The 2019–2020 Novel Coronavirus (Severe Acute Respiratory Syndrome Coronavirus 2) Pandemic: A Joint American College of Academic International Medicine-World Academic Council of Emergency Medicine Multidisciplinary COVID-19 Working Group Consensus Paper

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Abstract

What started as a cluster of patients with a mysterious respiratory illness in Wuhan, China, in December 2019, was later determined to be coronavirus disease 2019 (COVID-19). The pathogen severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel *Betacoronavirus*, was subsequently isolated as the causative agent. SARS-CoV-2 is transmitted by respiratory droplets and fomites and presents clinically with fever, fatigue, myalgias, conjunctivitis, anosmia, dysgeusia, sore throat, nasal congestion, cough, dyspnea, nausea, vomiting, and/or diarrhea. In most critical cases, symptoms can escalate into acute respiratory distress syndrome accompanied by a runaway inflammatory cytokine response and multiorgan failure. As of this article's publication date, COVID-19 has spread to approximately 200 countries and territories, with over 4.3 million infections and more than 290,000 deaths as it has escalated into a global pandemic. Public health concerns mount as the situation evolves with an increasing number of infection hotspots around the globe. New information about the virus is emerging just as rapidly. This has led to the prompt development of clinical patient risk stratification tools to aid in determining the need for testing, isolation, monitoring, ventilator support, and disposition. COVID-19 spread is rapid, including imported cases in travelers, cases among close contacts of known infected individuals, and community-acquired cases without a readily identifiable source of infection. Critical shortages of personal protective equipment and ventilators are compounding the stress on overburdened healthcare systems. The continued challenges of social distancing, containment, isolation, and surge capacity in already stressed hospitals, clinics, and emergency departments have led to a swell in technologically-assisted care delivery strategies, such as telemedicine and web-based triage. As the race to develop an effective vaccine intensifies, several clinical trials of antivirals and immune modulators are underway, though no reliable COVID-19-specific therapeutics (inclusive of some potentially effective single and multi-drug regimens) have been identified as of yet. With many nations and regions declaring a state of emergency, unprecedented quarantine, social distancing, and border closing efforts are underway. Implementation of social and physical isolation measures has caused sudden and profound economic hardship, with marked decreases in global trade and local small business activity alike, and full ramifications likely yet to be felt. Current state-of-science,

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mitigation strategies, possible therapies, ethical considerations for healthcare workers and policymakers, as well as lessons learned for this evolving global threat and the eventual return to a "new normal" are discussed in this article.

Keywords: 2019-nCoV, coronavirus, COVID-19, global impact, International Health Security, pandemic, severe acute respiratory syndrome coronavirus 2

Introduction

The modern world is increasingly interlinked. With an extensive network of air, ground, and sea transportation hubs, one can travel relatively seamlessly between any two places on the planet within just a few days' time.[1-8] When this is superimposed on the ever-present danger of zoonotic-to-human transmission of both established and emerging infectious agents, the possibility exists of a rapidly evolving novel pathogen pandemic.[9] Despite previous planning and preparations, the current 2019 novel coronavirus disease (COVID-19) pandemic illustrates how even the most extensive efforts may be inadequate and exemplifies the need to adapt to quickly changing and unpredictable circumstances.[10-14] The COVID-19 pandemic has revealed gaps in current preparedness within and between nations. This narrative review is intended to provide the reader with a high level overview of what is known, what remains to be elucidated regarding the COVID-19 pandemic, and to suggest specific steps for moving forward as a global community.

Focus of the Current Article

Our objective is to provide insight regarding information gaps and blind spots that may exist in the available literature and relevant governmental or press reports regarding the SARS-CoV-2 pandemic. As academic organizations of international scope, the American College of Academic International Medicine and the World Academic Council of Emergency Medicine (ACAIM-WACEM) strongly feel that pandemic readiness has been suboptimal, there are lessons to be learned, and this article highlights some of the observed gaps in preparedness, based on state-of-the-art evidence. It is not the goal of the Working Group to provide another recap of the current state of the COVID-19 pandemic, nor is it our intent to reiterate much of the information already available on the Internet.

From Outbreak to Pandemic: An Overview of Origin and Human Pathogenicity of Severe Acute Respiratory Syndrome Coronavirus 2

In December 2019, Chinese authorities reported emergence of a cluster of severe respiratory infections of unknown etiology in Wuhan (Hubei Province, China).[15-17] Despite global efforts to slow the spread of the SARS-CoV-2 and "flatten the curve" [Figure 1], including population-level "social distancing" (physical separation of people so as not to contract the illness) and drastic travel restriction/quarantine measures, the disease relentlessly continued to expand its reach.[18-22] As of the writing of this Position Statement, the World Health Organization (WHO) has declared COVID-19 a pandemic[23,24] and the United States (US) has declared a National Emergency.[25,26] With more than 4.3 million people with documented SARS-CoV-2 infection and more than 290,000 deaths, the malady continues to spread around the globe.[27,28] The coronavirus responsible for COVID-19 has been likened to a bulldozer, capable of causing widespread severe illness and deaths with terrifying speed, and affecting those who are most vulnerable.[29,30]

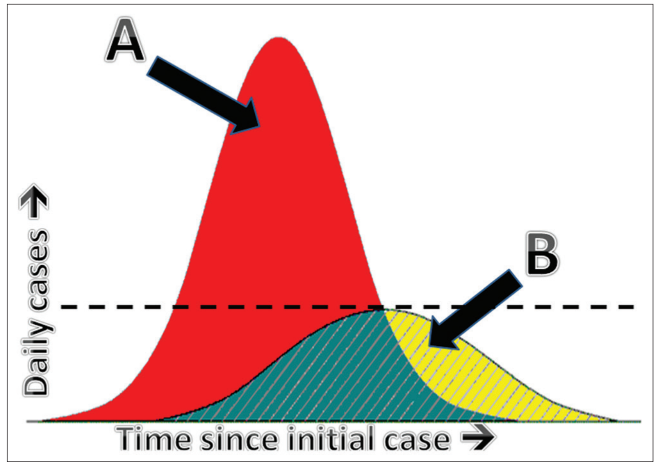

Figure 1: Schematic representation of "flattening the curve" during an outbreak. (A) Typical course of a pandemic without targeted intervention (e.g. physical distancing). This scenario places undue burden on healthcare institutions and is likely to exceed preoutbreak capacity (indicated by dashed horizontal line) and resources available to treat affected patients; (B) modified curve resulting from the prompt implementation of mitigation measures (e.g. physical distancing). In this scenario, both the rate of increase of new cases and the peak number of cases are significantly lower, permitting the existing infrastructure to reasonably handle the increased demands associated with an outbreak

Severe Acute Respiratory Syndrome Coronavirus 2 Virus

The seventh identified human coronavirus and third novel coronavirus to emerge in the past 17 years, SARS-CoV-2 was isolated in January 2020 as the cause of the SARS-like atypical pneumonia called COVID-19.[31-35] Phylogenetics has indicated that SARS-CoV-2 is closely related to bat-derived SARS-like coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21.[32,34,36] Human and zoonotic coronaviruses belong to the *Sarbecovirus* subgenus of the family *Coronaviridae*.[37,38] Currently, there are four genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*. Before the current COVID-19 pandemic, there were six recognized human respiratory coronaviruses: HCoV-229E (*Alphacoronavirus*), HCoV-OC43 (*Betacoronavirus*), HCoV-NL63 (*Alphacoronavirus*), and HKU1 (*Betacoronavirus*), which often cause mild respiratory tract infection; and SARS-CoV (*Betacoronavirus*) and Middle East respiratory syndrome (MERS-CoV) (*Betacoronavirus*), which may lead to severe or even fatal lower respiratory tract disease.[39] Coronaviruses are well established as being causative of respiratory, enteric, and systemic infections across various animal hosts, including fish, birds, mammals, as well as humans.[40,41] Of interest, the approximately 96% similarity of the SARS-CoV-2 at the whole-genome level to a bat coronavirus strongly suggests the latter as the point of origin,[42] although there is some controversy over this.[43]

Pathogenesis of Severe Acute Respiratory Syndrome Coronavirus 2

Although much still remains to be learned about the pathogenicity of SARS-CoV-2, the virus appears to spread primarily via the droplet nuclei or small particles (which can travel a considerable distance), and requires contact points within the mouth, nose, eyes, or other parts of the upper aerodigestive system.[44,45] There is also early evidence of fecal–oral transmission.[46,47] The mechanism of cellular entry is being elucidated and is beyond the scope of the current review. However, it is now understood that SARS-CoV-2 utilizes the angiotensin-converting enzyme 2 (ACE-2) receptor as its principal entry portal,[48-51] and possibly as a route of secondary "metastatic" end-organ disease. Of interest, outside of the kidney, the greatest concentrations of ACE-2 are found in the lung and the gastrointestinal tract,[50] with more recent identification on the nasal epithelial cells.[52] In addition, evidence shows that CD147-spike protein, furin, as well as GRP78 receptors all may play a role in viral entry.[53-55] Finally, there is controversy regarding the possibility that SARS-CoV-2 may be gradually evolving and increasing in its genetic diversity; a handful of strains have been discovered that appear to be mutating, but the observed process appears to be slower than that seen in influenza.[56,57]

Pathology of Patients with Severe Acute Respiratory Syndrome Coronavirus 2

Pathology studies of patients who underwent partial lobectomy procedures and were found to have subclinical COVID-19 infections demonstrated proteinaceous and fibrin exudate formation, scattered large protein globules, diffuse expansion of alveolar walls and septa, plugs of proliferating fibroblasts in the interstitium, macrophage infiltration of airspaces, and type II pneumocyte hyperplasia (sometimes associated with suspected viral inclusions).[58] Postmortem studies of the lung tissue demonstrated predominantly lymphocytic infiltration, with copresence of multinucleated giant cells alongside the large atypical pneumocytes.[59] There was evidence of pulmonary fibrosis that was less severe when compared with SARS, but there was relatively more tissue edema relative to SARS.[60] Additional microscopic findings included diffuse alveolar damage and exudative changes.[59] In addition to large amounts of viscous secretions found within the alveoli, there is also the suggestion of regional changes affecting other intrathoracic structures including the heart.[60]

Epidemiology of Severe Acute Respiratory Syndrome Coronavirus 2

The SARS-CoV-2 infection has been estimated to have a mean incubation period of 5.1–6.4 days[36,61] and a basic reproduction number in a range of 2.2–3.6.[36,62] The majority of patients (97.5%) develop symptoms within 11.5 days (95% confidence interval [CI] 8.2–15.6 days).[61] Furthermore, a nontrivial proportion of patients (2.5%–17.9%) who tested positive may remain asymptomatic, supporting the hypothesis that active asymptomatic transmission occurs.[63-66] Even more striking, the island nation of Iceland conducted extensive testing, suggesting that 50% of coronavirus cases exhibited no symptoms.[67] It has been estimated that the overall proportion of presymptomatic transmission may be as high as 48%–62%,[64,68] with viral transmission anywhere between 1 and 3 days before symptom onset,[69] providing a strong rationale for physical distancing. Interesting clinical correlations have also emerged about the relationship between the ABO blood group type and COVID-19 susceptibility,[70,71] but more investigation is required before more definitive statements can be made in this area. Finally, familial (e.g., genetic) predisposition cannot be excluded at this time, with reports of severe presentations and deaths among close relatives.[72-75] Further investigation into such multiple cases involving close relatives will be important to our overall understanding of the SARS-CoV-2 pathophysiological behavior and clinical disease characteristics.

Clinical Presentation and Patient Characteristics

Symptoms of COVID-19 may range from mild to severe, with sizable yet varied fatality rates of 2.3% in China, 7.2% in Italy, and 1.0% in South Korea.[76-80] Most adults and children with COVID-19 develop a mild-to-moderate, flu-like illness with fever, malaise, cough, and/or dyspnea that resolves in about 1 week.[81] It has been reported by some patients that the symptoms may be phasic, with relatively asymptomatic spells interspersed among severely symptomatic periods,[82-85] while others report that the illness can be likened to "a slow burn" with symptoms that linger on before worsening.[85,86] Of importance, fever is not always present in early illness and among the elderly.[33] Early anosmia and dysgeusia may be present.[87] Children and teenagers usually exhibit mild symptoms as severe infection is rare among younger patients, but deaths in younger age groups have occurred (e.g., infants less than 1 year of age may have higher morbidity and mortality).[88-91] Anecdotally, seen mainly among children with COVID-19, erythematous toe lesions have been described. Dubbed 'COVID toes,' their clinical significance or impact are unclear. Consistent with adult mortality patterns, recent data also show that children and teenagers with preexisting conditions, such as asthma, chronic lung disease, cardiovascular disorders, history of smoking/vaping, or hemoglobinopathies, may be more likely to experience severe or even fatal COVID-19.[92-97] In addition, it is now emerging that morbid obesity also constitutes a major contributor to mortality, with a magnitude of risk that rivals that of age.[98] Age distribution of COVID-19 cases, compiled from numerous sources around the globe, is provided in Figure 2.[79,89,90,99-104]

In terms of symptoms, systemic and pulmonary manifestations predominate, with an increasing emphasis placed on gastrointestinal symptoms as both diagnostically and prognostically important (note, gastrointestinal symptoms are more prevalent than initially thought).[105-107] In one study from Wuhan, China, examining >1000 cases of COVID-19, the predominant symptoms were fever and dry cough, with 80% suffering only from mild-to-moderate disease and approximately 13% experiencing severe disease.[81] The most commonly reported symptoms are fever, dry cough, myalgias, fatigue, pneumonia, and dyspnea. Even a clinical picture compatible with acute pancreatitis has been described.[108] High temperature is not always recorded at initial presentation. In particular, elderly patients can be afebrile in the early stages, with only chills, with or without respiratory symptoms.[33] Less common symptoms include the production of sputum, headache, hemoptysis, and rhinorrhea.[16,47,105,106,109] Other studies noted that gastrointestinal symptoms, such as diarrhea (2%–10.1%) and nausea and vomiting (1%–3.6%), were present in a nontrivial proportion of patients.[16,105,106,109] Moreover, a significant proportion of patients presented initially with those atypical gastrointestinal symptoms.[110] Anosmia and dysgeusia have recently been reported as early symptoms associated with COVID-19.[87,111] Of importance, many frontline healthcare workers (HCWs) and caregivers

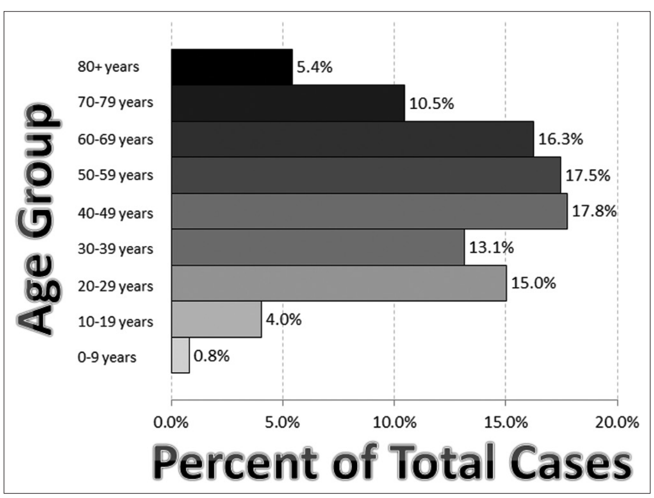

Figure 2: Age distribution of COVID-19 cases based on composite data from around the globe[79,89,90,99-104]

report the finding of "red eyes" as one of the manifestations of COVID-19.[112,113] A detailed listing of signs and symptoms of COVID-19 is provided in Table 1.[16,33,47,81,85,109,112-121]

