Epidemiological Alert
Complications and sequelae of COVID-19

12 August 2020

More than 7 months following the first report of novel coronavirus disease (COVID-19), knowledge of the complications and sequelae of this disease has increased substantially. Through this alert, the Pan American Health Organization / World Health Organization (PAHO/WHO) urges Member States to keep health professionals informed as new information continues to become available in order to strengthen the timely detection and proper management of COVID-19 cases, complications, and sequelae.

Introduction

Between 10 July and 10 August 2020, an additional 4,433,115 cases of COVID-19, including 114,480 additional deaths, were reported in the Region of the Americas, for a cumulative total of 10,697,800 confirmed cases of COVID-19 including 390,849 deaths. This represents a relative increase of 64% in cases and 37% in deaths compared to the number of new cases and deaths reported during the previous 4-week period (12 June to 9 July). The highest proportion of new cases were reported in the United States of America (44%) and Brazil (30%), while the highest proportion of new deaths were reported in Brazil (29%), the United States of America (26%), and Mexico (17%).

More than 7 months following the notification of the first COVID-19 cases (Joint Report of the WHO and the Government of China in February 2020) (1), there have been advances in the knowledge of the disease, including but not limited to the source of infection; the pathogenesis and virulence of the virus; transmissibility; risk factors; effectiveness of prevention measures; surveillance; diagnosis; clinical management; and complications and sequelae, amongst others. However, there remain several gaps pertaining to these factors that still require contribution from the entire scientific community.

The intense transmission of COVID-19 in most of the countries and territories of the Americas, along with evidence generated from the scientific community, has increased our knowledge of several of these factors including those related to complications and sequelae from COVID-19. Knowledge of these factors is necessary to improve and adjust the prevention and control strategies of the pandemic.

The following is a summary of the available evidence regarding complications and sequelae of COVID-19.

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Complications from COVID-19

According to what has been documented to date, it is known that 40% of COVID-19 cases develop mild symptoms (fever, cough, dyspnea, myalgia or arthralgia, odynophagia, fatigue, diarrhea, and headache), 40% have moderate symptoms (pneumonia), 15% develop severe clinical manifestations (severe pneumonia) that require oxygen therapy, and 5% develop a critical clinical picture presenting with one or more of the following complications (2-5): respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism and coagulation disorders (6-9), and/or multiple organ failure including acute renal failure (10-13), liver failure (13, 14), heart failure, cardiogenic shock, myocarditis (15-17), or cerebrovascular accident (18, 19), amongst others. Furthermore, complications attributed to invasive or non-invasive procedures during the course of clinical management of the case have also been documented.

Complications from COVID-19 occur mainly in persons with risk factors: older adults, smokers, and those with underlying comorbidities such as hypertension, obesity, diabetes, cardiovascular disease, chronic lung disease (for example, chronic obstructive pulmonary disease and asthma), chronic kidney disease, chronic liver disease, cerebrovascular disease, cancer, and immunodeficiency (2, 20-22).

The main complications documented with COVID-19, in addition to those related to the respiratory system, are neurological (18, 19, 23, 24), including delirium or encephalopathy, cerebrovascular accident, meningoencephalitis, alteration of the senses of smell (anosmia) and taste (hypogeusia) (25-27), anxiety, depression, and sleep disorders (28, 29). In many cases, neurological manifestations have been reported even in the absence of respiratory symptoms. There are also reports of cases of Guillain-Barré Syndrome (GBS) in patients with COVID-19 (18, 30, 31).

Available evidence suggests that COVID-19 can induce various gastrointestinal clinical manifestations in COVID-19 patients, which are more common in cases with severe clinical manifestations. Diarrhea, anorexia, vomiting, nausea, and abdominal pain can occur, and complications such as gastrointestinal bleeding in children can occur (32).

The clinical manifestations of COVID-19 in children are generally mild compared to adults (33). However, since May 2020, cases of a hyper-inflammatory syndrome have been observed in the pediatric population that can lead to multiple organ failure and shock, now described as multisystem inflammatory syndrome (MIS) in children and adolescents that coincides temporally with COVID-19 (34, 35). Several countries in Europe (36) and in the Region of the Americas have reported cases of MIS, such as Argentina, Brazil, Chile, Ecuador (37), the United States of America (38, 39), Honduras, Paraguay, Peru, and the Dominican Republic.

