Review Article

Acute management of COVID-19 in the emergency department: An evidence-based review

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Abstract

Coronavirus disease (COVID-19) has been relentlessly battering the world wave after wave in different countries at different rates and times. Emergency departments (EDs) around the globe have had to constantly adapt to this ever-changing influx of information and recommendations by various national and international health agencies. This review compiles the available evidence on the guidelines for triaging, evaluation, and management of critically ill patients with COVID-19 presenting to the ED and in need of emergency resuscitation. The quintessential components of resuscitation focus on airway, breathing, and circulation with good supportive care as the cornerstone of acute management of critically ill COVID-19 patients. Irrational investigations and therapeutics must be avoided during these times of medical uncertainty and antibiotic stewardship should be diligently followed.

Keywords: Coronavirus, COVID-19, emergency department, pandemic, SARS-CoV-2

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak that began in December 2019 continues to ravage the world wave after wave.[1,2] Over these months, substantial information has been compiled and published on COVID-19. Emergency departments (EDs) have been adapting to this everchanging influx of information and recommendations by various National and International health agencies like the world health organization (WHO), centre for disease control (CDC), national institutes of health (NIH), indian council of medical research (ICMR), and the ministry of health and family welfare (MoHFW) in India. The deluge of rapidly published literature on this enigmatic disease often leaves physicians confused regarding which guidelines to follow. This review compiles evidence on guidelines for triaging, evaluation, and management of patients with COVID-19 presenting to the ED in need of emergency resuscitation.

Methods

We performed a literature search on published data related to the evaluation and management of COVID-19 patients in the ED by using the keywords "SARs-CoV-2," "ÇOVID-19," "emergency department" in PubMed, Web of Science, Google Scholar, and EMBASE databases from inception in December 2019 through to May 2021. We included randomized controlled trials, retrospective studies, case series, systematic reviews, meta-analysis, and clinical guidelines from WHO, CDC, NIH, ICMR, and MoHFW.

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Discussion

Triaging and segregation

Due to the extremely high infectivity rate of the virus, and the consequential risk to healthcare workers (HCWs), EDs began cohorting patients into "COVID-suspect zones," and "green zones," In the initial stages of the pandemic, triaging was based on the patient's epidemiological profile with those traveling from "high risk" or "containment" areas being cohorted as "suspected COVID-19." Once the level of community transmission increased, all hospitals improvised and modified their existing triaging criteria using either only clinical features or a combination of clinical, radiological, and laboratory findings to segregate patients.[3,4] The WHO recommends two triage options, based on the resources available and the size of the healthcare facility.[5] In the ED of Christian Medical College, Vellore, the following triaging criteria have been in use throughout most of the COVID-19 pandemic, except in the initial months where epidemiology and travel history were given consideration to determine risk and segregation [Table 1]. Physical separation of the "COVID-19-suspect" and "green" zones with separate pathways for patients as well as donning and doffing areas for HCWs is of utmost importance. In short, a unidirectional flow of both patients and HCWs must be established.

Safety of HCWs

HCWs have been at the frontline since the beginning of the pandemic and unless they are kept safe, no hospital or country can keep its patients. In addition to exposure to aerosols containing SARS-CoV-2, HCWs also had to contend with violence from relatives, harassment, stigma, and discrimination from the general public, effects of prolonged use of personal protective equipment (PPE), not to mention the physical and mental fatigue of such a prolonged ordeal.[6,7] Recommendations for PPE use have been constantly updated by CDC, MoHFW, and WHO and must strictly be adhered to.[8-10]

Evaluation

Clinical presentation and risk stratification

Patients with SARS-CoV-2 infection present with a variety of clinical manifestations, ranging from very mild symptoms to critical illness. Common symptoms include fever (72.4%), cough (55.5%), myalgia (22.1%), breathlessness (18.8%), sore throat (16.2%), headache (10.5%), rhinorrhea (9.2%), and loose stools (7.9%).[11] A meta-analysis of 212 studies from 11 countries comprising 281,461 patients in 2020 showed the mean age to be 46.7 years with a mortality rate of 5.6%.[12] Diabetes mellitus, underlying immunosuppression, and malignancy were associated with severe illness, whereas older age, diabetes mellitus, hypertension, and male sex were associated with increased mortality.[12]

Table 2 shows the risk stratification and severity of illness categories proposed by the NIH and WHO.[10,13] Excluding the asymptomatic patient who merely requires self-isolation, it is possible to group the unwell patients into four broad categories for the purpose of developing clinical management protocols. These are as follows: mild illness, moderate illness, severe illness, and critical illness. Naturally, a patient's clinical status and severity category may change with time.