A smaller proportion of COVID-19 patients will progress to develop severe illness (8%–15%) including respiratory failure, acute respiratory distress syndrome (ARDS), multiple organ failure, and potentially death.[36,115,121,122] Among those admitted to the intensive care unit (ICU), mortality ranged from <14% to >66%, depending on patient-specific factors.[121,123,124] Common ancillary findings include lymphocytopenia;[125] increased neutrophil-to-lymphocyte ratio; decreased percentages of basophils, eosinophils, and monocytes;[126] thrombocytopenia (severe disease);[122] elevated lactate dehydrogenase (LDH), elevated C-reactive protein (CRP), elevated ferritin, elevated D-dimer, elevated interleukin-6 (IL-

Table 1: Reported symptoms of COVID-19 infection

Category	Symptom	Reported incidence*
General/systemic	Fever	83-98.6%
	Malaise and fatigue	11-69.6%
	Body aches and myalgias	11-44%
	Chills	11%
	Cyclical nature of symptoms, clinical ups and downs	Reported
	Acute cardiac injury/dysfunction	Reported
	Acute renal failure	Reported
Respiratory	Dry cough	46-82%
	Productive cough	12-28.2%
	Shortness of breath	19-31.2%
	Hemoptysis	1-5%
	Chest pain	2%
	Feeling of "chest pressure"	Reported
	Silent or exertional hypoxia	Reported
HEENT	Pharyngitis/pharyngalgia	5-17.4%
	Nasal congestion/rhinorrhea	4%
	Watery eyes	<1%
	Cyanotic, "blue lips"	Reported
	Loss of smell and taste	Reported
	Conjunctival injection/"red eyes"	Reported
Gastrointestinal	Loss of appetite	39.9-50%
	Diarrhea	2-15%
	Nausea and vomiting	1-10.1%
	Abdominal pain	2.2%
	Pancreatitis	Reported
Neurological	Headache	6.5-12.1%
	Dizziness	9.4%
	Confusion	9%
	Delirium, especially non-agitated delirium in the elderly	Reported
	Encephalopathy	Reported
	Meningitis	Reported
	Seizures	Reported

More than one sign of symptom was present in 90% of patients; fever, cough, and shortness of breath were present in 15% of patients. *Range provided whenever available. HEENT: Head, ears, eyes, nose, and throat. Data sources[16,33,47,81,85,109,112-121]

6);[81] new pulmonary infiltrates on chest radiography or computed tomography (CT); and no improvement in symptoms after 3 days of directed treatment.[127] Known contact with another COVID-19-positive individual may be reported, but the importance of this will become less relevant with community spread. Patients at increased risk of mortality include those with advanced age, medical comorbidities/preexisting illnesses (e.g., diabetes, hypertension, malignancy), active tobacco smoking/vaping, morbid obesity, and high sequential organ failure assessment (SOFA) score.[77,94,95,98,117,118,128]

The time course for mild symptoms may be as short as 1 week, while severe cases may extend far beyond that.[129] One retrospective study of 191 hospitalized patients in Wuhan reported that the median time from illness onset to initiation of mechanical ventilation was 14.5 days and from onset of illness to day of discharge was 22 days.[116] Mortality is primarily among middle-aged and elderly patients with preexisting diseases (malignancy, cirrhosis, hypertension, coronary heart disease, diabetes, kidney failure, immunodeficiency, cerebrovascular diseases, and neurodegenerative diseases) [Figures 3 and 4].[28,79,102,116,127,130-137] Finally, several countries reported that the mortality rate is significantly higher (by approximately a factor of 2) among men [Figure 5].[138-141] The latter finding may be related to recent data showing that SARS-CoV-2 is more prevalent in male children and adolescents (57%) compared to female children and adolescents (43%), suggesting a more fundamental difference between genders, based on immune and/or other mechanistic considerations.[92]

Of importance, early testing policies have significantly influenced reported mortality rates. For example, in Italy or the US, where surveillance testing was limited and reserved for more acutely ill patients, reported mortality has been significantly higher than for countries such as the Republic of Korea or Germany where widespread surveillance testing captured a greater proportion of patients with less severe manifestations.[77,142] Variance in mortality figures depends on the demographic profile of countries and the governmental response to the pandemic in the initial stages.

Biomarkers and Other Prognostic Correlates of COVID-19

Complicated COVID-19 infection carries a high mortality, with multiorgan dysfunction characterized by respiratory failure, encephalopathy, acute cardiac injury and cardiac failure, renal failure, and other end-organ damage.[143,144] In a recently published paper, retrospective data from a cohort of patients from Wuhan, China, showed that older age and comorbidities including diabetes and hypertension, high SOFA scores, and D-dimer > 1 μg/L are associated with poor prognosis at an early stage.[128] In the same study, other biomarker abnormalities were associated with higher incidence of mortality including a low platelet count, high levels of LDH, and elevated creatinine.[128] Guo *et al*.[145] published the MuLBSTA (multilobar infiltrates, lymphocytes ≤0.8 × 10^9/L, bacterial infection, smoking status,

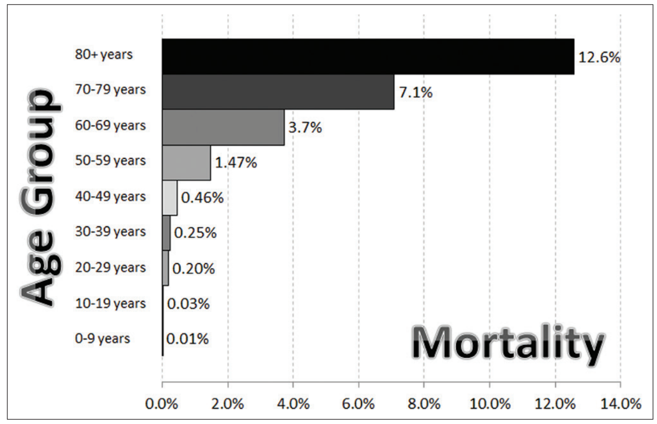

Figure 3: Mortality associated with COVID-19 infections by age. Composite global data compiled from multiple sources[28,79,102,130-132]

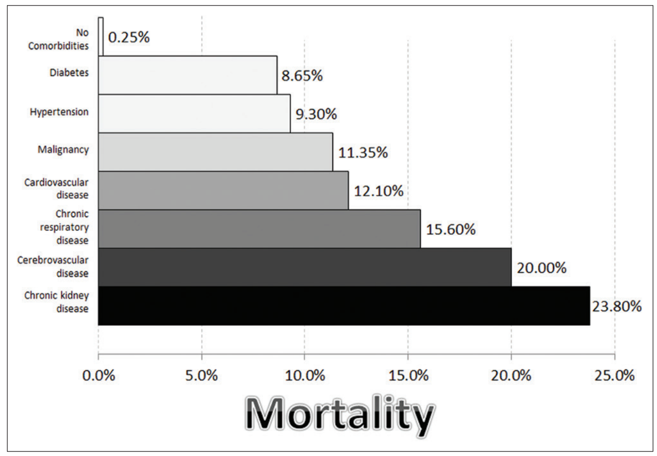

Figure 4: Mortality rates associated with different comorbid conditions. Additional factors that may predispose to increased mortality include morbid obesity, neurodegenerative diseases, and immunocompromised status. Data from Italy demonstrate that 25.1% of mortalities had 1 comorbid condition, 25.6% had two, and 48.5% had three or more illnesses. A report from China demonstrated 15.4% mortality for those with ≥2 comorbidities, compared to mortality of 5.6% for those with one or no comorbid condition[116,133-137]

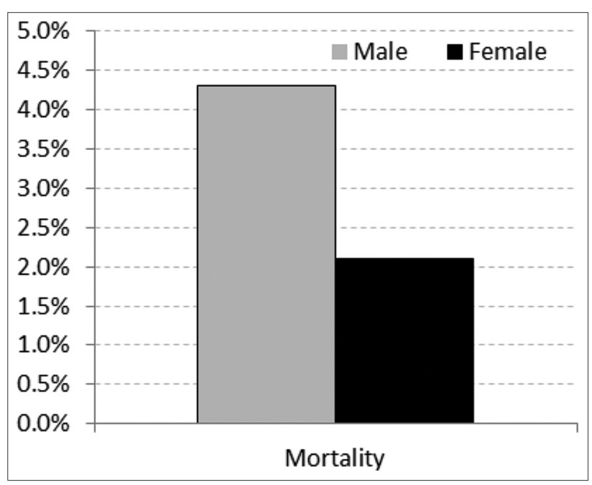

Figure 5: Comparison of composite global mortality rates by patient gender[138-141]

hypertension, and age ≥60 years) score, which may help prognosticate outcomes in COVID-19 patients.[109] The Brescia-COVID Respiratory Severity Scale (BCRSS) incorporates four simple data elements into a clinically useful stratification system: (a) patient wheezing or unable to speak in full sentences while at rest or with minimal effort; (b) respiratory rate >22; (c) PaO_2 <65 mmHg or SpO_2 <90%; and (d) repeat chest X-ray (CXR) shows significant pulmonary worsening.[146] Other prognostic biomarkers including D-dimer, high-sensitivity troponin I, serum ferritin, LDH, IL-6, and procalcitonin also showed both clinical and predictive utility.[128,143,147] Repeated procalcitonin "typical" assessments may be useful in determining complicated COVID-19, especially in the setting of clinical deterioration and bacterial superinfection.[148]

Among early findings in Wuhan, China, was the appearance of dysregulated immune response, with observed relatively higher leukocyte (5.6 vs. 4.9 × 10^9) and neutrophil (4.3 vs. 3.2 × 10^9) counts; relatively lower lymphocyte counts (0.8 vs. 1.0 × 10^9); higher neutrophil-to-lymphocyte ratio (5.5 vs. 3.2); as well as lower percentages of basophils, eosinophils, and monocytes.[126] Others noted that lymphopenia may be a part of a COVID-19 clinical signature[125,143,149] and that thrombocytopenia may be a hallmark of severe COVID-19 cases.[122,143] Although generally highly sensitive and nonspecific, CRP, erythrocyte sedimentation rate (ESR), and ferritin may offer prognostic utility when combined with other indicators of disease acuity and/or when followed over time for trending purposes.[121,143,149-151] A plethora of other, likely nonspecific laboratory derangements were also noted among nonsurvivors.[143]

In a study utilizing an artificial intelligence (AI) approach to determine the factors most strongly associated with ARDS, several surprising observations emerged.[152] The first factor is elevated levels of alanine aminotransferase (ALT). The second was the presence of reported myalgias. The final strong predictor of respiratory distress was elevated levels of hemoglobin (possibly related to male gender or undeclared tobacco use or vaping). Taken together, these three factors exhibited 70%–80% accuracy in predicting the risk of ARDS.[152] Finally, observations have been made of the high prevalence of hypokalemia in COVID-19 patients, apparently attributable to continuous renal potassium loss associated with the degradation of ACE-2.[153] It was also noted that the end of renal potassium loss constitutes a good prognostic sign and may represent a reliable, in-time, and sensitive biomarker reflecting the normalization of renin-angiotensin system pathology of COVID-19.[153]

Diagnostic Imaging

Although diagnosis of COVID-19 is definitively made through laboratory testing, diagnostic imaging can be helpful in supporting the diagnosis or identifying alternative pathology. CXR is often used as a first line diagnostic tool in patients with respiratory complaints, but it lacks sensitivity and specificity relative to CT in patients with COVID-19 and often temporally lags CT in findings.[154] Specifically, CXR may not be able to detect ground-glass opacities (GGO), and the bibasilar nature of their distribution in COVID-19 may be obscured by the cardiomediastinal silhouette or in the area overlying the diaphragm.[154] Both CXR and CT of the thorax can demonstrate a range of findings, from "normal appearance" to "pulmonary consolidations" to "diffuse multifocal GGO" characteristic of ARDS [Table 2].[65,155-158] In one study, pulmonary changes on CT were noted in 54% of asymptomatic cases, compared to 80% in the symptomatic group.[65] In the same study, asymptomatic cases tended to have more GGOs whereas symptomatic patients demonstrated more consolidations.[65] In another study, chest CT was found to be highly sensitive for COVID-19 diagnosis, and disease severity on the CT appeared to correlate with both clinical severity and subsequent recovery.[159] The most "typical" CT findings of COVID are changes (usually GGOs or multifocal infiltrates), that are located bilaterally and mainly distributed in the posterior and peripheral portions of the lungs.[154] For CXR, the severity of findings appears to peak at approximately 10–12 days following symptom onset.[65]

In terms of COVID-19-related changes seen on CT scanning, GGOs were more prevalent than consolidations in 74% of cases, with the opposite noted in 26% of instances.[65] A majority of opacities were noted to be peripheral (56%) or mixed (37%) in distribution, with only 7% being more central in location.[65] In a study from Japan, the distribution of "lobes affected," from 1 to 5, was fairly even (the least frequent being four lobes involved in 13% of cases and the most being two lobes involved in 26%).[65] However, another study from Italy demonstrated that approximately 84% of patients had evidence of four lobes (10%) or five lobes (74%) involved.[157] When evaluating available reports,

Table 2: Key computed tomography and chest X-ray features of COVID-19 infection

Finding	Computed tomography (%)	Chest radiography (%)
Multifocal lung lesions with peripheral distribution	>50	41
Ground-glass opacities	40.3-100	33
Consolidation	13-72	47
"Crazy paving" pattern	12-39	-
Interlobular thickening	13-37	-
Linear opacities combined	27-61	-
"Airway abnormalities"	17.7-27	
Pleural thickening	48.4	
Pleural effusion	3-9.7	3
Pericardial effusion	5	-
Lymphadenopathy	58	-
Normal	23 (initially, especially in asymptomatic patients, but many progress)	21

Data compiled from several sources[65,155-158]

>2 lobes were found to be affected in 76%–93% of cases, with bilateral lung involvement in 82%–91% of cases and slight right lung (60%) predominance.[65,157]

Debate continues regarding the utility of contrast-enhanced chest CT, with proponents indicating that the additional information gained from intravenous contrast administration (e.g., the identification of pulmonary embolism [PE]) is more important than the associated risks. Indeed, more and more cases of coincident PE (and other thrombotic and/or thromboembolic events) with COVID-19 infection are being reported, and many feel that the infection may predispose to venous thromboembolism.[160,161] If this is the case, foregoing CT angiography may leave the patient with unidentified, severe, and potentially treatable conditions. Opponents of contrast-enhanced chest CT cite the time delay for terminally cleaning the CT machine in busy centers when the management is largely clinical; the risk of contrast nephropathy exacerbating renal failure in potentially critical patients; the risk of systemic reactions to contrast medium; as well as the low incidence of findings that require additional radiographic information.[162-165]

In resource-limited settings, including healthcare facilities overwhelmed with rapid increases in patient volumes, the use of point-of-care ultrasonography (POCUS) can be of immense value. Reports from the most severely affected countries and regions indicate that there is a good clinical correlation between CT thorax and pleural ultrasound.[166,167] Mild GGOs visualized on CT scanning correlate well with scattered B-lines on bedside ultrasound.[166] As disease progresses and GGOs become confluent on CT, so, too, will ultrasound B-lines coalesce.[166] More severe disease will demonstrate peripheral consolidation and pleural thickening, with progression of consolidation in cases of advanced illness.[166,167] Because pulmonary findings are more common in the posterior portions of the lungs, it is important to ensure that these areas are adequately visualized during POCUS examination, which can pose technical limitations in high acuity patients. Given the need to assess the peripheral and posterior regions of the lung, the sensitivity and specificity of POCUS for diagnosis of COVID-19 in dyspneic real-time scenarios are presently not known. Among other applications of POCUS is the assessment of intravascular volume status, including inferior vena cava or subclavian venous collapsibility measurements.[168,169]

Diagnostic Confirmatory Viral Testing

Several different diagnostic assays are available due to emergency use authorizations from the US Food and Drug Administration (FDA).[170] The testing methodologies consist of a variation on nucleic acid amplification technology intended for the *in vitro* qualitative detection of SARS-CoV-2 viral ribonucleic acid (RNA). Manufacturers are publishing analytical reactivity (sensitivity) as low as 80% and as high as 100%. Each assay reviewed, at the time of this article, only noted SARS-CoV as a cross-reactive test result (analytical specificity).