Recent studies of pregnant women have reported cases with severe manifestations and perinatal deaths (40). Preterm delivery, abortion, preeclampsia, perinatal death, and/or indication of preterm caesarean section have occurred among pregnant women infected with SARS-CoV-2 who developed pneumonia (41, 42). There have been reports of possible vertical transmission from the mother to the fetus, which has seemed to occur in the third trimester of gestation, so vertical transmission cannot yet be ruled out (43-49). Given the limited information of first trimester data, an assessment of vertical transmission in early pregnancy, as well as the potential risk and consequent fetal morbidity and mortality, cannot yet be made.

Sequelae from COVID-19

As part of the pathophysiological process of COVID-19, an intense inflammatory response is generated that first affects the respiratory tract, mainly the lungs. However, several studies suggest that sequelae of this infection are not only limited to the respiratory system, and that sequelae have been recorded in the cardiovascular system and in the central and peripheral nervous systems (51). Psychiatric and psychological sequelae have also been documented (52).

Sequelae in the respiratory system

The main sequelae of patients who developed a severe clinical picture of COVID-19 is the development of pulmonary fibrosis. During the acute phase of SARS-CoV-2 infection, lung damage causes edema, alveolar shedding of epithelial cells, and deposition of hyaline material on the alveolar membranes. During the next phase of infection, which usually occurs between the second and fifth week, the lungs show signs of fibrosis, with fibrin deposition and infiltration of inflammatory cells and fibroblasts near the epithelial cells in the alveolar spaces. During the final stage, between the sixth and eighth week, the lung tissue becomes fibrotic. Additionally, there are several reports of bilateral lesions with a predominance of the lower lobe (51, 53-55).

Sequelae in the cardiovascular system

It has been documented that patients with severe forms of COVID-19 presented with significant myocardial lesions, including infection-related myocarditis, with reduced systolic function and arrhythmias. These injuries could be secondary to severe lung damage. Unfortunately, little is yet known about the mechanisms responsible for these sequelae. Preliminarily, it is assumed that angiotensin-converting enzyme 2 (ACE 2) would be involved, which allows the virus to enter cells and facilitates viral replication. Significantly high levels of ACE 2 have been found in cardiac tissue (cardiomyocytes and pericytes), mainly in patients with pre-existing cardiovascular conditions (56). Myocardial injury has been reported, which could be due to direct damage to cardiomyocytes, systemic inflammation, myocardial interstitial fibrosis, and hypoxia (57). Due to the significant myocardial injuries in patients with severe clinical manifestations of COVID-19, the morbidity and lethality of the disease could be high, especially in patients with pre-existing cardiovascular conditions (58-60).

Neuropsychiatric sequelae

In severe cases of COVID-19, the systemic hyper-inflammatory response could cause long-term cognitive decline, such as deficiencies in memory, attention, processing speed, and functioning, along with diffuse neuronal loss (61). Furthermore, it has been documented that systemic inflammatory processes in middle-aged persons could lead to cognitive decline decades later. However, more evidence is needed to assess the independent and synergistic effects of COVID-19 sequelae on short- and long-term cognitive functions. Therefore, long-term evaluation of multiple sclerosis features and signs will be necessary in recovered COVID-19 patients.

Additionally, there are reports that SARS-CoV-2 can reach the central and peripheral nervous systems, with hematogenous spread or direct neural spread through the respiratory tract by possible mechanisms of viral neurotropism. The ACE 2 receptor would play a role in the mechanism by which the SARS-CoV-2 virus enters the cell and is expressed in the brain.

Various types of neuropsychiatric clinical manifestations have also been observed, such as acute encephalopathy, mood changes, psychosis, neuromuscular dysfunction, or demyelinating processes, which can accompany an acute viral infection or can follow an infection in recovered patients for weeks, months, or potentially longer. Therefore, prospective neuropsychiatric follow-up of individuals exposed to SARS-CoV-2, as well as evaluation of their neuroimmune status, is crucial to fully understand the long-term impact of neuropsychiatric manifestations of COVID-19 (28, 50, 62).

Further assessment of the direct neuropsychiatric consequences and indirect effects of COVID-19 on mental health is necessary for mental healthcare planning.