Table 1: ED triage protocol for segregation of patients into the "COVID-suspect" zone and the "green" zone

COVID-suspect zone	Green zone
Patients with influenza-like illness	Patients with fever and an obvious focus of infection (e.g., cellulitis)
Patients with fever or cough or breathlessness <10 days	All other medical and surgical emergencies
Epidemiological criteria (used before community transmission started during early pandemic):	Trauma
Patients with any emergency from high-risk areas/hot spots	
Triage priority levels for COVID-suspect zone	
Triage priority 1: Patients with critical illness requiring advanced ventilatory supports (high-flow nasal cannula/noninvasive ventilation or invasive mechanical ventilation)	
Triage priority 2: Patients with severe illness requiring supplemental oxygen alone to maintain SpO_2 >94% (nasal cannula/simple mask/venturi mask/simple nonbreathing mask)	
Triage priority 3: Patients with mild-moderate illness with SpO_2 >94% and hemodynamically stable	

Table 2: Severity of illness categories according to NIH and WHO

Severity category	NIH severity classification[13]	WHO severity classification[10]
Asymptomatic infection	Patients who test positive for SARS-CoV-2 using a virologic test but have no symptoms associated with COVID-19	
Mild illness	Patients with any symptom of COVID-19, without evidence of dyspnea and abnormal chest imaging	Patients with any symptom of COVID-19 without evidence of viral pneumonia and hypoxia
Moderate illness	Patients with evidence of lower respiratory tract infection on clinical examination but with normal saturation (SpO_2 >94% on room air)	Patient with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but SpO_2 ≥90% on room air
Severe illness	Patients with SpO_2 >94% on room air, PaO_2/FiO_2 <300 mmHg, RR >30/min, or lung infiltrates >50%	Patient with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but also with one of the following: RR >30/min, SpO_2 <90% on room air, or severe respiratory distress
Critical illness	Patients with respiratory failure, septic shock, and/or multiple organ dysfunction	Patients with acute respiratory distress syndrome, sepsis with multiple organ dysfunction, and/or septic shock

Laboratory investigations

Asymptomatic and mildly ill patients need only a confirmatory diagnostic test by reverse transcription-polymerase chain reaction test (RT-PCR) or rapid antigen test (RAT). Basic evaluation of more unwell patients, those presenting with moderate to severe illness, includes a baseline complete blood count (CBC), electrolytes, renal function, and liver function tests. An absolute lymphocyte count (ALC) of 800/cm ($0.8 \times 10^3/\mu L$) has been consistently associated with severe illness, as is a high neutrophil: lymphocyte ratio (6.6 in severe illness vs. 3.3 in mild illness; $P < 0.001$).[14-16]

The following serum biomarkers have also been extensively studied in COVID-19 and found to be elevated in severe disease: D-dimer, lactate dehydrogenase (LDH), C-reactive protein (CRP), and ferritin, the majority of which are not specific to COVID-19. However, these tests could be considered in patients with moderate to severe illness for prognostication. Though guidelines recommend consideration of these tests in resource-rich settings, they are not considered part of standard of care, particularly not in EDs.