The majority of COVID-19 diagnostic assays available to date require the collection of nasopharyngeal swabs, which should be submitted to the laboratory in universal or viral transport media. Sputum and bronchial lavage (BAL) samples are also acceptable for these tests.[171] It is important to note that sample collection, handling, and transport directly impact an assay's analytical sensitivity.[171] In addition, a high-sensitivity assay may result in an increased risk of false positive reporting due to contaminated work areas (from previously processed positive samples).

Nonetheless, the diagnosis of COVID-19 requires a skilled clinician who can correlate real-time patient observations and disease-specific patterns, with the totality of available diagnostic information (e.g., clinical, laboratory, and radiographic evidence). For example, patients with pulmonary disease are often nasal swab negative and only positive on the sputum or BAL testing, thus necessitating a high index of clinical suspicion in all pneumonia patients. Speedy and accurate diagnosis is critical to avoid delays in the provision of critical medical care, especially when patients experience rapid pulmonary and systemic deterioration.

COVID-19 testing algorithms should be used to guide clinicians on whom to test, when to repeat testing, as well as alternative testing options (i.e., CT scans of the chest).[172] Other factors that may affect a COVID-19 testing algorithm include the clinician's urgency to receive the result, medical facility setting, and the availability of testing and collection resources in the laboratory. Current testing algorithms include some version of a polymerase chain reaction (PCR) test and/or other SARS-CoV-2 testing. Due to the high false-negative rates in some tests, treatment algorithms may opt for approaches that call for one or more repeat COVID-19 test on the same patient over multiple days to increase the chances of identifying and/or confirming a positive. To expand testing capacity, veterinary laboratories can be retooled to assist in such repeat testing by running human COVID-19 diagnostics.[173]

Judicious utilization of available diagnostic infrastructure is of critical importance, especially during the early phases of the outbreak when testing capacity may not be fully developed (e.g., before transition to active community spread takes place) and within active disease hotspots when resource considerations predominate. Pooled sampling techniques for COVID-19 surveillance have been described in crisis situations.[174] Samples from multiple cases can be tested simultaneously, thereby cutting down on cost, time, and requirement for reagents, with improved overall efficiency. Revised testing policies warrant such interventions, especially amid severe shortages of testing kit supplies.[175] This surveillance strategy is capable of quickly grading the severity of the disease spread in a given population and thus providing early warning signals to public health officials.[175,176] Negative results of a "sample pool" will save a lot of resources. However, a positive

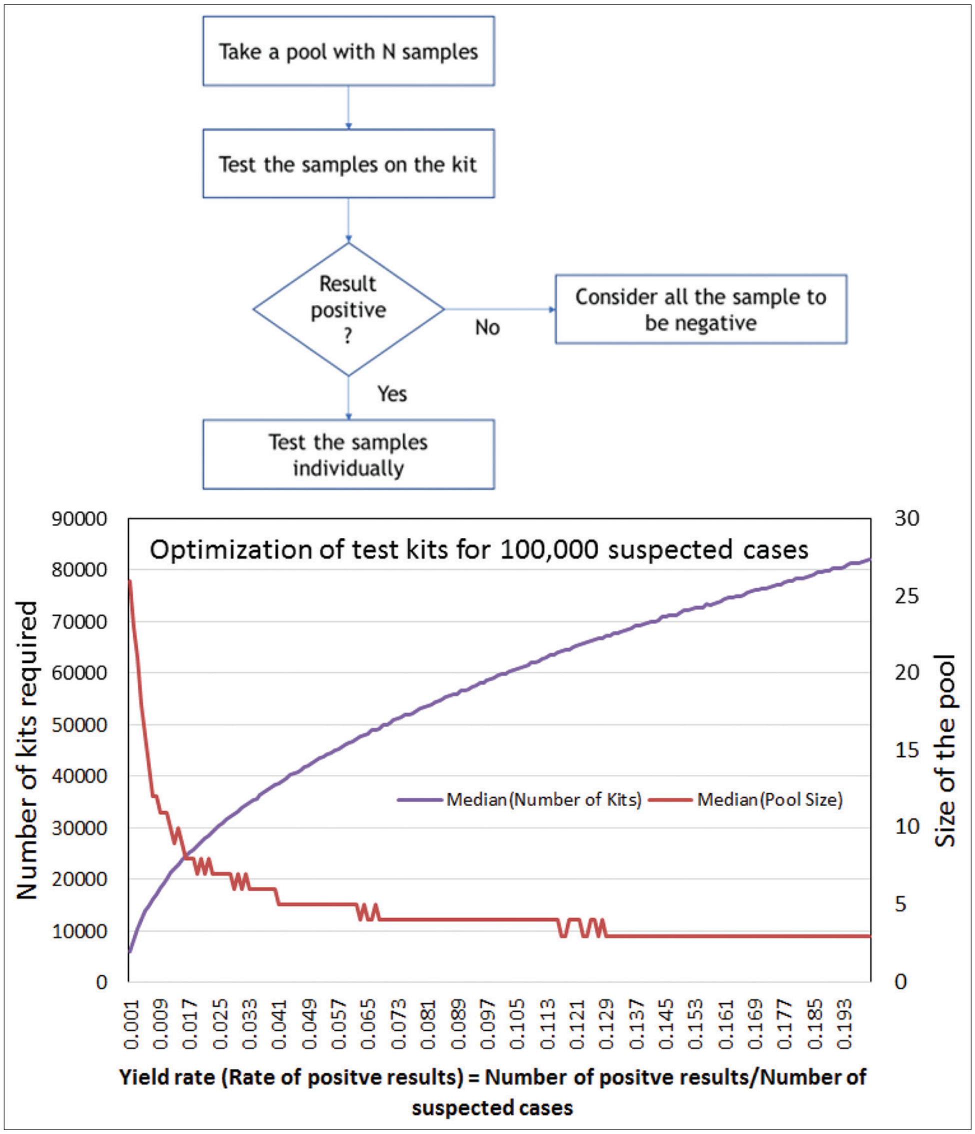

Figure 6: Pooled testing algorithm (top) and optimization curves showing the relationship between the median testing pool size and the median number of testing kits required (bottom). Algorithm and graph courtesy of Dr. S Venkataramanaiah, Indian Institute of Management, Lucknow[177]

result in a pooled test will require further analysis to detect individual positives. An associated algorithm and testing optimization graph are provided in Figure 6.[177]

Synopsis of Clinical Management of COVID-19, with Focus on Protocol-Driven, Evidence-Based Practice

The clinical management approach for SARS-CoV-2 infection is an evolving process. Consequently, we would like to focus our effort in this area on a practical survival guide for frontline clinical personnel [Appendix A]. In addition, the Combined ACAIM-WACEM Consortium created a dedicated resource hub for centralized clinical protocol storage from around the world, available for all to access, adopt, and use.[178] Of importance, this also includes critical intrafacility and interfacility patient transfer logistics.[179] Finally, there are important COVID-19 considerations that directly impact the areas of surgery,[180-182] endoscopy,[183,184] anesthesiology,[180,185] and related disciplines.[186-188]

Although patients with COVID-19 pneumonia and respiratory distress share many clinical similarities with patients suffering from other types of severe viral pneumonia, and often meet the Berlin definition of ARDS, accumulating clinical evidence suggests that there are important phenotypic differences in their presentation.[189] While most patients do not require immediate intubation on emergency department (ED) arrival, patients can decompensate quickly depending upon their viral load, comorbidities, and length of clinical illness among other factors. A systematic, escalating, stepwise approach to respiratory support is essential. A patient who arrives to the ED with hypoxia should immediately be placed on nasal cannula (NC) or facemask (FM) with appropriate supplemental oxygen levels and their response should be monitored closely. Patients who present on a spectrum from "normal" to "tachypneic" with normal oxygen saturation should have an ambulatory pulse oximetry recorded for a 60-s period to ensure that exertional (a.k.a., silent or occult) hypoxia does not develop or worsen.[190,191] For patients with normal oxygenation (or hyperoxemia), it is critical for a clinical care team to downtitrate oxygen to preserve precious resources.

Patients with acute hypoxemic respiratory failure who fail NC and/or FM oxygenation may be considered for a trial of high-flow NC (HFNC). Some patients can be managed using this strategy alone and do not require escalation to endotracheal intubation; however, this approach may be considered controversial by some provider groups who favor closed-system noninvasive positive pressure ventilation (NIPPV) instead. When transitioning to NIPPV, it is essential to utilize a closed loop setup or to place the patient in a negative pressure room because this approach may increase viral dispersal into the environment. It should be noted that this specific area is continuously evolving and recommendations may change. Small studies have shown that patients with severe COVID-19 infection-related ARDS assisted by mechanical ventilation who do not respond well to high-positive pressure may respond better to prone positioning in attempts to increase lung recruitment.[192] The postulated mechanism is that proning allows recruitment of posterior lung units and improves ventilation/perfusion matching.[193] Interestingly, this benefit may also extend to COVID-19 patients not yet mechanically ventilated, who are receiving NC, HFNC, or NIPPV as a maneuver to improve oxygenation and prevent intubation.[194,195] In one study, physicians were able to keep invasive mechanical ventilation use to a minimum using awake prone positioning.[196] Other studies in viral pneumonia (non-COVID-19) reported similar success with proning to stave off invasive mechanical ventilation.[197] The awake patient can turn prone, move about, and turn on their sides. Published algorithms outline that the progression of patients with persistently low levels of blood oxygenation on NC can be sequentially scaled to HFNC to HFNC with proning, then NIPPV, and finally NIPPV with proning in an attempt to prevent intubation [Figure 7].[197]

The use of HFNC, FM, and NIPPV may pose a risk to providers because of aerosolization of pathogens. HFNC use with a surgical mask placed over it may decrease the risk.[198] During all airway and respiratory maneuvers, extreme caution should be exercised, and the patient should be closely monitored for factors that would indicate a need for intubation, including decreasing or increasing respiratory rate, depressed mental status, worsening hypoxia despite escalating therapy, and inability to protect the airway.[190] During these advanced procedures, it is important to maintain the safety of HCWs by limiting the number of those directly caring for the patient to essential personnel and utilizing a negative pressure room (if available). The following diagram demonstrates a suggested oxygenation escalation strategy [Figure 8].

When the decision to intubate is undertaken, the most experienced intubator, dressed in full personal protective equipment (PPE, that at minimum includes an N95 mask, protective eye wear, fluid impervious gowns, and gloves), should perform the intubation using video laryngoscopy if available. Although the Surviving Sepsis Campaign Guidelines recommend an ARDSNet ventilator strategy in these patients (tidal volumes of 4–8 ml/kg of predicted body weight; higher positive end-expiratory pressure [PEEP] strategy), there is emerging evidence suggesting that more than one phenotype of COVID-19 respiratory failure may exist. Gattinoni *et al*. have recently described two primary patient groups in this context: (a) L-type with low elastance (normal compliance), low lung weight, and low lung recruitability; and (b) H-type with high elastance (low compliance), high lung weight, and high lung recruitability.[189] Obviously, the respiratory management strategies in these two patient types will be markedly different. L-type patients are more likely to respond to NC, HFNC, and NIPPV than H-type patients. Once intubated, a lower PEEP strategy may improve outcomes since there is little recruitable lung. H-type patients should be approached as in a traditional severe ARDS scenario where one would be treated with an escalating PEEP strategy. It is important to remember that the observations from Gattinoni *et al*. are based on a small cohort of patients and that the number of primary types of lung injury in the

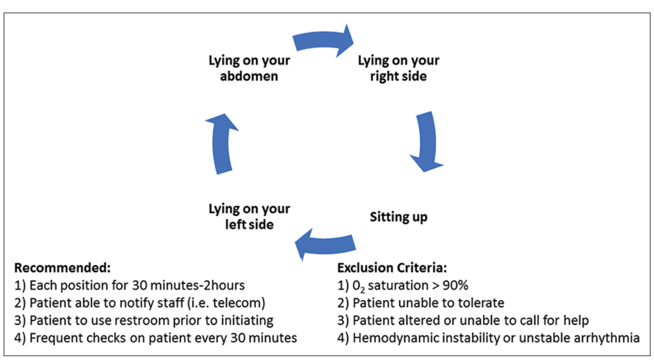

Figure 7: A schematic depicting the steps of the proning procedure to improve lung recruitment in COVID-19 patients; it is recommended that proning is initiated early in the hospital course, well before considering noninvasive or invasive ventilator support

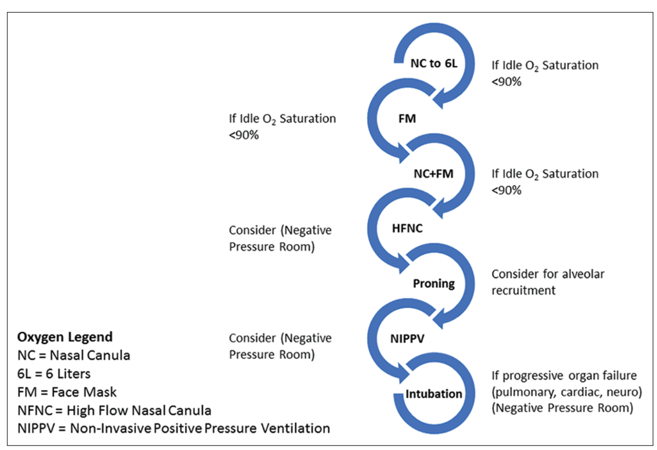

Figure 8: Diagram showing the gradual, step-wise escalation of supplemental oxygen therapy, from nasal cannula to intubation and mechanical ventilation

very heterogeneous COVID-19 pulmonary syndrome can be even more diverse.[189]

With variations in the number of ventilators at different institutions, there has been a lot of discussion about allocation of available devices to the most appropriate patients, low-cost ventilator substitutes, use of manual ventilators for some patients, and the possibility of ventilating multiple patients on a single ventilator circuit. Experimental work in a sheep model by Paladino *et al*. demonstrated the feasibility of ventilating four sheep on a single ventilator with a modified circuit.[199] Algorithms to apply this to two or four humans during a pandemic have been developed. However, due to the complexity of such a ventilator circuit, a number of safety concerns exist and consequently this approach should only be considered as an "absolute last resort" option.[200] A summary of the most commonly utilized types of oxygenation/ventilation support is provided in Table 3.[201]

For patients with profound respiratory failure, conventional mechanical ventilatory therapies – including salvage therapies such as prone ventilation, inhaled nitric oxide, or inhaled prostacyclin – might not be sufficient to support physiologic oxygenation and ventilation. Extracorporeal membrane oxygenation (ECMO) is an established therapeutic modality for the treatment of advanced ARDS refractory to maximal medical therapy.[202,203] Typically, for ARDS, ECMO is used in a venovenous configuration in which deoxygenated blood is drained from the venous system and actively pumped through an "oxygenator membrane" in which a sweep gas diffuses out the carbon dioxide and oxygenates the blood as it is returned to the body – typically as close to the right heart and pulmonary arterial tree as possible. This is differentiated from venoarterial ECMO in which the oxygenated blood is returned back to the arterial tree (i.e., the aorta) to augment the cardiac output and provide a more active, mechanically assisted, supply of oxygen to the tissue beds and end organs. In essence, venovenous ECMO is used for isolated pulmonary failure in the setting of preserved cardiac function while venoarterial ECMO is used in the setting of cardiac failure with a need for oxygenation and ventilation support (as opposed to isolated cardiac failure with preserved pulmonary function in which a ventricular assist device might be a preferred option).[204] While there is extensive literature supporting the use of ECMO for ARDS, regardless of the etiology, there are concerns regarding the appropriate use of ECMO in COVID-19 infections. Some of the early data and experiences from China have suggested poor outcomes with ECMO in these critically ill patients,[116] with additional concerns raised by anecdotal experiences of unfavorable outcomes in certain higher-risk populations.[205] Nevertheless, there is growing advocacy to support the use of ECMO in centers with experience in this very complex and resource-intensive modality.[206] Proponents of ECMO have speculated that poor patient selection, delayed initiation of therapy, and limited center experiences are the significant factors contributing to suboptimal outcomes; hence, they advocate for ECMO use only by established programs, specifically recommending that new program development should not be undertaken at this time for the sole purpose of supporting COVID-19 patients.[207,208] Clearly, while the use of ECMO in this population is highly controversial, it is imperative that ECMO providers participate in ongoing registry and research studies to help better define the role of extracorporeal support in this extremely ill and heterogeneous group of patients [Table 4].