Psychological sequelae

The spread of COVID-19 globally has resulted in efforts to ensure social distancing, which could lead to negative psychological effects due to social isolation. All age groups—children, adolescents, young adults, and the elderly—are at-risk of suffering from psychological consequences due to the public health measures implemented during the pandemic (63, 64), as well as specific groups such as health personnel that could particularly experience mental health impacts (65, 66). It will be important to prioritize and implement comprehensive public health strategies to address this problem within the general population and within specific groups.

Guidance for national authorities

The Pan American Health Organization / World Health Organization (PAHO/WHO) recommends that Member States address the challenges of characterizing and comprehensively managing complications and sequelae of COVID-19, while also ensuring the continuity of follow-up and assistance for patients with sequelae from the disease.

PAHO/WHO recommends that Member States follow the guidelines and recommendations outlined in the PAHO/WHO Guide for the Care of Critical Adult Patients with Coronavirus Disease (COVID-19) in the Americas (4), published on 29 July 2020 and available in Spanish at https://bit.ly/3fguSHb, and the WHO Guidelines for Clinical Management of COVID-19, published on 27 May 2020 and available at https://bit.ly/30MVHyC .

The following are provisional guidelines for healthcare personnel in charge of caring for patients in the emergency and emergency services and/or the intensive care unit (ICU), related to the management and prevention of some of the complications. These recommendations are based on the evidence available to date, which is periodically reviewed.

Acute respiratory distress syndrome (ARDS)

The mortality in hospitalized and critically ill patients has varied substantially in different case series throughout the pandemic. The following recommendations are aligned with current international standards for management of all cause ARDS.

The following recommendations pertain to adult and pediatric patients with mild ARDS who are treated with non-invasive or high-flow nasal oxygen (HFNO) systems:

- In selected patients with COVID-19 and mild ARDS, a trial of HFNO, non-invasive ventilation – continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP) may be used. Refer to definitions of mild, moderate and severe ARDS.

The following recommendations pertain to adult and pediatric patients with ARDS who need intubation and invasive mechanical ventilation:

- Prompt recognition of progressive acute hypoxemic respiratory failure when a patient with respiratory distress is failing to respond to standard oxygen therapy and adequate preparation to provide advanced oxygen/ventilatory support.

- Endotracheal intubation performed by a trained and experienced provider using airborne precautions.

The following recommendations pertain to mechanically ventilated adult and pediatric patients with ARDS:

- Implementation of mechanical ventilation using lower tidal volumes (4–8 mL/kg predicted body weight [PBW]) and lower inspiratory pressures (plateau pressure <30 cmH_2O).

- In adult patients with severe ARDS (PaO_2/FiO_2 <150), prone ventilation for 12–16 hours per day.

- Use a conservative fluid management strategy for ARDS patients without tissue hypoperfusion and fluid responsiveness.

- In patients with moderate or severe ARDS, a trial of higher positive end-expiratory pressure (PEEP) instead of lower PEEP is suggested and requires consideration of benefits versus risks. In COVID-19, we suggest the individualization of PEEP where during titration the patient is monitored for effects (beneficial or harmful) and driving pressure.

- In patients with moderate-severe ARDS (PaO_2/FiO_2 <150), neuromuscular blockade by continuous infusion should not be routinely used.

- Avoid disconnecting the patient from the ventilator, which results in loss of PEEP, atelectasis and increased risk of infection of healthcare workers.

- In patients with excessive secretions, or difficulty clearing secretions, consider application of airway clearance techniques (such as suctioning and aspiration), which should be performed only if deemed medically appropriate. Whenever these procedures are performed, healthcare workers should comply with infection prevention and control (IPC) measures, including appropriate use of personal protective equipment (PPE) (such as N95 masks and face shields or goggles) (67).

The following recommendations pertain to adult and pediatric patients with ARDS in whom lung protective ventilation strategy fails to achieve adequate oxygenation and ventilation:

- In settings with access to expertise in extracorporeal membrane oxygenation (ECMO), consider referral of patients who have refractory hypoxemia (e.g. including a ratio of partial pressure of arterial oxygen [PaO_2] to the fraction of inspired oxygen [FiO_2] of <50 mmHg for 3 hours, a PaO_2:FiO_2 of <80 mmHg for >6 hours) despite lung protective ventilation.