- D-dimer: A marker of thrombosis, D-dimer has been found to be elevated in patients with severe COVID-19 illness.[17-19] In one of the earliest studies, Zhou *et al.*[17] reported D-dimer levels >1 μg/mL (1,000 ng/mL) to be an independent predictor of mortality (Odds Ratio [OR]: 18·42, 95% CI: 2·64–128·55; $P = 0·0033$). Yu *et al.*[18] reported patients with severe illness to have significantly higher median D-dimer levels at admission (1,800 ng/mL) compared with those with mild illness (500 ng/mL). Rostomi *et al.*[19] further corroborated the finding of a three- to four-fold elevated D-dimer level at admission to be associated with poor prognosis.
- C-reactive protein: CRP is a nonspecific marker of inflammation and is elevated in severe illness.[17,20] Luo *et al.*[20] reported that CRP levels at admission correlated with disease severity and could be a predictor of adverse outcomes. In another study, the median CRP levels at admission were significantly higher among patients who died when compared with those who survived (206 mg/L vs. 114 mg/L; $P < 0.001$).[21] A meta-analysis by Zhang *et al.*[22] comprising 1,905 patients showed elevated CRP to be significantly associated with illness severity (OR 3.0, 95% CI: 2.1–4.4). This was further corroborated by Amiri-Dashatan *et al.*[23] analyzing 23 studies with 4,313 patients (standardized mean difference: 3.26 mg/L; 95% CI: 2.5, 3.9); $P < 0.05$).
- Lactate dehydrogenase: Elevated LDH levels reflect tissue hypoperfusion and hence logically may be associated with poor prognosis. In a pooled analysis of nine studies that included 1,532 patients, elevated LDH levels were shown to be associated with a six-fold and 16-fold increased chance of developing severe disease and mortality, respectively.[24] In a systematic review of 21 studies including 10,339 patients, elevated LDH levels indicated a 44% posterior probability for poor prognosis.[25]
- Ferritin: Serum ferritin levels have been shown to be a predictor of increased severity and mortality due to COVID-19 in many studies.[26-28] A meta-analysis of 52 studies including 10,614 patients, showed ferritin to be increased in severe illness as opposed to a mild-moderate illness (weighted mean difference: 397.77; 95% CI 306.51–489.02, $P < .001$).[28] Elevated levels were also found among those who died when compared with the survivors (WMD 677.17 [95% CI 391.01–963.33], $P < .001$).[28]

Radiological imaging

- Chest radiograph: A CXR has a sensitivity of 68%–90% in the diagnosis of COVID-19 pneumonia and gives valuable information to clinicians in resource-limited settings.[29-31] Typical CXR findings of COVID-19 pneumonia include multifocal and bilateral air-space opacities and/or consolidation with a peripheral and basal predominance.[29,31] However, a normal CXR does not rule out COVID-19.
- Ultrasonography: Where expertise is available, lung ultrasound (LUS) can be an extremely reliable tool in diagnosing and monitoring COVID-19 pneumonia with a diagnostic accuracy better than CXR and comparable with computed tomography (CT) imaging.[32,33] Other advantages include the absence of radiation, low cost, and bedside availability. Typical LUS patterns of COVID-19 pneumonia include B lines in large numbers (separate or coalescent forms: light beam pattern), giving the appearance of a shining white lung, especially in the posterior and inferior lung fields.[32,34] Focal breaks in the pleural line, and subpleural consolidations are other typical features. These findings were shown to have a strong correlation with concurrent CT scans.[35]
- CT chest: Chest CT is considered the gold standard among radiological techniques in diagnosing early COVID-19 pneumonia.[36,37] A meta-analysis of 103 studies including 9,907 patients described the following to be the most common CT findings: ground-glass opacities (77.18%), reticulation (46.24%,), air bronchogram (41.61%), pleural thickening (33.35%), and bronchial wall thickening (15.48%).[38] Lesions are predominantly distributed bilaterally (75.72%) and peripherally (65.64%).[38]

Diagnosis

The diagnosis of COVID-19 can be confirmed by a direct viral test like RT-PCR, which is considered as the gold standard or using a rapid antigen test. Since a positive COVID-19 test may indicate incidental COVID-19 positivity rather than true infection, in the absence of the typical signs of COVID-19 infection it is important to consider coinfections (influenza, malaria, scrub typhus, dengue) in endemic areas and other chronic infections like tuberculosis. These may be confirmed by appropriate testing and managed according to local or national guidelines.[39,40] It must be remembered that a positive result for a non-SARS-CoV-2 pathogen does not rule out COVID-19 nor vice versa.