In summary, in those patients with advanced respiratory failure, failing prone positioning maneuvers, and maximal ventilatory therapy, who are otherwise reasonable candidates based upon current risk assessment scoring systems,[209,210] ECMO should be considered to treat severe COVID-19 pulmonary infections. This view is supported by the American Thoracic Society and the Extracorporeal Life Support Organization.[206,211]

End-of-Life Decisions and Cardiopulmonary Resuscitation for the Clinician

Decisions at the end-of-life, especially those pertaining to cardiopulmonary resuscitation (CPR), have come to the forefront during the COVID-19 pandemic.[212,213] Truog *et al*.[214] and Di Blasi[215] have highlighted the shortage of ventilators, basic disinfectants, and PPE and the important discussions needed on rationing of care, both in regard to equipment and its association with end-of-life decisions in regard to COVID-19 patients; Emanuel *et al*.[216] have highlighted the fair allocation of resources from an American perspective.

In the United Kingdom (UK), Mahase and Kmietowicz call for a re-examination of CPR during this crisis.[217] They discuss the guidance from the National Health Service (NHS) Foundation Trust at the University Hospitals, Birmingham, UK, which states:

Table 3: Reported type of oxygenation support required by patients with COVID-19 admitted to the intensive care unit[201]

Modality	Percentage of ICU Cases (%)
Mechanical ventilation	~50%
NIPPV	~42%
Hi-flow	~11%
ECMO	2-5%

ECMO: Extracorporeal membrane oxygenation, NIPPV: Noninvasive positive pressure ventilation; ICU: Intensive care unit

Table 4: Sites for extracorporeal membrane oxygenation and COVID-19 references and registry/outcome tracking and reporting

Extracorporeal Life Support Organization Registry: https://www.elso.org/Registry/FullCOVID19RegistryDashboard.aspx
Extracorporeal Life Support Organization Registry: https://www.elso.org/Registry/FullCOVID19RegistryDashboard.aspx
Extracorporeal Life Support Organization COVID-19 Resources: https://www.elso.org/COVID19/ECMOCARD.aspx

"…patients in cardiac arrest outside the emergency department can be given defibrillator treatment if they have a 'shockable' rhythm. But if this fails to restart the heart, further resuscitation is futile."

There is variation on some of this guidance throughout the UK. The Birmingham UK NHS Trust Foundation advises providers to only use one shock, whereas the guidance from the UK Resuscitation Council advises three shocks.[218] The Council's guidance also says that staff should put on full PPE for aerosol-generating procedures before initiating CPR in patients with COVID-19. In the US, the Emergency Cardiovascular Care Committee and 'Get with the Guidelines'-Resuscitation task forces of the American Heart Association recently released the "Interim Guidance for Basic and Advanced Life Support in Adults, Children, and Neonates with Suspected or Confirmed COVID-19."[219] Their guiding principle in developing interim recommendations was "... to balance the competing interests of providing timely and high-quality resuscitation to patients while simultaneously protecting rescuers."[219] Their general approach to resuscitation includes (a) maximum protection of CPR providers by donning appropriate PPE; (b) prioritization of oxygenation and ventilation approaches that minimize aerosolization risk; (c) consideration for using mechanical CPR devices; and (d) evaluation of the appropriateness of CPR efforts in individual patients. For out-of-hospital cardiac arrest compressions, only CPR or mechanical CPR and defibrillation should be prioritized; for in-hospital cardiac arrest, emphasis should be placed on establishing advanced directives for critically ill COVID-19 patients, placing those at greatest risk of cardiac arrest in negative pressure rooms if available, with close monitoring of vital signs for clinical deterioration.

As indicated above, the approach toward CPR and end-of-life care during this pandemic will vary from country to country and from organization to organization. It will be difficult to establish a consistent approach in these times of rapid disease spread and the ensuing fear. The mindset of providers, the public, and the families of victims is important during this crisis. Wax and Christian put it well:

"The psychologic effects of perceived risk to healthcare providers and the public, especially for those with confirmed or suspected 2019-nCoV infection, cannot be ignored. Clear and transparent communication from governments and healthcare facilities to staff and public will be essential. The Canadian experience with SARS taught many lessons, and hopefully, those lessons will serve in keeping health care workers safe and providing optimal care to patients infected with 2019-nCoV."[220]

COVID 19 and Pregnancy

The current data about pregnancy and COVID-19 infections are heavily biased toward the third trimester patients. Specific guidance and practice advisories for obstetricians are available and should be followed.[221,222] Pregnant patients may be more susceptible to infections as they have decreased immunity, and also they may be more susceptible to respiratory diseases as functional residual capacity, end-expiratory volume, and residual volume all decrease as gestation progresses. The common symptoms associated with COVID-19 are cough, fever, dyspnea, and lymphopenia, and this remains the same for pregnant patients. Due to heightened metabolism, relative anemia, and increased maternal oxygen consumption, it may be difficult to distinguish normal shortness of breath from pathologic dyspnea.[223]

Universal testing of symptomatic pregnant females is variable because of the testing policies that depend on the overall community burden and resources for COVID-19 in each country. The United Arab Emirates, as an example, is offering drive-in tests for the symptomatic pregnant woman for free, and it takes less than 5 min to complete the sampling process.[224] A review of 55 reported cases of COVID-19 in pregnancy has shown promising results compared to the SARS-CoV and MERS-CoV. Pooled analysis of pregnant women shows a case-fatality rate of 0%, 18%, and 25% with COVID-19, SARS, and MERS, respectively.[225] The reported pregnancy complications associated with COVID-19 are miscarriage (2%), intrauterine growth retardation (IUGR, 10%), and preterm delivery (39%).[225,226] At the time of this publication, there is no definitive support for the presence of vertical transmission,[225,227] although elevated antibody levels in infants suggest the possibility of such an occurrence.[228,229]

As mentioned above, COVID-19 has been studied mainly in the setting of late pregnancy. A retrospective study of nine patients was done in Wuhan, China. All nine patients underwent cesarean sections. The amniotic fluid, breast milk, and respiratory swabs of infants in six cases were negative.[227] Current COVID-19 guidance covers all aspects of care during pregnancy, including office visits, labor, and the postpartum period.[221] Specific recommendations include electronic fetal monitoring; epidural analgesia for labor to minimize the need for general anesthesia if urgent surgery is needed; avoidance of birthing pools; shortening of the second stage of labor for women who become hypoxic; cautious use of intravenous fluids (250–500 ml boluses); and maternal stabilization before delivery.[221] Consensus guidelines from China provide 10 key recommendations for managing pregnancy and labor during COVID-19 infection.[230] Two sources state that there is no clear evidence regarding optimal route and timing of delivery and the decision should be based on obstetric indications and maternal–fetal status.[225,230] In terms of breastfeeding, the Royal College of Obstetricians and Gynaecologists, the American College of Obstetricians and Gynecologists, and the WHO recommend the practice even in the setting of active COVID-19 maternal infection.[221,222,231,232] Since there is a risk of viral transmission through the respiratory tract, affected mothers should wash their hands and wear a mask while breastfeeding. If the mother is severely symptomatic, a recommendation would be to pump milk and have another provider feed the infant.

Therapeutic considerations, including the use of specific pharmacological agents, are outlined later in the manuscript, and will depend on the ultimate outcome of ongoing clinical trials. Current guidelines regarding the safety of various therapeutic agents during pregnancy should be consulted before commencing pharmaceutical interventions. Pregnant women recovering from COVID-19 infection should have at least one ultrasound to monitor fetal growth due to 10% incidence of IUGR. Appropriate PPE should be utilized for all labor and delivery based on the SARS data; delayed umbilical cord clamping and avoiding skin-to-skin contact are recommended. Corticosteroids for fetal lung development should be utilized on a case-by-case basis. Breastfeeding is not currently specifically contraindicated, but appropriate hand-washing and PPE to include FMs should be utilized.[233,234]

Patient Frailty, Physiological Age, Comorbidities, and Risk Stratification

Rapid accurate risk stratification is essential for ensuring appropriate resource allocation and mitigation of morbidity and mortality.[235-237] In the setting of SARS-CoV-2 infection, patients at markedly increased risk of mortality include those with advanced age and medical comorbidity/preexisting illness.[76,77,117] It is broadly understood that patient frailty, representing a conglomerate of "physiological age" and "chronological age," is among the key outcome determinants.[238-243] Although COVID-19 tends to be less severe in younger populations, no age group is truly spared, and mortality among the younger patients may be related with symptomatic severity of the infection and comorbid conditions (e.g., morbid obesity, asthma, insulin-dependent diabetes, and malignancy).[244] In face of a rapidly evolving pandemic, the simpler and easier it is to implement a risk stratification protocol for comorbidity-related risk, the better the ability to quickly and accurately triage patients.[235-237] It is also well established that certain comorbid conditions may predispose patients to higher COVID-19 acuity and associated mortality [Figure 4].[133] The Italian National Health Institute reported that while only 0.8% of mortalities had no other reported comorbidity, approximately 25.1% of those who died had one other illness, 25.6% had two other illnesses, and 48.5% had three or more preexisting conditions.[133] Both Italy and China report that hypertension and diabetes are among the most dominant comorbid factors, along with heart disease.[133,245] Chronic respiratory conditions including asthma and increased rates of tobacco use have also been linked with poor outcomes.[245,246] Finally, it is recognized that immunocompromised status, malignancy, chronic renal failure, liver disease, and severe obesity (body mass index >40) may all be associated with worse prognosis.[247,248] The presence and specific patterns of comorbidities may help explain emerging findings of racial disparities in mortality of patients with COVID-19 in the US, although the full understanding of these findings has yet to be elucidated and requires further investigation.[249]

Physical Distancing

In the midst of the 1918 Spanish flu pandemic, city authorities in Philadelphia decided to proceed with the Liberty Loan Parade, bringing approximately 200,000 people together. A few months later, there were more than 16,000 influenza deaths in the city.[250] Early in the COVID-19 pandemic, on February 25, 2020, Mardi Gras celebrations took place in New Orleans, Louisiana. Within a few weeks, the city experienced the fastest uptick in COVID-19 cases and deaths in the world.[251,252] When the travel ban for visitors from Europe to the US was announced in mid-March 2020, two important factors may have contributed to the accelerated growth of COVID-19 cases in major air travel hub cities across the US and the UK. First, the ban excluded the UK which provided a potential route for individuals to circumvent the restrictions in place.[253] Second, witnesses reported widespread lack of preparation, with airport authorities conducting "zero checks" in Britain, including travelers from the global COVID-19 hotspot at the time – Italy.[254] Similarly, alarming travel experiences were reported in the US in the early March 2020, with neither the major nor the regional airport hubs performing any organized COVID-19 checks for those returning from Italy.[255] Air travel can be just as effective in spreading the disease as any large human gathering, and contact tracing may not be possible given the intricacies of the air transportation system and the multitude of global intersection points involved. Similar concerns are present when examining the cruise ship industry.[256,257]

Physical distancing strategies (PDSs), ranging from less restrictive social distancing to complete closure of society, or "shelter-in-place" orders, have been suggested as an approach to contain and mitigate the severity of the COVID-19 pandemic.[79,258] PDSs are designed to drastically shift social mixing patterns and are often used in epidemic settings.[259,260] In this context, they can be likened to "circuit breakers" that over time assist in stopping the transmission chain and flattening the epidemic curve [Figure 1].[260,261] Since the WHO declaration of a pandemic, governments around the world have advised against public gatherings and encouraged people to stay at home as much as possible.

Containment efforts help prevent transmission of the disease from documented cases imported by international travelers, thus mitigating transition toward community spread, where disease growth in the local setting occurs without the ability to clearly identify an exposure.[262] Contact tracing of emerging cases can aid in making containment more effective.[262,263] This strategy can succeed by decreasing the total percentage of infected cases during the period required for vaccine development, thereby helping to flatten the curve. Thus, contract tracing reduces the rate of increase in cases in various geographic clusters, so the number of cases is spread out over time and healthcare resources are not overwhelmed.[264]

The mildest form of PDS is social distancing, which requires people to limit the size of gatherings (recommendations range from <10 people to <50 people), to maintain distance between individuals in social spaces (recommendations range from 1 to 2 m), and to remain at home whenever possible.[265] If any gatherings of more than 10–50 people were absolutely required and could not be conducted using virtual platforms, relevant steps such as temperature checks, screening questionnaires, and collection of contact tracing details must be implemented. Consequences of noncompliance, combined with lack of adequate contact tracing, can be severe, including significant attributable disease spread and preventable mortality.[260,266-268] Sustained PDS may reduce the magnitude of the epidemic peak of COVID-19, may lead to a smaller number of overall cases, and should be designed to minimize the spread of the disease, especially by asymptomatic or minimally symptomatic cases.[21,22] Lowering (and flattening) of the epidemic peak is particularly important as it provides critical time to develop vaccines, identify effective therapeutics, and reduce the acute pressure on the healthcare system.[22] To support this point, countries with effective testing and contact tracing (e.g., Germany, Denmark, Czech Republic, Greece, Poland, Slovakia, Singapore, United Arab Emirates, and South Korea) appear to have passed the peak of their local epidemics well within national health system capabilities,[80,142,269,270] while countries/locales that had a delayed response or a public health policy transition from "herd immunity" to "strict isolation" are seeing more severe and prolonged peaks, as well as higher case-fatality rates.[271-273]

To better protect the elderly and other vulnerable populations, the suspension of any nonessential activities involving such groups should be mandated immediately (including family visitations). This is most evident in the setting of nursing homes and long-term care facilities, where susceptible residents are at especially high risk of contracting and dying from COVID-19.[274] Beyond this, places of business, food and beverage outlets, shopping malls, entertainment venues, and all public institutions must comply with the above-outlined PDS methodologies. Awareness should be raised regarding common modes of transmission in public places, including grocery stores, pharmacies, bathrooms, and elevators.[275-277] In terms of workforce management, PDSs include working from home, utilization of teleconferencing for meetings and discussions, staggered shifts/schedules/hours, staggered meal times, and other necessary precautions specific to certain industries.[265,278] Educational institutions and businesses are beginning to utilize AI, virtual reality, and high fidelity simulation to help address some of the challenges associated with COVID-19 disruptions.[279,280] Flexible electronic learning (e-learning) is being utilized more frequently for students to ensure uninterrupted curriculum completion during the remainder of the school year, without the risk of transmitting the disease.[281,282] At the tertiary and postgraduate levels, some face-to-face courses and examinations are being transitioned to video conferencing.[282,283]

In response to the pandemic, Singapore implemented a "whole of government" and a "whole of nation" approach, where everyone's buy-in was crucial. Advertisements and posters were used to help educate and create awareness in the community, with simultaneous media/smartphone messaging and reinforcements.[284] Being socially responsible must become a way of life during COVID-19, where every person plays their required part.[265] Persons who are unwell and have symptoms suggestive of COVID-19 must seek medical consultation and stay at home. Good personal hygiene practices are crucial and hand-shaking has been discouraged (e.g., substitute gestures including the use of elbows or feet are acceptable, as are friendly facial expressions). In countries and regions able to successfully manage their COVID-19 outbreaks, the population was advised to take their body temperature twice a day to evaluate for fever.[285] Utilization of tele-triaging, online self-triage tools, or COVID-19 symptom tracker applications has reduced ED visits. Places of religious worship such as temples, mosques, synagogues, and churches, where devotees congregate regularly to practice their faith, have modified their gathering practices temporarily to help enforce appropriate PDS.[286] When COVID-19 clusters are contact traced to religious institutions, rapid interventions and social isolation and distancing strategies must be put in place immediately. Scheduling population-wide events, such as elections, is highly controversial and requires extreme efforts to prevent active disease spread during the pandemic.[287,288] Remote voting using secure, blockchain-based approaches may be the safest and most reliable solution to this challenge.[289,290] A recent example of PDS for a large event occurred with the South Korean parliamentary elections where voting booths were frequently disinfected, citizens wore masks and gloves, people stayed 1 m apart, and voters underwent temperature checks.