Septic shock

Recognize septic shock in adults when infection is suspected or confirmed AND vasopressors are needed to maintain mean arterial pressure (MAP) ≥65 mmHg AND lactate is ≥2 mmol/L, in the absence of hypovolemia.

Recognize septic shock in children with any hypotension (systolic blood pressure [SBP] <5th centile or >2 SD below normal for age) or two or more of the following: altered mental status; bradycardia or tachycardia (heart rate [HR] <90 beats per minute [bpm] or >160 bpm in infants and HR <70 bpm or >150 bpm in children); prolonged capillary refill (>2 sec) or feeble pulses; tachypnoea; mottled or cold skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia.

The following recommendations pertain to resuscitation strategies for adult and pediatric patients with septic shock:

- In resuscitation for septic shock in adults, give 250–500 mL crystalloid fluid as rapid bolus in first 15–30 minutes.

- In resuscitation for septic shock in children, give 10–20 mL/kg crystalloid fluid as a bolus in the first 30–60 minutes.

- Fluid resuscitation may lead to volume overload, including respiratory failure, particularly with ARDS. If there is no response to fluid loading or signs of volume overload appear (e.g. jugular venous distension, crackles on lung auscultation, pulmonary edema on imaging, or hepatomegaly), then reduce or discontinue fluid administration. This step is particularly important in patients with hypoxemic respiratory failure.

- Do not use hypotonic crystalloids, starches, or gelatins for resuscitation.

- In adults, administer vasopressors when shock persists during or after fluid resuscitation. The initial blood pressure target is MAP ≥65 mmHg in adults and improvement of markers of perfusion.

In children, administer vasopressors if signs of fluid overload are apparent or the following persists after two fluid boluses:

  - signs of shock such as altered mental state;
  - bradycardia or tachycardia (HR < 90 bpm or >160 bpm in infants and HR <70 bpm or >150 bpm in children);
  - prolonged capillary refill (> 2 seconds) or feeble pulses;
  - tachypnoea; mottled or cool skin or petechial or purpuric rash; increased lactate; oliguria persists after two repeat boluses;
  - or age-appropriate blood pressure targets are not achieved.

Prevention of complications in hospitalized patients and critically ill patients with COVID-19

Thromboembolism

In order to prevent venous thromboembolism in patients (adults and adolescents) hospitalized with COVID-19, use pharmacological prophylaxis, such as low molecular weight heparin (such as enoxaparin), according to local and international standards, to prevent venous thromboembolism, when not contraindicated. For those with contraindications, use mechanical prophylaxis (intermittent pneumatic compression devices).

Monitor patients with COVID-19, for signs or symptoms suggestive of thromboembolism, such as stroke, deep venous thrombosis, pulmonary embolism, or acute coronary syndrome. If these are clinically suspected, proceed immediately with appropriate diagnostic and management pathways.

Measures to prevent procedural complications during the clinical management of COVID-19

Prevention of procedural complications	
Anticipated outcome	**Interventions**
Reduce days of invasive mechanical ventilation	Use weaning protocols that include daily assessment for readiness to breathe spontaneously.
	Minimize continuous or intermittent sedation, targeting specific titration endpoints (light sedation unless contraindicated) or with daily interruption of continuous sedative infusions.
	Early mobilization
	Implementation of the above as a bundle of care (may also reduce delirium); such as the Awakening and Breathing Coordination, Delirium assessment/management, and Early mobility (ABCDE)
Reduce incidence of ventilator-associated pneumonia	Oral intubation is preferable to nasal intubation in adolescents and adults.
	Keep patient in semi-recumbent position (head of bed elevation 30–45º)
	Use a closed suctioning system; periodically drain and discard condensate in tubing.
	Use a new ventilator circuit for each patient; once patient is ventilated, change circuit if it is soiled or damaged, but not routinely.
	Change heat moisture exchanger when it malfunctions, when soiled, or every 5–7 days.
Reduce incidence of catheter-related bloodstream infection	Use a bundle,with completion verified by a real-time observer as a reminder of each step needed for sterile insertion and as a daily reminder to remove catheter if no longer needed.
Reduce incidence of pressure ulcers	Turn patient every 2 hours.
Reduce incidence of stress ulcers and gastrointestinal bleeding	Give early enteral nutrition (within 24–48 hours of admission)
	Administer histamine-2 receptor blockers or proton-pump inhibitors in patients with risk factors for GI bleeding. Risk factors for GI bleeding include mechanical ventilation for ≥ 48 hours, coagulopathy, renal replacement therapy, liver disease, multiple comorbidities, and higher organ failure score.
Reduce the development of antimicrobial resistance	Utilize de-escalation protocols as soon as patient is clinically stable and there is no evidence of bacterial infection.
Reduce the development of adverse drug effects	Expose patient to empiric antimicrobial therapy for the shortest time possible, to prevent nephrotoxicity, cardiac and other side-effects from unnecessary antimicrobial use.
Promote appropriate antimicrobial prescribing and use during the COVID-19 pandemic	Do not prescribe antibiotics to suspected or confirmed COVID-19 patients with low suspicion of a bacterial infection, to avoid more short-term side-effects of antibiotics in patients and negative long-term consequences of increased antimicrobial resistance.