Management

Guidelines for the management of COVID-19 patients are issued and updated regularly based on emerging evidence by the WHO, NIH, Surviving Sepsis Campaign (SSC) COVID-19, and MoHFW.[9,10,41,42] These guidelines are quite similar to one other and are summarized here in the form of the standard resuscitation protocol of EDs: airway, breathing, circulation (ABC), and D (drugs).

Airway

In critically ill patients, securing the airway is of utmost importance. Early recognition of failed oxygen therapy or noninvasive ventilation (NIV) is important and a definitive airway must be immediately secured. Since the pandemic began, emphasis has been laid on the risk of high aerosol generation during efforts to secure the airway. Hence, all safety protocols, especially full PPE (full-length surgical gown, face shield/goggles, N95 facemask, and gloves) must be strictly adhered to.

Endotracheal intubation

In patients with a compromised airway, plan for rapid sequence induction (RSI). Passively preoxygenate with 100% FiO_2 for 3–5 min and avoid manual ventilation after paralysis to minimize potential aerosolization of virus from the airways. If manual ventilation is required, use small tidal volumes.[43-45] If available, consider using a video laryngoscope (VL) to improve the chances of first-pass intubation and to maintain distance from the oropharynx.[44] Confirm the correct placement of the endotracheal tube (ETT) by 5-point auscultation, waveform capnography, and postintubation CXR.

Safety measures for HCWs

- Video laryngoscope: Most airway management guidelines have recommended VL over direct laryngoscopy as the preferred method of intubation of COVID-19 patients.[46-48] VL offers the advantage of increased distance between the operator's and the patient's faces, thus protecting the operator from aerosols generated during the procedure.[49] In addition, VL offers better visualization and improves the first-pass success rate of intubation.[50]
- Aerosol box (AB): This was one innovation that gained immense popularity during the early months of the pandemic as it provided an additional physical barrier from aerosol generation during intubation [Figure 1]. Several variations and improvements of the device have been tried out. In a meta-analysis by Lim *et al.*,[51] eight mannequin-based studies reported a statistically significant increase in time taken for intubation (TTI) using an AB (mean difference: 3.9 s; 95% CI: 2.2–5.5; $P < 0.001$). However, in critically ill COVID-19 patients, the median TTI was found to be significantly shorter with no AB (42.9 s vs. 82.1 s; $P = 0.002$) compared with a first-generation AB and a significant increase in first-pass success rate without an AB (100% without; 75% and 83% with 1st and 2nd generation AB, respectively).[52] Recommendation: AB may be used as a physical protective barrier if intubation is performed by an experienced physician using video laryngoscope. Inexperienced physicians must be cautious about the longer TTI while intubating critically ill patients with difficult airways, which could potentially worsen the patients' clinical condition.
- Mechanical viral filters: Disposable membranes using high-efficiency particulate air (HEPA) filters placed between the endotracheal tube and the breathing circuit have been recommended and used extensively to reduce virus spread and contamination of the breathing circuit.[9,10,53] The active medium of these mechanical viral filters is a hydrophobic membrane of coated glass fibers, which is impervious to potentially contaminated fluids.