Nonpharmaceutical interventions (NPIs) are inclusive of PDS. They represent the personal, environmental, and community expectation standards to reduce spread of infectious disease, decrease the overall burden on healthcare facilities, and reduce morbidity and mortality [Table 5].

A summary of common strategies used to limit the spread of infection is provided in Table 6. Optimally, when an individual develops symptoms suggestive of infection with SARS-CoV-2, they should practice self-quarantine for 14 days, which is thought to be a sufficient period to monitor for the development of the presenting signs and symptoms of COVID-19.[258,291]

Table 5: Summary of the personal-, environmental-, and community-accepted norms during and outside of a pandemic

Category	NPIs recommended always	NPIs at time of pandemic
Personal	Voluntary home isolation when ill Respiratory etiquette Hand hygiene	Voluntary home quarantine facemask use by ill (source control)
Environmental	Routine surface cleaning	-
Community	-	School closures Mass gathering cancellations Other social distancing measures

NPIs: Nonpharmaceutical interventions

Table 6: Summary of measures available to help reduce disease transmission in the context of physical distancing, starting with widespread, society-wide educational efforts, and ending with strict quarantine orders

Education	LOA	SHN	Quarantine order
Social media, television, internet platforms to educate public	For asymptomatic people who have no COVID-19-positive contacts. Allowed to leave residence	Individuals with international travel <14 days but no COVID-19-positive contacts. Not allowed to leave	Either COVID-19 positive or a PUI

LOA: Leave of absence, SHN: Stay home notice, PUI: Person under investigation

Individuals who have tested positive for SARS-CoV-2 and have mild COVID-19 should be in isolation until they are symptom-free. This effectively separates them from those unaffected. When geographic hotspots appear where the rate of increase in cases is rapid, partial shutdown, such as what has occurred in New York City, or the stricter government lockdown, may be employed.[19,292] One recent controversy in the US surrounded the recommendation to use facial coverings to help reduce person-to-person transmission.[293] This particular recommendation is based on the observations that SARS-CoV-2 may spread via droplets generated during ordinary conversations or even during regular breathing activity and does not require one to cough or sneeze to transmit the pathogen.[294,295] The initial lack of widespread face covering usage may explain some of the differences between observed US viral spread patterns and those in Asia, where citizenry was using masks in much higher numbers at baseline (presumably due to previous experiences with SARS). In response, a massive US grassroots effort took place to design and distribute home-made FMs.[296,297]

Billions under Quarantine or "Stay-at-Home" Orders

Given that the infectivity of SARS-CoV-2 is significantly higher than that of influenza, and there is much greater variability in incubation times, challenging questions arise regarding the logistics of any quarantine and/or containment effort(s).[61,62] From an outbreak mechanics perspective, using a conservative set of assumptions, approximately only one in 100 cases will develop symptoms after 14 days of active monitoring and quarantine.[61] Given these parameters, an unprecedented decision to effectively quarantine an entire province of China was made in an attempt to contain the COVID-19 outbreak.[20,298,299] In the US, Europe, Russia, and many other countries and regions around the globe, "stay-at-home" orders have been issued, effectively confining entire populations to their residences, with exceptions for certain essential (e.g., healthcare, food supply, transportation, and public safety) workers, as well as very limited essential (e.g. shopping, healthcare visits) and recreational (e.g. exercise in open spaces) activities under the regime of continuous physical distancing and FM use.[300-303] While such strategies might be perceived as an appropriate response to try and contain the spread of a highly contagious infection, there also must be concurrent collection and access to timely, transparent, and accurate data, resources, and action plans. This will limit, or prevent, the spread of misinformation, opportunistic preying on public fear, and mass hysteria.[304,305] The decisions to quarantine or otherwise geographically confine a population must also consider the larger implications of removing that population from the global community. Unless such decisions are made on sound social and medical principles, data, and objective information, the risk for chaos and panic becomes magnified. Finally, the appearance of various scams touting "cures for COVID-19" and engaging in price gouging as it relates to the sales of toiletries, N95 respirators, and other essential products to an already vulnerable and fearful communities are of grave concern.[306-308]

Evolving Containment Strategies

Much has been learned about containment strategies, with relevant experiences from the SARS, MERS, and Ebola virus disease outbreaks over the past two decades.[309-313] Isolation of infected patients and quarantine of potentially infectious individuals are two containment strategies utilized. In general, mass quarantine can inflict significant social, psychological, and economic costs while the ability to detect newly infected individuals is limited. Probabilistic modeling has shown that the effectiveness of mass quarantine is inversely related to the ability to effectively isolate all infected individuals within the population.[314] Given the previous SARS experience, China initially tried to contain COVID-19 in Wuhan by adopting isolation methods. There may have been an opportunity to institute mass quarantine in Wuhan earlier, perhaps 3 or so weeks before the official declaration, which may have resulted in less vigorous transmission of COVID-19 within Hubei Province and its spillover to the rest of China.[315] The number of cases and mortality did not rise exponentially in any other city of China once mass quarantine plus isolation of infected individuals were jointly adopted.[316]

This experience represents the first modern example of a large-scale containment action and will certainly serve as a model for planning and preparation that will influence similar events in the future. Of note, quarantine is included within the legal framework of the International Health Regulations.[317] The 196 member states have a sovereign right to legislate and to implement legislation for quarantine, even if this involves restriction of movement of individuals to enhance International Health Security (IHS).[318,319] To assist governments and various local authorities in their responses to COVID-19, the WHO has released the following documents that can help countries plan containment measures: (a) management of travelers at points of entry – airports, ports, and ground crossings; (b) rational use of PPE; (c) quarantine of individuals at mass levels; (d) issuing national guidance on the use of masks in the community, during home care and in healthcare settings; (e) infection prevention and control in healthcare settings; and (f) home care for COVID-19-positive patients with mild symptoms and management of contacts.[318,320-323]

Human and Economic Aspects of the COVID-19 Pandemic

The prelude of the COVID-19 pandemic as an IHS threat was brought into the forefront of attention of both biomedical research and IHS communities in the early 2000s by the SARS-CoV outbreak followed by the subsequent MERS-CoV outbreak.[324-326] What sets the COVID-19 pandemic apart from previous novel coronavirus outbreaks is both the magnitude of the current event and the scale of the coordinated governmental responses, both locally and around the globe. Unlike previous events that tended to be regionalized, the speed at which this outbreak has become global is much more dramatic. Within an extremely short time, the impact on multiple industries and the global economy has been catastrophic.[327] For example, many airlines have suspended nearly all flights to impacted regions.[328] Diverse supply chains, including those for medical supplies, hospital equipment, and pharmaceuticals, depend on global integration, often with deep links with COVID-19-affected regions.[329] In addition to the inherently deleterious effects of PDS on routine healthcare, access to elective surgery, office visits, and dental care in many affected areas is becoming rationed due to disruptions in the supply chain of disposables.[330] The crisis extends well beyond these considerations and includes the impact of disruptions in the global supply chains that affect basic hospital supplies, medications, and items that everyone depends on for daily routine activities. Recent decisions by the US FDA to suspend overseas inspections of foreign drug, device, and food producers will likely further exacerbate current supply chain disruptions and may negatively affect patient safety.[331]

Economic consequences of the COVID-19 pandemic are difficult to estimate but will certainly reach a magnitude sufficient to adversely affect economic growth around the planet for years to come. According to the Center for Strategic and International Studies, significant reductions in gross domestic product (GDP) will be observed around the globe,[332,333] although it would be premature to declare "how bad and for how long" economic activity will be negatively affected.[333] Ultimately, the magnitude of the decline will be dependent on each individual/regional economy's GDP structure (e.g., percentage of GDP attributable to services, industrial production, finances, and tourism).[333,334] Despite massive stimulus measures,[335] unemployment claims in the US skyrocketed past the unprecedented level of 6 million in a single week,[336] with no sign of immediate slowing. The most recent precipitous drop across global financial markets shows how interconnected our economy is with human health, health security, and wellness.[337]

One of the most striking phenomena seen during outbreaks and pandemics, directly linked to social distancing, is a marked reduction in the quantity, duration, and closeness of individuals' interactions outside of their closest circles of family or friends.[337,338] Subsequently, this reduction in social interaction leads to further significant economic slowing, including freezing of the so-called "gig economy."[339,340] As financial markets attempt to price "fear and risk" into existing valuation structures, the behavior of global equity markets will likely fluctuate while attempting to account for "various unanticipated risks."[341,342] Simple fear-based responses, such as "hoarding" of toilet paper in the US – a commodity with limited risk for disruption – illustrate a social reaction that is founded in fear, misinformation, and a general sense of individual and social loss of control.[343]

Perhaps, even more concerning is the misallocation and maldistribution of precious healthcare-suitable PPE.[344,345] It has been emphasized that although there may not be an actual shortage of certain types of PPE or other medical equipment, the maldistribution may result in effective shortages due to mismatch between regional supply and demand.[345] This includes industrial-grade N95 respirator masks that briefly became more available for purchase at local hardware and construction stores than through routine medical supply chains.[346] In response, large allocations of such PPE were subsequently donated by industry, private individuals, veterinarians, and dentists to help alleviate acute healthcare shortages.[347-350] Nonetheless, a more robust and reliable production and distribution capacity will be required to adequately address the acute needs of medical community as it fights the COVID-19 pandemic. As astutely pointed out by Pirkle, "a health system is more than just hospitals."[351] Another thought that is important in the context of the current approach to the COVID-19 pandemic is that the unprecedented sacrifices made to help save lives must not result in greater downstream loss of life, due to long-term economic consequences, reduced access to care, loss of healthcare insurance coverage, migrations, social unrest, crime, and other forms of violence.[352-358]

Telemedicine

The combination of PDS and the diversion of frontline healthcare personnel to fight COVID-19 resulted in a significantly limited access to routine emergency, maintenance, and follow-up care.[359-361] Under such conditions, the development and utilization of telemedicine-based services are critical to allowing high-risk and vulnerable patients to continue receiving care.[319,362] Further, telemedicine can provide home-based care to stable COVID-19 patients who do not require hospitalization.[363] In the past, telemedicine support has been shown to significantly reduce the number of infected people visiting healthcare settings during influenza outbreaks.[364] Similar benefits could be achieved in the setting of COVID-19. According to published experiences, there are important considerations for effective implementation of telemedicine across multiple domains of healthcare delivery, including obstetrics,[365] psychiatry,[366] endocrinology,[367] wound care,[368] rural health,[369] and many other areas. Perhaps, most relevant to the COVID-19 global context, telemedicine capabilities can be utilized to institute more effective point-of-care triage capabilities, cross-border medical expertise sharing, ongoing large-scale patient follow-up efforts, platform for quarantined physicians to contribute and remain productive remotely, as well as dissemination of critical knowledge and skills.[370]

Protecting and Supporting Healthcare Workers

The risk of HCW exposure is substantial during the COVID-19 response, especially when faced with limited PPE supplies and a surging volume of infected patients.[371] Protecting HCWs is paramount in successful management and containment of an infectious outbreak. Occupational Safety and Health Administration and the Centers for Disease Control and Prevention (CDC) have developed guidelines for protecting HCWs including using standard precautions and PPE training. For example, performing as many tasks as possible away from the bedside in less-contaminated areas is ideal.[100] Limiting the number of HCWs interacting with COVID-19 patients and optimizing the number of room entries (e.g., bundling tasks) are important considerations.[372] One good example of this strategy is the placement of intravenous infusion pumps outside of patient room so that nursing staff can adjust infusion rates without having to enter the actively isolated environment. Telemedicine, drive-through testing, and the eventual development of at home test kits and health screening robots can help decrease the risk to providers.[373,374] This will allow HCWs to have more capacity to treat the sickest patients in an effective manner without overwhelming the system. Of importance, different countries, regions, and institutions have different standards for PPE when managing patients with COVID-19, and this may be partly responsible for differences in infection rates among HCWs [Figure 9].[316,375-378]

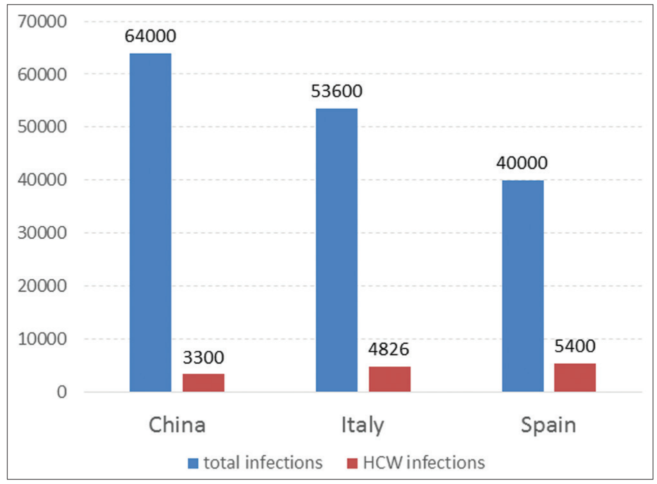

Figure 9: Comparison of total reported infections versus the number of infected healthcare workers in three countries affected by high volumes of COVID-19 infections. Reported healthcare workers infection rates ranged from 5.2% in China to 13.5% in Spain as of mid-March 2020[316,375-378]

Emotional support of frontline personnel is very important. Exposure to potentially large numbers of severely affected patients, including the repeated witnessing of fatal hypoxic respiratory failure with concomitant do-not-resuscitate/do not intubate (DNR/DNI) goals of care discussions where families rely on the HCW as the intermediary, can be extremely draining and will lead to burnout.[379-381] The upfront presence of counseling and other forms of support was deemed of high importance by both Chinese and Italian healthcare providers during reflective exercises.[17] Adequate logistical support and accommodations were important in mitigating the psychological impact of COVID-19 among hospital workers.[17] Moreover, better and more optimal management of the pandemic in the community may, to a degree, help protect the overworked and dangerously exposed frontline personnel.[382] Finally, it should be noted that due to physician workforce demographics, especially in countries such as the US and Italy, a significant proportion of providers are inherently in high-risk groups for severe COVID-19 presentations if infected.[383]

For COVID-19, PPE may be divided into four categories: (a) respiratory, (b) eye, (c) body, and (d) hand. Providers should wear a filtering face piece (FFP) respirator class 2 or 3 (FFP2 or FFP3), and an FFP3 respirator should always be used when performing aerosol-generating medical procedures (AGMPs).[384] Cloth (e.g., cotton or gauze) masks are not recommended in performing medical care.[385] In addition, a face shield or goggles that fit the contours of the user's face and are compatible with the respirator should be used.[384] Finally, gloves and a long-sleeved water-resistant gown should be donned.[384]