Management of neurological and mental manifestations associated with COVID-19

People with COVID-19 are at high risk for delirium, and sometimes delirium may be a presenting feature without respiratory symptoms. Anxiety and depressive symptoms may constitute common reactions for people in the context of COVID-19 diagnosis, especially for those who may be hospitalized, due to concerns for one's own health or the health of others, the need for physical isolation (which can lead to social isolation), potential risk of death, concerns over the risk of infecting others, and concerns over leaving family members alone who may need care. Stressors particular to COVID-19 include: fear of falling ill and dying, fear of being socially excluded/placed in quarantine, loss of livelihood and loss of loved ones, and feelings of helplessness, boredom, and loneliness due to being isolated. These stressors may trigger new symptoms or exacerbate underlying mental or neurological conditions. Patients with pre-existing mental health conditions and substance abuse disorders may also be adversely impacted. People with COVID-19 are at higher risk for sleep problems owing to acute stress responses, as well as additional reasons for those who are hospitalized such as environmental factors, invasive medical procedures (e.g. mechanical ventilation) and the frequent combination of multiple medications possibly disrupting sleep patterns.

Delirium

It is recommended that for patients with COVID-19, measures to prevent delirium, an acute neuropsychiatric emergency, be implemented, and patients be evaluated using standardized protocols, for the development of delirium. If detected, then immediate evaluation by a clinician is recommended to address any underlying cause of delirium and treat appropriately.

Mental health and psychosocial support

It is recommended to provide basic mental health and psychosocial support (MHPSS) for all persons with suspected or confirmed COVID-19 by asking them about their needs and concerns and addressing them.

It is recommended to conduct prompt identification and assessment for anxiety and depressive symptoms in the context of COVID-19 and to initiate psychosocial support strategies and first-line interventions for the management of new anxiety and depressive symptoms.

Psychosocial support strategies are recommended as the first-line interventions for management of sleep problems in the context of acute stress.

Rehabilitation for COVID-19 patients

Since COVID-19 is a novel disease, the rehabilitation needs for patients recovering from COVID-19 are anticipated based on evidence from the general critical care population. Based on this evidence, it is expected that acute interventions for the management of patients with severe and critical COVID-19, including mechanical ventilation, sedation and/or prolonged bed rest, may result in a range of impairments including (but not limited to) physical deconditioning, respiratory, swallow, cognitive and mental health impairments. These symptoms are collectively referred to as post-intensive care syndrome (PICS). Older people and patients of all ages with chronic diseases may be most susceptible to its impacts. Patients recovering from severe COVID-19 who did not require admission to an ICU may also experience some degree of these symptoms.

Among the following groups of patients, routinely assess for mobility, functional, swallowing, and cognitive impairments and mental health concerns, and based on that assessment, determine discharge readiness, and rehabilitation and follow-up requirements:

- patients who are in or have been discharged from intensive care;
- older patients who have suffered from severe illness; and
- patients that exhibit signs of any of these impairments.

When rehabilitation needs are identified, refer for inpatient, outpatient, or community-based follow-up as indicated and based on rehabilitation needs.

It is recommended to provide tailored rehabilitation programs from post-acute to long-term, according to patient needs.

For the management of sequelae, comprehensive evaluation and follow-up of recovered patient cohorts is recommended.

The specific management of complications and sequelae should be carried out in accordance with current national protocols.

Finally, it is recommended to ensure the continuity of follow-up and assistance to patients who have recovered from COVID-19.

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