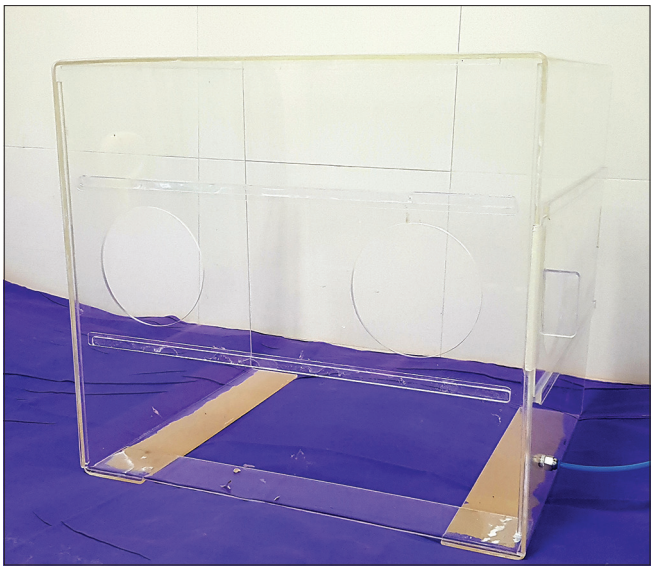

Figure 1: Aerosol box commonly used for intubation during the COVID-19 pandemic

Breathing

Ventilatory support is extremely important in managing hypoxic patients with COVID-19 with or without acute respiratory distress syndrome (ARDS). All patients in the severe illness category must be managed in places with adequate oxygen delivery interfaces like nasal cannulae, simple masks, venturi masks, and nonrebreathing masks. Patients in the critical illness category require advanced respiratory supports.

- *Management of COVID-19: severe pneumonia*

COVID-19 patients with hypoxia must be administered supplemental oxygen aiming to maintain target SpO_2 >92%. Oxygen flow rates must be adjusted and delivered using appropriate delivery devices

- Nasal cannula: Oxygen flow rate up to 5 L/min
- Simple mask or Venturi mask: Oxygen flow rates 6–10 L/min
- Nonrebreather mask/face mask with reservoir bag: Oxygen flow rates 10–15 L/min

- *Management of COVID-19: critical illness with ARDS*

Patients with acute hypoxemic respiratory failure despite supplemental oxygen therapy require additional respiratory support with either Hi-Flow Nasal Cannula (HFNC) or Noninvasive ventilation (NIV). In the ED, a patient who continues to be hypoxic on other oxygen delivery systems may be considered for a trial of NIV. This may reduce the work of breathing and obviate the need for intubation and invasive mechanical ventilation (IMV). Once stabilized, the patient may be transferred to the intensive care unit.

- *HFNC:* Oxygen flow rate up to 60 L/min at a FiO_2 up to 100% can be delivered by these devices. It helps in decreasing respiratory rate, providing positive end-expiratory pressure (PEEP), physiological dead space washout of CO_2, increased tidal volume, and end-expiratory volume.[54,55] Drawbacks include lack of availability of HFNC units in sufficient number, and high flow rate resulting in high oxygen consumption and cost.
- *NIV:* NIV provides pressurized ventilatory support (improving gas exchange and/or reducing the work of breathing) by a face mask without the need for an advanced airway. NIV can be provided by Continuous Positive Airway Pressure (CPAP), Bilevel Positive Airway Pressure (BPAP), a helmet device, or a ventilator on NIV mode. These devices have been found to be useful in the management of respiratory failure due to COVID-19 and a trial of NIV should be considered unless there are contraindications for the same.
- Invasive mechanical ventilation (IMV): Indications include severe or persistent hypoxemic respiratory failure, multiorgan failure, or altered mental status. A meta-analysis by Lim *et al.*[56] showed IMV to have a mortality rate of around 47.9% in the <40 years age group and 84.4% in the >80 years group.

In the absence of an indication of invasive ventilation, the NIH guidelines recommend HFNC over NIV.[9,10] However, with disastrous oxygen shortages during the second COVID-19 wave in India, it is prudent to give a trial of NIV as the first choice given that the oxygen flow rates are significantly lower with NIV than with HFNC. With an eye once more to the risk of these devices to HCWs, the aerosol dispersal distance is greatest from nasal cannulae, then, in descending order, from an NIV-vented mask, simple oxygen mask, venturi mask, CPAP, HFNC, nonrebreathing mask, and finally is shortest for a helmet NIV.[57]

- *Prone positioning*

During the COVID-19 pandemic, proning of patients has been widely adopted in ICUs to treat patients with ARDS on IMV. There is consistent evidence that it improves oxygenation in patients on IMV due to better ventilation-perfusion matching.[58,59] Many guidelines recommend awake proning in nonintubated patients by extrapolating physiological principles from available evidence on mechanically ventilated patients and previous evidence on non-COVID-19 patients.[59] A meta-analysis on awake proning in nonintubated COVID-19 patients also showed significant improvement in PaO_2: FiO_2 ratio, SpO_2, and PaO_2.[60]