All PPE, except the N95 respirator (if used for an AGMP), should be removed before leaving the patient's room and discarded into a no-touch receptacle.[386] The N95 respirator (if used) should be removed after leaving the patient's room and optimally discarded into a no-touch waste receptacle (see below for potential considerations for safely reusing N95 respirators).[386] Hand hygiene should be performed after removing gloves and gowns, before removing facial protection, and upon exiting the patient's room and removing the N95 respirator (if used).[386] Handling linen, dishes, cutlery, and waste management require no special precautions beyond routine practice.[386]

To aid entities in planning the acquisition of PPE materials, the US CDC has published a PPE burn rate calculator that is free for public use.[387] Conversely, the European CDC has provided the following PPE set estimates: suspected case (3-6 sets); confirmed case, mild symptoms (14–15); and confirmed case, severe symptoms (15–24).[384]

Finally, resource and supply chain disruptions may limit the supply of vital resources (e.g., N95 respirator masks). There is no way of determining the maximum possible number of safe reuses for an N95 respirator as a generic number to be applied in all cases.[388] Safe N95 reuse is affected by several variables that impact respirator function and contamination over time.[388] Some have proposed rotational reuse through 72-h cycles.[389] Others have promoted use of reusable elastomeric respirators (e.g. respirators with exchangeable filter cartridges). However, the idea gaining the most traction seems to be N95 mask disinfection using moist heat (e.g., autoclave) or ultraviolet (UV) light.[389]

Strategies to Address Shortages of Essential Supplies And Facilities

Shortages of N95 masks prompted many institutions to decontaminate and reuse PPE.[390,391] Others innovate by utilizing three-dimensional (3D) printing techniques to fabricate PPE, from face shields to specialized FMs.[392,393] There are also examples of innovative 3D printing approaches to produce custom medical equipment, test swabs, and ventilator parts.[392,393] In this respect, 3D printing can be very versatile and represents a creative, low-resource approach of addressing critical needs as it relates to the ongoing pandemic.[394]

Many different solutions were proposed to address the acute ventilator device shortages. One approach describes the modification of continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP) machines that effectively turns them into low-level ventilators capable of supporting patients with less severe forms of COVID-19 respiratory failure.[395,396] Another strategy advocates the use of anesthesia machines as back-up ventilator capacity in times of COVID-19 surge.[397] Similar paradigms have been described with the use of veterinary ventilators to increase the capacity to address the pandemic surge.[398] Novel devices are also being introduced to help with the acute ventilator shortage, such as the CPAP device designed by the carmaker Mercedes-AMG High Performance Powertrains.[399] Finally, when an insufficient number of ventilators places providers and institutions in a situation where the availability of life-saving therapy might be at risk, strategies to place more than one patient on a single ventilator or "co-venting," have been described by Paladino *et al*.,[199] more than a decade ago. "Co-venting" should be a last resort option as it is not the ideal method to ventilate patients with lung injury, but rather a means to save the most lives possible. It is a temporizing maneuver, supplying the crude minimum to sustain life until additional ventilators are obtained. Although "co-venting" can be scaled to help multiple patients, it is recommended to limit the number to two as the addition of more patients becomes sequentially more complex and harder to manage. Pressure cycle modes should be employed to minimize adverse effects of volutrauma and barotrauma. Additional instructions and resources on " co-venting" can be found on the Health and Human Services website maintained by the White House Coronavirus Task Force on "co-venting."[400] Regardless of the approach, it must be emphasized that personnel who operate nonstandard ventilator equipment must be well versed with the technical parameters, logistical considerations, and any clinical limitations associated with the device/methodology being employed.

Facing increasing pressure to deliver critical equipment, including PPE and ventilators to US hospitals, the Defense Production Act was recently invoked to compel industrial manufacturers to make ventilators and other essential supplies.[401] In another executive order, the US President set out to empower the executive branch to prevent hoarding and price gouging of supplies critical to COVID-19 frontline efforts.[402] Similar efforts should be in place to prevent intellectual property/patent laws from delaying the availability of life-saving drugs and technologies due to the imposition of inherently unethical barriers to production and market entry.

Numerous initiatives around the globe are focusing on generating much needed capacity to care for and isolate low-acuity COVID-19 patients while freeing much needed high-acuity healthcare infrastructure. To this end, a phethora of highly creative options includes: (a) mobilizing and modifying non-patient care areas within existing facilities to acutely serve patient care purposes; (b) re-purposing non-healthcare facilities and buildings to server various healthcare or ancillary functions; and (c) mobilizing military, public infrastructure, and other resources to generate surge capacity for beds and non-COVID-19 related indications / procedures [656-661]. In on example, healthcare resource nationalization has been exercised by the Government of Spain [661].

At times overlooked during pandemics, blood banks reported acute shortages of blood and blood products due to decreased donation volume and increased demand related to COVID-19.[403,404] It must also be emphasized that critical equipment shortages are not isolated to high-income countries (HICs) and that such shortages are likely both more prevalent and more deleterious in low-and-middle income countries (LMICs) around the globe.

Health Equity and Ethical Considerations

Vulnerable and marginalized populations will disproportionately bear the brunt of this crisis. Underrepresented minorities, low socioeconomic workers, incarcerated and detained populations, immigrant and refugee communities, orphans, and housing-insecure individuals, are all likely to be disproportionately affected by COVID-19 and the response to its spread.[405-410] Advocacy for equitable policies, practices, and procedures that protect our vulnerable populations can help (at least in part) mitigate this undue burden. In the US, persistent attempts to dismantle expanded health coverage added another layer of complexity to the already tense situation characterized by record unemployment and the vulnerability of underinsured populations with an already limited access to care.[411] Reports are emerging of an increasing number of individuals who died from the illness in their homes, thus contributing to an under-reporting of mortality and compounding the overall public health risk.[412] At the same time, Latino and African-American communities were noted to have significantly higher COVID-19 mortality compared to other groups.[413-415]

An unprecedented confluence of social and economic factors is pushing populations to their breaking point. The COVID-19 outbreak heralded an uptick in hurtful and unfounded anti-Asian racist sentiment around the world.[416-418] Across the globe, LMICs face both healthcare and economic devastation.[419-421] To help ease the situation, the International Monetary Fund recently announced that it will cancel debt payments for 6 months for 25 LMICs battling COVID-19.[422] It has been noted that the approach to COVID-19 in Sub-Saharan Africa cannot be "copied and pasted" based on Chinese or Italian experiences. Instead, unique solutions will be required that consider important population structure differences, high prevalence of endemic diseases, and already overstretched health systems with minimal critical care capacity.[423] A preview of what may come can be seen in Guayaquil, Ecuador, where bodies of the deceased have been left in the streets in cardboard coffins due to the overwhelmed mortuaries and insufficient healthcare resources in the midst of the local COVID-19 outbreak.[424,425]

Global health crises, including the COVID-19 pandemic, bring into the forefront important ethical considerations as societies struggle with balancing medical capabilities, available resources, economic factors, and societal well-being. Dialogue regarding clinical ethics during a Public Health Emergency of International Concern (PHEIC) should take place on an ongoing basis beginning long before an outbreak occurs.[426] The Ebola outbreak of 2014 was a seminal event highlighting the need for the international medical and public health communities to discuss and prepare for the ethical challenges regarding therapies, treatment limitations, duty to treat, and family-centered care and communications.[426,427] Key issues to consider in the above contexts include fair allocation of scarce health resources, PPE availability, patient confidentiality and privacy, social isolation of both affected patients and providers, ethical framework for research studies, and professional liability.[428-430] While clinical ethics focuses on individual patients, public ethics deals with the protection of community health at large. All of these aspects are discussed in the following sections.

Outbreaks can occur in any country, regardless of income level. However, when dealing with LMICs, HICs must avoid being paternalistic and must be cognizant of the structure of communities, understand family dynamics and interactions in affected locations, know the religious implications of medical interventions/public health actions being proposed, pay close attention to local and regional traditions, and understand potential economic consequences regarding any proposed actions. Transparency of communication is of great importance, especially in regard to decisions made by authorities, as there will be community uncertainty of the effectiveness of treatments, vaccines, and patient outcomes. In addition, there must be a structured plan to accept survivors back into the community while avoiding any disease-associated stigma.[427,431] Moreover, the duty of healthcare providers to treat the ill may become a contentious issue.[426] There likely will be medical providers questioning whether it is their duty to provide care to patients, the act of which may then jeopardize their lives or the lives of their loved ones.[432] There is also the question of access to COVID-19 testing, mechanical ventilation, and other services, including prioritization and allocation challenges given resource availability.[433-435]

Another evolving ethical development includes the concepts of information sharing and goals of care discussions while patients are isolated away from family members in the hospital. Patients at the end of life, those who are unable to advocate for themselves, and women in labor are especially vulnerable and dependent on the clinical staff to relay information back and forth. As new DNR/DNI orders are initiated, it is crucial for hospitals to support communication, resources, and protocols to assist patients, families, and caregivers.

Discussed in previous sections, the issue of quarantine continues to be highly controversial from ethical perspective.[436,437] Questions may arise as to whether quarantine is needed, how should quarantine be implemented, where affected individuals should be housed, and for how long. The fashion in which quarantine measures will be introduced to society is very important.[438] Quarantined populations must have appropriate access to all the basic human essential rights to continue to live safely, with access to water, food, energy, healthcare, and the social infrastructures that define humanity. As such, restriction of liberty is always of concern.[439]

Successful control of an outbreak will be dramatically affected by the ethical perceptions of patients, their families, the local community, and those providing healthcare.[440] Without community acceptance of quarantine measures, successful control will be impossible. Frontline staff who ensure that critical services (e.g., public transport, telecommunication infrastructure, supply chains) are functioning and supplies (e.g., food, water, healthcare equipment, medications, fuel) keep flowing may also be at increased COVID-19 risk and deserve support and recognition for their efforts.[441-444] An example of creative solutions in the area of supply chain logistics includes the utilization of trains to transport detachable semi-trailers due to a shortage of truck drivers.[445]

Field Clinical Trials

In times of a pandemic, human vulnerability increases, and the need to provide clinical care must be balanced with the need to conduct clinical and epidemiologic research to improve that care.[426] From an ethical perspective, research endeavors should be governed by the principles of respect for persons, beneficence, and justice.[446] A humanitarian crisis does not allow for the suspension of the ethical foundations governing human subjects research, including institutional review board (IRB) oversight and approval.[447] Indeed, federal regulations outline more—not fewer—research protections for such vulnerable populations.[447]

One unique situation in which research may be conducted without obtaining prior consent is "emergency research." As with other exceptions to the IRB review and informed consent requirements, the definition of "emergency research" is explicit and narrow.[448] The use of experimental strategies and interventions was deemed acceptable before the recent Ebola virus outbreak,[449] and it became evident during the outbreak that experimental approaches may be necessary, while recognizing the risks.[450] However, while it is important to rapidly gain new clinical and therapeutic knowledge during an outbreak, HICs or technologically advanced countries, which usually provide the interventions, therapies, vaccines, and research agendas, must be cautious in how medical research is conducted during a PHEIC. Particular concerns include rushed or poor research methods, misinterpretations of big data, unfair treatment and preventive service allocation, and safeguards for HCWs.[426]

Serious consideration must be given to SARS-CoV-2/COVID-19 study design to ensure the collection of impactful data while maintaining ethical standards, including the limitations of case studies without comparative control groups, the challenges of performing randomized, placebo-controlled studies, and the potential advantages of adaptive study designs.[451] Specific study design differences should be considered in regard to therapies, vaccines, and prophylactic versus therapeutic intervention groups.

There are important considerations and treatment limitations identified that tend to be common during most outbreaks.[426] These include (a) resource scarcity and its impact on treatments; (b) ability to operationalize goals while maintaining appropriate oversight by state and local authorities and triage officers; (c) potential treatment limitations based on provider risk; and (d) limiting the use of treatments with a low probability of benefit. Extensive recommendations on the ethics principles applicable to outbreaks and pandemics have been made by the Society of Critical Care Medicine.[426,427]

Important Legal Considerations

In addition to the specific ethical concerns discussed above, pandemics also present unique legal challenges for patients, law enforcement, and government policy as well as for healthcare entities and personnel. These legal issues can be divided into two broad categories: (a) the restriction of movement and implementation of quarantine policies and (b) medicolegal consequences for patients, families, physicians, and allied medical personnel due to overwhelmed systems. This may include, in the US, violations of the Emergency Medical Treatment and Labor Act (EMTALA), delays in diagnosis and treatment, and medical malpractice due to, or exacerbated by, rationing of available staff and resources.

First, the right to travel has long been asserted as a fundamental human right, internationally codified in Article 13 of the Universal Declaration of Human Rights (UDHR) and Article 12 of the International Covenant on Civil and Political Rights.[452,453] The authority to restrict and regulate the actions of citizens varies broadly across the globe. Moreover, most signatories of the UDHR recognize that an individual's right to move and travel within and across borders is not absolute. Moreover, regional or national authorities may threaten to fine or jail/confine citizenry when their movements or failure to comply with quarantine measures potentially threaten the health and welfare of the country or region as a whole.[454]

Isolation and quarantine policies and procedures are designed to protect the public health and interest during an outbreak and are often a compelling state interest that can take precedence over individual liberties. In the US, under Title 42 of the Code of Federal Regulations Parts 70 and 71, the CDC may detain, medically examine, and release persons arriving into the US and traveling between states if there is knowledge of an infection or suspected risk of transmitting communicable diseases.[455] State, local, and tribal authorities also have separate but co-existing powers translating into over 2000 individual departments of public health.[456,457] In the event of discordant views between federal and state authorities, the Supreme Court is the final arbiter and decision-maker in the US based on the scientific evidence of the individual's threat to community welfare, minimizing the restrictiveness of proposed confinement, and respect for due process.[458-461] It remains to be seen whether individuals will employ principles of common sense and follow directives of self-quarantine (or other required measures) to limit the spread of disease or whether more punitive measures will need to be implemented by state or federal authorities.[462]

Pandemics overwhelm existing systems in terms of both staff and fungible medical supplies and equipment.[463-465] With most hospitals already operating close to capacity, an unexpected influx of critically ill patients will easily cripple EDs and ICUs, leading to staffing shortages, as emergency physicians, intensivists, and their support staff fall victim themselves to the disease or are placed in quarantine.[465-468] In the era of "just-in-time" supply chains, critical equipment and drugs are also likely to be in short supply and physicians may have to make difficult decisions about rationing these supplies based on triage principles, allocating equipment to patients with the greatest chance of survival.[469,470] By proxy, these system-wide problems could affect both COVID-19 patients and non-COVID-19 patients, including those with various chronic medical conditions, as outlined in previous sections.

Under the current EMTALA law in the US, emergency physicians or qualified medical providers are required to perform a medical screening examination (MSE) and stabilize all patients who walk in the doors of the ED, irrespective of their ability to pay. During pandemic surges, delays to MSE are inevitable. Physicians, nurses, and other personnel trained in different specialties, possessing different skills sets, from general practitioners to surgical specialists, may be mobilized when staffing shortages reach a critical level. Depending on jurisdiction, Good Samaritan laws are often not applicable in professional settings like hospitals where physicians have a preexisting duty to provide care to patients, and where patients will also be billed for such services.[471] Across the world, many physicians are agents of the state, and as a result, when a patient is harmed under their care, the individual physician is not held financially liable, although they may be held professionally or even criminally liable depending on the circumstance.[472] This unique concept of attempting to make the patient or family whole under tort law does not take into account systemic failures but classically rests on individual culpability. Systemic errors, which can always contribute to individual error, are magnified during times of medical crisis. Thus, modification of tort law is needed during pandemics. Options include granting sovereign immunity to all medical personnel and increasing the agreed upon standard for malpractice claims from simple negligence to reckless indifference.[473,474] National and international specialty organizations must advocate for an equitable legal framework to protect physicians practicing on the COVID-19 frontlines.

