivimab plus etesevimab
- Bebtelovimab
- Casirivimab plus imdevimab
- Sotrovimab

Preexposure Prophylaxis for SARS-CoV-2 Infection

- According to the NIH guidelines, tixagevimab plus cilgavimab is authorized by the FDA for preexposure prophylaxis of SARS-CoV-2 in people who are not expected to mount an adequate immune response to COVID-19 vaccination; however, the prevalence of Omicron subvariants that are resistant to tixagevimab plus cilgavimab is noted to be increasing rapidly.
- In the absence of alternative options, the NIH still recommends tixagevimab 300 mg plus cilgavimab 300 mg at this time.
- Tixagevimab and cilgavimab are potent anti-spike neutralizing monoclonal antibodies obtained from antibodies isolated from B cells of patients infected with SARS-CoV-2 that have demonstrated neutralizing activity against SARS-CoV-2 virus by binding to nonoverlapping epitopes of the viral spike-protein RBD.[95][96][97]
- The EUA authorizes its use in adult and pediatric patients with no current evidence of SARS-CoV-2 infection and no recent exposure to SARS-CoV-2-positive individuals. They must be moderately or severely immunocompromised or be on immunosuppressive medications.

Differential Diagnosis

The symptoms of the early stages of the disease are nonspecific. Differential diagnosis should include the possibility of a wide range of infectious and noninfectious respiratory disorders.

- Community-acquired bacterial pneumonia
- Viral pneumonia
- Influenza infection
- Aspiration pneumonia
- Pneumocystis jirovecii pneumonia

- Middle East respiratory syndrome (MERS)
- Avian influenza A (H7N9) viral infection
- Avian influenza A (H5N1) viral infection
- Pulmonary tuberculosis

Prognosis

The prognosis of COVID-19 depends on various factors, including the patient's age, the severity of illness at presentation, preexisting conditions, how quickly treatment can be implemented, and response to treatment. The WHO currently estimates the global case fatality rate for COVID-19 is 2.2%. Results from a European multicenter prospective cohort study that included 4000 critically ill patients with COVID-19 reported a 90-day mortality of 31%, with higher mortality noted in geriatric patients and patients with diabetes, obesity, and severe ARDS.[98]

Complications

COVID-19 is a systemic viral illness based on its involvement in multiple major organ systems.

- Patients with advanced age and comorbid conditions such as obesity, diabetes mellitus, chronic lung disease, cardiovascular disease, chronic kidney disease, chronic liver disease, and neoplastic conditions are at risk of developing severe COVID-19 and its associated complications. The most common complication of severe COVID-19 illness is progressive or sudden clinical deterioration leading to acute respiratory failure and ARDS or multiorgan failure leading to death.
- Patients with COVID-19 illness are also at increased risk of developing prothrombotic complications such as pulmonary embolisms, myocardial infarctions, ischemic strokes, and arterial thrombosis.[55]
- Cardiovascular system involvement results in malignant arrhythmias, cardiomyopathy, and cardiogenic shock.
- GI complications such as bowel ischemia, transaminitis, gastrointestinal bleeding, pancreatitis, Ogilvie syndrome, mesenteric ischemia, and severe ileus are often noted in critically ill patients with COVID-19.[99]
- Acute renal failure is the most common extrapulmonary manifestation of COVID-19 and is associated with an increased mortality risk.[69]
- A meta-analysis study of 14 studies evaluating the prevalence of disseminated intravascular coagulation (DIC) in hospitalized patients with COVID-19 reported that DIC was observed in 3% (95%: 1%-5%, $P < 0.001$) of the included patients. Additionally, DIC was noted to be associated with severe illness and was a poor prognostic indicator.[100]
- More recent data have emerged regarding prolonged symptoms in patients who have recovered from COVID-19 infection, termed "post-acute COVID-19 syndrome." A large cohort study of 1773 patients performed 6 months after hospitalization with COVID-19 revealed that most exhibited at least one persistent symptom: fatigue, muscle weakness, sleep difficulties, or anxiety. Patients with severe illness also had an increased risk of chronic lung issues.[101]
- A retrospective cohort study that included 236,379 patients reported substantial neurological (intracranial hemorrhage, ischemic stroke) and psychiatric morbidity (anxiety disorder, psychotic disorder) 6 months after being diagnosed with COVID-19.[102]

- Secondary invasive fungal infections such as COVID-19-associated pulmonary aspergillosis and rhino-cerebro-orbital mucormycosis have increasingly been reported as complications in patients recovering from COVID-19. Risk factors for developing secondary fungal infection include comorbid conditions such as uncontrolled diabetes, associated lymphopenia, and excessive use of corticosteroids.

Deterrence and Patient Education

The NIH COVID-19 Treatment Guidelines recommend COVID-19 vaccination as soon as possible for all eligible individuals. The CDC's Advisory Committee on Immunization Practices (AI) determines eligibility eligibility. Four vaccines are authorized or approved in the United States to prevent COVID-19. According to the NIH guidelines, the preferred vaccines include: [NIH COVID-19 Treatment Guidelines]

- mRNA vaccine BNT162b2 (Pfizer-BioNTech)
- mRNA-1273 (Moderna)
- Recombinant spike protein with matrix-M1 adjuvant vaccine NVX-CoV2373 (Novavax)

The adenovirus vector vaccine Ad26.COV2.S (Johnson & Johnson/Janssen) is less preferred due to its risk of serious adverse events.[NIH COVID-19 Treatment Guidelines]

A primary series of COVID-19 vaccination is recommended for everyone older than 6 months in the United States. Bivalent mRNA vaccines that protect against the original SARS-CoV-2 virus strain and Omicron subvariants are recommended at least 2 months after receiving the primary vaccine series or a booster dose.[NIH COVID-19 Treatment Guidelines]

Enhancing Healthcare Team Outcomes

SARS-CoV-2 and its variants continue to cause significant morbidity and mortality worldwide. Prevention and management of this highly transmissible respiratory viral illness require a holistic and interprofessional approach that includes physicians' expertise across specialties, nurses, pharmacists, public health experts, and government authorities. There should be open communication among the clinical providers, pharmacists, and nursing staff while managing patients with COVID-19. Each team member should strive to keep abreast of the latest recommendations and guidelines and be free to speak up if they notice anything that does not comply with the latest tenets for managing COVID patients; there is no place for a hierarchy in communication that prohibits any team member from voicing their concerns. This open interprofessional approach will yield the best outcomes.

Clinical providers managing COVID-19 patients on the frontlines should keep themselves periodically updated with the latest clinical guidelines about diagnostic and therapeutic options available in managing COVID-19, especially considering the emergence of new SARS-CoV-2 variants, which could significantly impact morbidity and mortality. Continued viral surveillance of new variants is crucial at regular intervals with viral genomic sequencing, given the possibility that more highly transmissible, more virulent, and treatment-resistant variants could emerge that can have a more catastrophic effect on global health in addition to the current scenario. A multi-pronged approach involving interprofessional team members can improve patient care and outcomes for this potentially devastating disease and help the world end this pandemic.

Review Questions

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