Circulation

In most patients with COVID-19, hemodynamic abnormalities are uncommon, unless they present very late into the illness or the course is complicated by cardiac events or secondary infections. COVID-19 patients requiring fluid resuscitation and hemodynamic support should be treated and managed like patients with septic shock in accordance with standard guidelines.[10,61] For acute resuscitation of adults with shock, buffered/balanced crystalloids are preferred over unbalanced crystalloids.[61,62] Colloids like albumin and hydroxyethyl starches are not recommended for initial resuscitation as there was no mortality benefit found in large trials and meta-analyses.[63,64] The target for mean arterial pressure (MAP) should be >65 mmHg, with noradrenaline as the first-choice vasopressor.[10,61] Adrenaline or vasopressin may be added to noradrenaline infusion to achieve the target MAP. Dobutamine is recommended only in patients with cardiac failure and persistent hypoperfusion despite adequate fluid resuscitation and the use of first-line vasopressor agents.[61]

Drugs (Therapeutics)

From the beginning of the pandemic, many therapeutics like antivirals, antibiotics, anti-inflammatory agents, and plasma therapy has been tried. A prominent pathophysiological abnormality in COVID-19 seems to be "thrombo-inflammation" and this appears to be best treated with a combination of an anti-inflammatory agent (anti-inflammatory dose of corticosteroids) and an anticoagulant.[65] Currently, only the following are shown to be beneficial and are recommended for use in the ED.

- Corticosteroids:

In patients in the severe category with systemic inflammatory response threatening lung injury, the potent anti-inflammatory effects of corticosteroids could halt, or mitigate these deleterious effects. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, a randomized open-labeled study, demonstrated a mortality benefit of dexamethasone compared with standard care in patients either requiring supplemental oxygen or who were mechanically ventilated.[66]

Recommendation: Corticosteroids are currently recommended only for patients requiring supplemental oxygen to maintain SpO_2 > 94%.[9,10,66] The recommended dose of dexamethasone, assuming no contraindications, is 6 mg once daily (OD) IV/PO for 7–10 days or until discharge (if earlier), with blood glucose monitoring, and concurrent proton pump inhibitor use for gastroprotection. Prednisolone (40 mg OD PO) or methylprednisolone (32 mg OD PO or IV) are suitable alternative recommendations for women who are pregnant or breastfeeding.

- Anticoagulants:

Coagulopathy associated with COVID-19 has been extensively studied and is characterized by endothelial dysfunction, platelet activation, abnormal flow dynamics, and hypercoagulability

resulting in increased thrombotic complications. These include deep vein thrombosis, pulmonary embolism, cerebral venous thrombosis, and another microvascular thrombosis.[67,68] A meta-analysis of 83 studies including 28,173 hospitalized COVID-19 patients found a 14.1% incidence of venous thromboembolism as compared with 2.8% to 5.6% non-COVID-19 hospitalized patients prior to the pandemic.[69]

Pregnancy, being a hypercoagulable state, is associated with a higher risk of thromboembolism still.[70-72] A systematic review by Servante *et al*.[73] including 1,063 hospitalized pregnant COVID-19 patients also showed an increased rate of coagulopathy and thromboembolic events among pregnant patients.

Recommendation: In nonhospitalized patients, there is no indication to routinely measure coagulation markers (D-dimer, fibrinogen, or platelet count) or to initiate antiplatelet/anticoagulant therapy.[74,75] In hospitalized patients, increasing D-dimer has been shown to parallel worsening respiratory status.[65] Prophylactic dose anticoagulation is recommended for all hospitalized patients unless there is a contraindication.[75,76] In those with a higher risk of thrombosis or in the setting of an increasing D-dimer and worsening respiratory status, an intermediate dose of anticoagulation can be administered.[77] Therapeutic anticoagulation may be avoided unless there is proven venous thrombosis or thromboembolism.[78] Unfractionated and low-molecular-weight heparins do not accumulate in breast milk and hence are considered safe in lactating mothers. Due to a lack of data, direct-acting anticoagulants are not recommended for use in pregnancy and lactation.[75]