Severe Acute Respiratory Syndrome Coronavirus 2 Therapeutics

Because SARS-CoV-2 is related to SARS-CoV, certain known similarities between these two members of the genus *Betacornavirus* can be leveraged when developing therapeutic interventions for COVID-19.[475,476] For example, although SARS-CoV and SARS-CoV-2 share only 82% of the RNA sequence, their RNA-dependent RNA polymerase demonstrates 96% similarity.[477] Another strategy involves supercomputer-based strategies to estimate the effectiveness of existing therapeutic molecules (e.g., drugs or synthetic antibodies) in relation to viral proteins, receptors and functional complexes.[478,479] Finally, it is well recognized that advanced COVID-19 infection can be associated with an intense immune reaction, prompting interest in pharmacologically modulating such systemic responses.[15,39,291,480-485]

A diverse group of therapeutic agents and classes has been identified as potentially effective against SARS-CoV-2. Due to the extensive nature and diversity of these therapeutic candidates, a full discussion is beyond the scope of this review. A high-level overview of this topic now follows, and the reader is invited to consult any definitive materials referenced below. Table 7 provides a focused outline of key investigational agents and major takeaway points. To date, agents considered for clinical investigation in the context of COVID-19 include protease inhibitors (e.g., lopinavir, ritonavir);[501,505,509,540-546] nucleoside analogs (e.g., favipiravir, galidesivir, penciclovir, remdesivir, ribavirin);[515,547] 6′-fluorinated aristeromycin analogs;[548,549] acyclovir fleximer analogs;[550,551] interferon;[38,39,486,510,520-524,552-555] antimalarials;[231,486-498,556] neuraminidase inhibitors (e.g., peramivir, oseltamivir, zanamivir);[39,557,558] corticosteroids and immunomodulators;[15,39,291,480-485] antilice agent ivermectin;[559,560] as well as a highly heterogeneous group of other potential treatments.[528-531,561-575]

Based on recent reports suggesting that countries with mandatory Bacillus Calmette-Guerin (BCG) inoculations may be experiencing fewer COVID-19 deaths, there is renewed interest in this old tuberculosis vaccine.[535,536] The mechanism behind the effectiveness of a tuberculosis vaccine in the setting of SARS-CoV-2 infection is unclear but may involve BCG's immune boosting characteristics.[537] As a result, Germany initiated a clinical trial of a potential COVID-19 vaccine based on a BCG vaccine.[538] A similar study in Australia will focus on HCWs and will enroll approximately 4000 subjects.[538,539] In addition, plasma from COVID-19-convalescent patients has been advocated by some as it has been reported to decrease mortality with SARS-CoV and severe influenza infections.[525,576] However, plasma collection during the COVID-19 recovery period must be accurately timed to effectively capture appropriate antibodies in sufficiently high concentrations. The efficacy and safety of convalescent plasma in patients with COVID-19 infection is currently being evaluated in clinical trials,[577] with some encouraging reports from small case series.[578] Finally, the identification of SARS-CoV-2-specific antibodies, both in terms of temporal patterns and types, could lead to the synthesis of highly specific monoclonal or polyclonal antibodies against the virus. Such efforts are also under development and investigation at this time.[533,534,579] Of importance, the inclusion of specific agents and devices in this discussion should not be taken as an endorsement or proof of their efficacy. Despite the wealth of investigational COVID-19 therapies, it must be emphasized that as of the completion of this article (May 12, 2020), with the exception of marginally effective remdesivir, early promising reports of some multi-drug approaches, and mesenchymal stem cell applications, there are no established therapeutics against SARS-CoV-2 outside of emergency use authorizations and/or ongoing clinical trials.[500,515,580-582,662,665]

Environmental Parameter Controls

Airflow patterns within healthcare facilities can significantly affect the risk of nosocomial transmission of coronaviruses.[583] The susceptibility to germicidal kill of any microorganism is determined by its genomic sequence of nucleotides adenosine [A], cytosine [C], thymine [T], guanine [G], and in particular, the recurrence of the sequences TT and TTT.[584] At this time, highly efficient air purification technology (HEAFT) exists that will reliably deliver a kill/disinfection rate of 145-log against the airborne SARS-CoV-2 virus[585] (as a reference, sterility is defined by a 6-log reduction). The kill ability provided by this technology was intentional as the capture ability employed by standard hospital high-efficiency particulate arrestance (a.k.a., HEPA) filtration systems, the most common means of air filtration used in healthcare, cannot provide comprehensive remediation when pathogen sizes fall within the range of 0.1–0.3 μ.[586] The approximate size of SARS-

Table 7: Novel candidate therapeutics for COVID-19 by class, mechanism of action, and available evidence. There are currently no United States Food and Drug Administration approved therapeutics at this time

Therapeutic	Class	Theoretical mechanism of action	Evidence
Chloroquine, hydroxychloroquine	Antimalarial	May act nonspecifically at viral entry or at stages of viral production	Some promising *in vitro* and *in vivo* studies, but WHO still cites inefficient evidence for making specific therapeutic recommendations.[231,486-499] Reportedly used in combination with azithromycin.[498] On April 8, 2020, the US CDC dropped its guidance regarding antimalarials, stating "hydroxychloroquine and chloroquine are under investigation in clinical trials[500]"
Lopinavir-Ritonavir	Protease inhibitors	May block viral entry	Viral loads decreased in case series.[32,39,501-504] Currently undergoing clinical trials, but one randomized trial did not demonstrate difference in outcomes at 28 days.[505] There is a risk of interactions with other drugs[506-508] Finally, early data show that multi-therapies containing lopinavir-ritonavir in combination with other agents (e.g., lopinavir-ritonavir plus interferon-β1, plus ribavirin) may be more effective.[662]
Favipiravir, remdesivir, ribavirin	Nucleoside analogs	May block viral entry; lethal mutagenesis; inhibition of nucleotide biosynthesis	Ribavirin has not been shown to be effective and has severe side effects.[509-512] However, remdesivir has been shown to decrease viral titers in mice and reduce lung tissue damage.[513] It also has completed a phase 3 clinical trial for Ebola.[514] Clinical trials for COVID-19 are ongoing[513,515-519] and preliminary data show marginal clinical effectiveness of remdesivir (e.g., shortened hospital length of stay with no difference in patient mortality for those treated with the drug).
Interferon	Interferon	Coronaviruses are thought to have the ability to suppress counteracting interferons; using interferon may inhibit viral replication	Mixed efficacy; not routinely recommended[486,510,520-524] Early evidence shows that interferon-β1 may be more effective when combined with other antiviral agents.[662]
Systemic corticosteroids		Anti-inflammatory	Reported benefit in small observational study but have otherwise been shown to have negative effects with similar viruses; not routinely recommended[15,39,291,480,481,483]
Tocilizumab, siltuximab, sarilumab	Anti-IL-6 agents	Prevent T-cell and macrophage activation to manage cytokine storm complications	There are anecdotal reports of use; no formal or peer-reviewed publications in the setting of COVID; not routinely recommended while under investigation[484,485]
Convalescent serum	Blood product	Provides anti-viral antibodies that specifically target COVID-19 antigens	Theoretical benefit in some viral infections,[525]but no effect observed with Ebola,[526] which was thought to be due to low antibody titers during recovery period. A 5-patient case series did demonstrate improvement in symptoms but requires additional evaluation before any therapeutic recommendations[527]
Supplemental vitamin C, vitamin D	Vitamin	General immune system functioning	Some evidence supporting vitamin C use in SARS-CoV to reduce pneumonia risk;[528,529] However, there is no demonstrated efficacy in SARS-CoV-2, and thus, it is currently not recommended[528-532] A clinical trial is ongoing evaluating vitamin C infusion for the treatment of severe COVID-19 infection. [663] In addition, evidence is emerging that there may be an association between vitamin D deficiency and more severe COVID-19 illness.[664]
Monoclonal antibodies	Synthetic antibody product	Highly specific targeting and inactivation of SARS-CoV-2	Currently under active clinical investigation, including fast-track clinical trials[533,534]
BCG	Anti-tuberculosis vaccine	Unknown	Countries with mandatory BCG vaccination have been noted to have fewer COVID-19 deaths; However, the mechanism of such protection is not known; effectiveness unclear (posited to be due to immune boosting activity) and clinical trials are currently underway to better elucidate any potential benefits[535-539]

There are currently no US FDA approved therapeutics at this time. BCG: Bacillus Calmette-Guerin, FDA: Food and Drug Administration, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, CDC: Centers for Disease Control and Prevention, IL: Interleukin

CoV-2 is 0.125 μ.[587] Because the HEAFT comprehensively remediates the COVID-19 airborne virus, it may be useful in hospitals, nursing facilities, critical care infrastructure, and frontline modular containment/isolation areas, to protect patients, HCWs, and those in potential proximity to infected individuals (e.g., contractors, visitors/families, nonclinical personnel, and allied healthcare professionals). Because HEAFT also correlates with surface contamination, high efficiency air purification systems, in permanent or deployable/portable form, may represent an important adjunct in facilities caring for high-risk populations, such as geriatric patients and those with immunosuppressed status.[220] Although standard deployment of HEAFT systems across all patient-care areas is likely unnecessary, housing for at-risk individuals outlined above may benefit from high-efficiency air filtration with added viral kill capacity, especially in common areas (e.g., hallways, designated buffer zones/entry ways/anterooms, meeting, and dining rooms). It is questionable whether such air filtration capacity would prevent viral transmission within the close quarters of a single patient room or small, confined space where circulating infectious droplets would not likely be eliminated before reaching another individual.[220] However, makeshift anterooms, potentially featuring high-efficiency air filtration, can be constructed to help "buffer" the external environment from immediate exposure.[220]

There is some evidence that adjunctive use of UV germicidal irradiation may provide an additional layer of protection,[588-590] a potential consideration for high-traffic areas, designated buffer zones/entry ways/anterooms, elevators, bathrooms, and critical healthcare spaces and surfaces. Under such circumstances, UV lights should be coupled with motion detectors to temporarily deactivate potentially harmful UV light as people enter and transit through these areas. The effectiveness of UV light deployment in this setting is relatively less well explored than HEAFT, although there is some evidence of efficacy.[591] Finally, the use of hydrogen peroxide for viral inactivation has been described. It was determined that influenza and coronaviruses are sensitive to such environmental approaches.[592] Practical implementations of these findings remain to be fully elucidated, including the role of hydrogen peroxide in achieving environmental purity.

Lessons Learned and Future Directions

There are many lessons learned from the COVID-19 pandemic. The virus characteristics are similar to previous historical coronavirus infections, with a relatively stable transmission rate, deceptively slow incubation time, and a case-fatality rate that is higher than that of H1N1 influenza but lower than that of SARS-CoV or MERS-CoV.[593] It appears that the virus has largely impacted older patients and those with weakened immune systems or other risk factors [see earlier sections and Figures 4 and 5]; however, deaths in younger and previously healthy individuals do occur.[594]

There response is been a controversy surrounding nonsteroidal anti-inflammatory agents, with conflicting reports about potential adverse effects.[595,596] These concerns have not been substantiated. Used more extensively during the early pandemic, the benefit of corticosteroids has been a subject of significant scientific and clinical debate. Although steroids may provide clinical benefit if a patient has ARDS or lung fibrosis, they may be harmful by potentially prolonging the duration of viral shedding.[231]

With regard to frontline healthcare staff preparation, daily messaging of established best practices for emergency and critical care is paramount to contain the spread of SARS-CoV-2 and to ensure that optimal clinical management strategies are followed. It is important that hospitals ensure the presence of adequate resources (i.e., PPE) and available personnel who are properly instructed in contact, droplet, and respiratory precautions. Data-driven and consistently applied protocols for HCWs to report illness and voluntarily observe 'sick leave' and appropriate quarantine practices (e.g., effective isolation and its duration) will help decrease nosocomial spread of illness. Based on input from frontline personnel, it has been reported that having standardized processes and "best practices" established early on during the pandemic extremely helpful. In addition, early respiratory intervention (e.g., proning, orderly therapeutic escalation as shown in Figure 8) should be initiated to improve outcomes, reduce endotracheal intubations and ICU resource utilization.[15]

Future directions include the use of telemedicine for the evaluation of suspected patients; patient-administered, provider-supervised accurate point-of-care testing; best practices for pandemics from thought leaders; deployment of AI-based analytical systems and modeling; and vaccine development for COVID-19.[128,370,597,598] With the history of SARS-CoV, MERS-CoV, and now SARS-CoV-2, the systemic management approach requires a well-organized, collaborative effort that utilizes thoughtful innovation, from basic science laboratories to disaster planning. Scaling production capacity to meet global needs will require creative solutions, especially when promising new therapies or tests require mass production to reach the largest number of people in the shortest amount of time. Re-tooling of otherwise idle production capacity (e.g., transitioning car manufacturing into ventilator production) is one of such solutions.[401] In one example of cutting edge innovation, Mayo Clinic in Jacksonville, Florida, deployed AI-enabled, self-driving vans to ferry COVID-19 tests – a strategy that protects staff from infectious exposure while ensuring continued service to patients.[599]

In terms of restarting the global economy, healing our healthcare systems, and re-integrating those who recovered from COVID-19 into active workforce, several important considerations must be taken into account. First, rapid diagnostic testing on a massive scale will be required to identify and contain new cases and to minimize further disease spread.[80,142,600] Second, convalescent individuals who are certified to be fully recovered should be issued some sort of official document that certifies their status, followed by return to active workforce.[601,602] This should be a foundation of a very efficient system of easily identifying those who are considered to be "safe from infection" (including those who are immunized once SARS-CoV-2 vaccine becomes available) and those who remain "susceptible,"[601] with much more optimal resultant resource allocation, testing deployment, and expedited medical management of those affected. Blockchain-based solutions that allow robust tracking of cases while preserving individual autonomy and privacy rights will be most optimal.[289,603] Healthcare systems should quickly and efficiently shift focus toward treating patients with chronic health conditions and addressing all elective patient concerns

Table 8: Summary of some of the most important "lessons learned" regarding the COVID-19 pandemic; data compiled from multiple sources

Lesson learned	Comment	Source
Rapid development, dissemination, and implementation of diagnostic testing are crucial to allow clinicians to detect the first cases of disease during an epidemic and curb early spread. Drive-thru, rapid diagnostic testing is an effective strategy and may help implement more sensible and targeted isolation efforts	This worked well in South Korea and has been named as one of the key factors for reversing the COVID-19 outbreak in that country Additional positive experience reported by certain local authorities in Italy	[78,80,609-611]
Patients with less severe respiratory failure may benefit from ongoing trial of HFNC or NIPPV, especially when combined with early proning. However, in the event of clinical deterioration, prompt endotracheal intubation may be more beneficial than prolonged use of NIV	This statement is experience-based and not validated scientifically	[15,189,191]
It is important to have well-established protocols and practice guidelines, especially for the ED and critical care settings	This statement is experience-based and not validated scientifically	[15]
Key supplies, medications and PPE are necessary to stockpile. Healthcare institutions and systems should prepare accordingly	Such considerations may be most relevant in situations where the majority of a supply chain is limited to 1-2 sources or countries.[612] This statement is experience-based and not validated scientifically	[15,612]
Nosocomial transmission has been documented as an important source of spread of this disease. In some studies, up to 40% of cases were due to nosocomial transmission to uninfected hospitalized patients, HCWs, or uninfected visitors and family members. Appropriate PPE, in-hospital isolation measures, and visitor policies may help decrease likelihood of nosocomial spread	This statement is based on limited available testing data	[613]
Alternate strategies to prevent or decrease aerosolization during nebulization, high-flow nasal cannula, noninvasive ventilation, and intubation are being explored and may have a role in certain circumstances	Viral filters, nonaerosolizing masks, Lucite™ boxes/shields for intubation, and using surgical masks over NIV face mask have been suggested	[614,615]
Super-spreaders (or super-carriers) are infected individuals who remain asymptomatic but retain the ability to infect others	The presence of such individuals highlights the need for protocolized and highly standardized approach to triage and management of COVID-19, including large-scale testing; Super-spreaders are thought to be involved in multiple transmission aboard cruise ships and/or large public events	[610,616-619]
Triage planning is very important for adequate COVID-19 response. It is important to determine, ahead of time, how to handle patients with complaints of viral illness, detect suspected cases, confirm the diagnosis, and isolate as required	This statement is experience-based and not validated scientifically	[15]
Society-wide social distancing, home isolation and quarantine measures have been shown to suppress viral spread in some contexts; however, longitudinal effects of these suppression efforts, if not sustained in the long run, are thought to be limited	There have been good viral suppression efforts seen in multiple contexts, including China, Singapore, Hong Kong and South Korea. Some early reversal of that has been seen in countries that have since loosened restrictions. It is thought such efforts would be required until an effective vaccine is widely available	[620]