The following are the recommended prophylactic doses of some of the more common anticoagulants:

- *Enoxaparin:* For <80 kg, 40 mg subcutaneously OD; For >80 kg, 60 mg subcutaneously OD (consider dose adjustment in renal failure).
- *Dalteparin*: For <80 kg, 5,000 units subcutaneously OD; For >80 kg, 7,500 units subcutaneously OD (consider dose adjustment in renal failure).
- *Unfractionated heparin*: 5,000 units subcutaneously BD
- *Fondaparinaux*: 2.5 mg subcutaneously OD (consider dose adjustment in renal failure).

- Antivirals, anti-inflammatory agents, antibodies, and antibiotics:
  - Primary antivirals against SARS-CoV-2

  Many drugs like hydroxychloroquine, ivermectin, ritonavir, remdesevir, and favipiravir have been tried for their antiviral properties against SARS-CoV-2 and have now fallen out of favor with most guidelines and recommendations.
    - *Hydroxychloroquine*: Hydroxychloroquine is widely used to treat malaria and many autoimmune diseases. We strongly recommend against its use for COVID-19 patients, regardless of disease severity as it was conclusively proven to be ineffective.[10,79-81]
    - *Lopinavir/ritonavir*: A HIV-1 protease inhibitor, Lopinavir was tried for COVID-19 in view of its intro activity against SARS-CoV-2. With available data, we strongly recommend against its use for COVID-19 patients, regardless of disease severity.[10,79,82]
    - *Ivermectin*: Ivermectin with its antiparasitic, antiviral, and immunomodulatory effects was extensively used for COVID-19. With available data, we strongly recommend against its use for COVID-19 patients, regardless of disease severity.[10,83,84]
    - *Remdesivir*: A nucleoside analog prodrug that inhibits SARS-CoV-2, Remdesivir has been extensively used and studied. Though it shortens the time to recovery in hospitalized adults, there is no evidence of improved survival or other outcomes and hence not recommended for routine use.[10,79,85]
    - *Favipiravir*: An oral antiviral drug (600–800 mg twice daily), previously used for influenza and Ebola, too has fallen out of favor with most guidelines as there was no proven mortality benefit.[86]

- Anti-inflammatory agents for host-directed therapy: Several targeted immunomodulatory drugs have shown promise against SARS-CoV-2-induced cytokine storm. These include tocilizumab (IL-6 inhibitor), canakinumab (IL-1 inhibitor), and baricitinib (Janus Kinase inhibitor).

  Tocilizumab: An IL6 inhibitor, tocilizumab (single dose of 8 mg/kg, maximum 800 mg) may be considered for patients with rapidly deteriorating respiratory status despite being on corticosteroids associated with features of significant systemic inflammation (CRP > 100 mg/L) and in the absence of overt bacterial or fungal coinfection.[87]

  Baricitinib: The kinase inhibitors prevent phosphorylation of key proteins involved in the signal transduction that leads to immune activation and inflammation and hence are therapeutic options. Baricitinib is not recommended in patients without hypoxia. It can be considered in hypoxic patients with moderate, severe, or critical illness, as an adjunct to steroids. Tocilizumab and baricitinib should not be given together.[88]
- Monoclonal antibodies: Casirivimab/imdevimab are monoclonal antibodies used as artificial "antibody cocktail" designed to produce resistance against the SARS-CoV-2. These have only been tried against asymptomatic/mild infections and are not recommended for moderate or critical COVID-19.[89]
- Empiric antibiotics: During viral epidemics and pandemics, though clinical management and therapeutics are mainly focussed on the primary viral illness, it is imperative to consider secondary or superimposed bacterial infection, especially among critically ill patients. These "secondary infections," or "coinfections," or "super-infections" are largely a consequence of immune susceptibility caused by the primary virus, and in the case of COVID-19 are compounded by the generous use of corticosteroids. These infections have been responsible for significant proportions of deaths during previous pandemics such as the 1918 Spanish flu and the 2009 H1N1 influenza.[90-92]

Table 3: CMC Vellore ED evaluation and management protocol of patients with COVID-19

Severity category	Evaluation	Management
Mild illness SpO_2 >94% on room air RR <20/min	No laboratory tests or radiological imaging needed	Home isolation recommended Symptomatic management with paracetamol
Moderate illness SpO_2 >94% on room air RR <24/min 1 or more high-risk factors*	CBC profile Metabolic profile: Serum electrolytes, BUN, Serum creatinine, LFT	Home isolation can be considered with pulse oximetry monitoring. Symptomatic management with paracetamol Consider admitting high-risk patients for monitoring
Severe illness SpO_2 <94% on room air RR >24/min	CBC profile, ABG, ECG Metabolic profile: Serum electrolytes, BUN, Serum creatinine, LFT Prognostication markers: Consider D-dimer, LDH, Ferritin, CRP Radiological imaging: CXR	Corticosteroids: Dexamethasone 6 mg IV OD or another equivalent steroid Prophylactic thromboprophylaxis for all patients. Change to therapeutic dose if evidence of thromboembolism Proning if no contraindication Oxygen supplementation, targeting a SpO_2 of 94% with nasal cannulae/simple mask/venturi mask/nonrebreathing mask. Consider NIV/HFNC if indicated Consider Remdesivir or Tocilizumab (if no contraindication)
Critical illness SpO_2 <94% on room air RR >30/min PaO_2/FiO_2 <300	CBC profile, ABG, ECG Metabolic profile: Serum electrolytes, BUN, Serum creatinine, LFT Blood culture ×2 Prognostication markers: Consider D-dimer, LDH, Ferritin, CRP Radiological imaging: CXR	Corticosteroids: Dexamethasone 6 mg IV OD or another equivalent steroid Prophylactic thromboprophylaxis for all patients. Change to therapeutic dose if evidence of thromboembolism Proning if no contraindication Oxygen supplementation, targeting a SpO_2 94% NIV/HFNC as indicated. Consider IMV for acute severe respiratory failure or if trial of NIV fails Broad-spectrum antibiotics if secondary infection Consider Remdesivir or Tocilizumab (if no contraindication)

RR: respiratory rate; CBC: complete blood count; BUN: blood urea nitrogen; LFT: liver function tests; LFT: liver function tests; LDH: lactate dehydrogenase; CRP: C-reactive protein; CXR: chest X-ray. High-risk factors*: Age >60 years, diabetes mellitus, hypertension, obesity, immunocompromised state, pregnancy

Similarly, early studies of COVID-19 outcomes from Wuhan attributed 50% of the deaths to secondary bacterial infections.[17] A systematic review of 19 studies including 2,834 patients found a mean rate of broad-spectrum antibiotic use of 74% with half the studies comprising 17.4% of all patients reporting secondary bacterial infections or complications.[93]

Recommendation: Antimicrobial resistance remains a major concern with indiscriminate use. Hence, it is advisable to administer empiric broad-spectrum antibiotics only when a secondary infection is suspected, after taking appropriate cultures. There is no proven efficacy or indication for empiric oral antibiotics for any nonhospitalized patient with mild to moderate illness and the practice must strongly be discouraged.

A summary of a pragmatic protocol for the evaluation and management of patients based on severity criteria as determined by vital signs and oxygen saturation assessed in the ED is given in [Table 3].

Conclusion

With the rapidly emerging flood of information on the spectrum of presentation of the original strain and the new variants, an evidence-based approach to the evaluation and management of patients in the ED is essential. However, the quintessential components of resuscitation focused on the airway, breathing, and circulation with good supportive care remains the cornerstone of the acute management of critically ill COVID-19 patients. Irrational use of investigations and therapeutics must be strongly condemned and avoided during these times of medical uncertainty and antibiotic stewardship should be diligently followed.

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Conflicts of interest

There are no conflicts of interest.

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