HFNC: High-flow nasal cannula, NIPPV: Noninvasive positive pressure ventilation, PPE: Personal protective equipment, HCWs: Healthcare workers, ED: Emergency department, NIV: Noninvasive ventilation

that were placed on hold during the pandemic.[604,605] This will help reduce preventable morbidity and mortality related to non-COVID-19 conditions, especially chronic medical diseases and mental health concerns. Appropriate immunization programs should be seamlessly introduced and efficiently executed, quickly providing an "insurance policy" that will be needed before any subsequent waves of COVID-19 or another pandemic emerge. Finally, our preparedness for the "next pandemic" should be placed high on the global priority list and should become an inseparable part of mainstream political agendas. It would not be unreasonable to require our elected leaders and those aspiring to become elected leaders, to demonstrate competency in the area of outbreak preparedness. If anything is to be learned from the current pandemic, it is that "no one really knows what is going on" early in the evolution of the process, delays in response are very likely, and coordinated global action incorporating adaptive strategies and "lessons learned" is the only way to effectively tackle these problems.[309,310,606,607] Moving forward, one thing is certain – the COVID-19 pandemic will change how we shop, travel, socialize, and work for years to come.[608] And not to be forgotten – social distancing may stay with us for quite some time to ensure that all preventable SARS-CoV-2 transmission is halted.

Summary of the most important "lessons learned" thus far during the COVID-19 pandemic is provided in Table 8, focusing on the most important, easily implementable, most impactful, and when possible empirically proven approaches and strategies.

Miscellaneous Topics – Post-Covid-19 Lung Damage/Disability/Shedding

Previous studies of the SARS-CoV have identified the presence of a significant autoimmune component during the resolution phase of the infection.[621,622] This heightened immune response within the pulmonary system may lead to severe pneumonia or ARDS. Moreover, there have been anecdotal reports that SARS-CoV-2 is associated with worsening of existing pulmonary conditions, such as chronic obstructive pulmonary disease (COPD) and asthma in convalescent patients. Subsequently, evidence began emerging regarding residual pulmonary dysfunction among COVID-19 survivors, mainly affecting those with more severe disease manifestations.[623,624] SARS-CoV-2 appears to have affinity for nasal goblet and ciliated cells within human airways, leading to potentially significant damage.[625] In addition to direct viral damage to the lung, immune hyper-reactivity may play a role in further exacerbating pulmonary tissue pathology and subsequent scarring.[623]

It is also now emerging that there is significant incidence of end-organ dysfunction across many body systems, in line with the associated and previously described organ failure patterns in the ICU.[626,627] Biochemical evidence of end-organ damage such as elevations in highly sensitive Troponin, ALT, serum creatinine, as well as immune system depression all appear to be prognostically important.[124,125,152,628,629] It is unclear how these parameters translate into longer-term, postrecovery disability, and chronic end-organ dysfunction. One important piece of evidence that has emerged recently is the appearance of Kawasaki-like vasculitis in children who reportedly recovered from COVID-19.[666] If confirmed, this development would corroborate both the pro-inflammatory changes secondary to SARS-CoV-2 infection and the persistence - and potentially the evolution of - such changes over time. Another important piece of the puzzle potentially related to the "vasculitis" theory is the presence of thrombotic and thromboembolic phenomena in the adult COVID-19 patient population [160,161]. Anecdotally, these changes may occur well into the convalescent period, perhaps representing a process similar to the "vasculitis" seen in the pediatric patient.

Much remains to be learned about SARS-CoV-2 shedding, including the average duration of postrecovery shedding and any modulating factors. The reported duration of SARS-CoV-2 shedding among survivors ranged from 17 to 24 days, with a median of 20 days.[128] One factor associated with prolonged viral shedding is the use of corticosteroids.[15,231] The magnitude and duration of this phenomenon are not known at present; however, given the above, the CDC is discouraging corticosteroid use.[291,483] In another report, stool testing for SARS-CoV-2 using qRT-PCR between 0 and 11 days after symptom onset demonstrated viral persistence in fecal samples.[63] Similar to Ebola virus disease, there is anecdotal evidence of SARS-CoV-2 presence in semen for some time after the acute illness ends. Related to viral shedding and long-term immune-related behavior, the topic of recurrent COVID-19 infections warrants a brief mention. Several cases have been described of patients who reportedly recovered, as proven by negative confirmatory testing, and experienced a subsequent short-term relapse of symptoms and positive viral testing.[630-633] Although exact circumstances of each case of recurrent infection are unique, it will be important to determine both viral (e.g. strain differences) and host (e.g. immunosuppression) factors associated with such occurrences, as well as their clinical and epidemiologic significance. Finally, potential exists for human-to-animal transmission for SARS-CoV-2 as demonstrated by anecdotal reports of household pets testing positive for the virus. This, in turn, opens the possibility of a long-term, zoonotic SARS-CoV-2 reservoir and reciprocal animal-to-human transmission. Implications of such development may be significant and far reaching.

Effect of COVID-19 on Long-Range International Medical Programs

COVID-19 has affected international medical programs (IMPs) significantly. For instance, on March 12, 2020, the Fulbright Scholar Award program was put on pause for 60 days by the Bureau of Educational and Cultural Affairs (ECA) of the US Department of State.[634] All current Fulbright Scholars who are overseas have been ordered to return home. The ECA will review this order every 30 days, and the fall program is in danger of cancelation. Similarly, the Fogarty International Clinical Research Scholars and Fellows Program has been temporarily closed.

Many universities have active medical and cultural exchanges with other countries. Faculty and trainees have been required to cease programs while abroad, and many returnees were required to undergo a mandatory 14 days of quarantine upon arrival back to the home country. This is an example of lost educational opportunities for both universities and a loss of funds that were allocated for the opportunity and required for emergency return travel arrangements. In addition, the mandatory quarantine contributed to significant loss of productivity to home departments.[635]

Medical institutions in LMICs may face a loss of staff, overburdened infrastructure, and limited ability to connect using high-speed, readily available, and reliable Internet.[636] This often precludes the use of the primary alternative to direct person-to-person contact – telemedicine and e-learning.[282,370] Consequently, despite significant technological progress in learning platforms, and increasing use of such platforms in HICs,[637] partners in LMICs may not be able to take full advantage of bidirectional information exchanges and various other virtual educational opportunities.[638,639]

In many cases, students and trainees involved in IMP activities will not be able to complete or even begin their curricula.

Offline digital education may be an alternative solution for this pandemic, allowing trainees to learn at their own pace, with or without the need for a working or reliable internet connection. However, this assumes that appropriate arrangements are in place and that there was forethought and anticipation of this PHEIC. The sudden and tectonic changes in medical education and healthcare in general caused by the COVID-19 pandemic will not easily allow such a transition. Subsequent systems strengthening must include better preparedness for similar events in the future.

The balance of international health equity relies on multilateral strategic partnering between HICs and LMICs. The current pandemic has resulted in a return to home base for vast majority, if not all IMP members, and this will negatively impact IMP maturation. Global partners will need to find creative solutions to keep this important work moving forward.

Psychological Aspects of the Pandemic

Posttraumatic stress disorder (PTSD), both among survivors and relatives of victims, may be another "unseen epidemic" following the COVID-19 pandemic.[640] Such phenomena were observed on a large scale in Africa following the 2014–2016 Ebola outbreak.[641] In similar fashion, early reports from China indicate that the COVID-19 outbreak has resulted in significant number of new PTSD cases.[642] It should be expected that PTSD will be increasingly evident across the affected areas of the globe, and it will be equally important to ensure that local resources are available to help individuals cope with the immense emotional stress of a pandemic. In addition, significant rates of anxiety, depression, and other mental health disorders are to be expected, involving both the general population and healthcare providers.[640,643-646] Perhaps, the most dreaded mental health consequence is the increase in suicidal ideation and suicide during the pandemic.[647-649]

The concept of "cabin fever" clearly applies in the current context of prolonged quarantine or "stay-at-home" orders and is inherently associated with feelings of isolation, loneliness, and distress.[650] Common manifestations of "cabin fever" include restlessness, lack of motivation, difficulty concentrating, irritability, lack of patience, hopelessness, irregular sleep patterns, lethargy and difficulty waking up, distrust of those nearby, and persistent sadness/depression.[650] Some strategies that may be potentially useful in coping with "cabin fever" include spending time outdoors, creating a structured daily routine, maintaining a social life, engaging in creative activities, physical exercise, mindfulness strategies, and ensuring scheduled times away from others.[650] There are also growing concerns about the potential for domestic abuse in the presence of home confinement, fear and anxiety, and poor coping mechanisms.[651-653] Finally, in environments where fear and anxiety are prevalent, there may be greater propensity toward abusive behaviors from those tasked with enforcing quarantine or "stay-at-home" orders.[654,655]

Ongoing Exploration, Flexible Adaptation, and Evolving Understanding of the COVID-19 Pandemic

COVID-19 is an evolving phenomenon. At the weekly ACAIM-WACEM Global Taskforce meetings, multiple aspects of the COVID-19 pandemic have been explored including disease models, disease prevention, pathophysiologic mechanisms, bedside diagnosis and individual clinical observations, basic and advanced imaging, clinical testing, and evidence-based management guidelines, among other topics. Innovative treatment options are discussed, from combinations of medications to clinical trials involving monoclonal antibodies and vaccines, various forms of ultraviolet light therapy including intratracheal applications and extracorporeal blood irradiation, as well as convalescent serum therapy, to name just a few. Finally, non-clinical topics such as socio-economic disruptions, medical education, social distancing strategies, global health equity, and post-pandemic future, tend to invoke some of the most controversial and vibrant discussions.

Conclusions

Due in part to the increased mobility of modern societies, SARS-CoV-2 has spread rapidly beyond China's borders and has reached pandemic levels. The WHO named the crisis as the sixth PHEIC before its status was upgraded to a global pandemic. Case-fatality rates remain high, most notably among the elderly and those with comorbidities. Pandemic preparation and response take time, so healthcare and public health systems need to move forward quickly in their efforts to confront this disease around the globe, actively anticipating new disease hotspots and allocating resources accordingly. The most important public health interventions to slow the spread include rapid identification and isolation of cases, along with early implementations of physical distancing measures. A serious challenge in responding to COVID-19 is protecting HCWs and preventing nosocomial infection. Reliably sustainable supplies of PPE and ventilators are urgently needed. Novel therapeutics must be studied in expedited but rigorous clinical investigations to reduce therapeutic ambiguity, potentially harmful therapeutic applications, and the possibility or undue pressure from non-expert influencers. Postpandemic transition to a new global baseline will require deliberate planning, thoughtful implementation, and close international coordination.

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Appendix

Appendix A: The American College of Academic International Medicine-World Academic Council of Emergency Medicine Practical Survival Guide for COVID-19 Clinical Management

Situational Adaptation

1. Embrace flexible and adaptive approaches, modifying external data/evidence to local realities
2. All patients should be considered COVID positive; a majority of patients admitted with no respiratory symptoms are showing chest X-ray (CXR)/computed tomographic (CT) findings characteristic of COVID-19; many nurses and doctors became infected initially by not suspecting infection in all patients and instead perceiving infection risk mainly from those with respiratory symptoms
3. Be prepared for the whole hospital to become overwhelmed with COVID positive patients despite attempts to separate COVID-positive and -negative individuals
4. You must adapt fast, learn quickly, listen to others, and share clinical experiences frequently
5. Look at your own institutional data; focus on things that are going well and opportunities for improvement
6. Institutions and departments should have a "tactical commander" who is not directly responsible for care of COVID-19 patients but closely coordinates patient care and resources
7. Many centers are evolving toward a 1:6 nursing ratio with a high level of support for the emergency department (ED) frontline and the intensive care unit (ICU); optimally, there should be one support worker per patient; as patient volumes increase, specific COVID-19 training tends to be "just in time" or "on the job"
8. Discontinuation or postponement of elective procedures should be initiated with space reallocated to deal with capacity constraints (i.e., for overflow or critical care)
9. Medical screening examinations for specialty complaints (i.e., obstetric or orthopedic) should direct these patients efficiently to specialty care and avoid the highest risk locations for COVID acquisition
10. Redeployment of clinicians and trainees should be directed toward the ED frontline and critical care with a focus on maximizing skill sets; consider ED surgical/procedural teams and trained telemedicine for clinicians who are not participating on emergency medicine (EM)/critical care frontlines.

Positive Signs Regarding Healthcare Capacity

1. Evidence of organizational flexibility, interdisciplinary collaboration, and ability to rapidly adapt to evolving needs
2. Efficient, flexible, real-time, clear, and transparent coordination by the "COVID-19 Crisis Team"
3. Well-defined parameters regarding adequate proportions of beds in ICU, stepdown unit, general ward, and ED capacity
4. Positive attitude across the institution regarding flexible approaches to structural and organizational changes based on the evolving COVID-19 needs
5. Ability to implement rapid infrastructure modifications, including construction of appropriate isolation capacity and donning/doffing areas
6. Adequate and timely maintenance of supplies and critical capacity/infrastructure
7. Transparency at the administrative level about resource availability, pending shortages, and operational solutions
8. Ability to rapidly change organizational and practice patterns based on emerging new evidence and needs
9. Hardwired system "holds" during both initial and subsequent peak COVID-19 patient flows
10. Focus on healthcare worker (HCW) resilience and well-being; formal programs to address COVID-19-related mental health needs (i.e., grief and posttraumatic stress disorder [PTSD]).

Red Flags Regarding Healthcare Capacity/Functionality

1. ED saturated with occupied beds/stretchers
2. ICU saturated with occupied beds
3. ICU with all patients on ventilator support
4. Nonintensive care patient areas at or near capacity
5. Inadequate number of available ventilators
6. Depletion of disposable and critical materials (i.e., hospital supplies, medications, oxygen-related equipment, personal protective equipment [PPE])
7. Absence of a clear chain of command
8. Insufficient direction from the institutional "COVID-19 Crisis Team"
9. Lack of standardization of care, with diffusion of different clinical protocols within the same hospital

10. Increase in psychological and physical symptoms/complaints among HCWs
11. Conflict/disengagement between management and clinicians on processes and PPE.

Clinical Management

Initial resuscitation

1. Identify critical or deteriorating patients and treat them with priority
2. Prioritize PPE for providers before initiating resuscitation procedures
3. Minimize number of providers in the treatment room
4. Follow principles of the Airway-Breathing- Circulation (ABCs) of resuscitation
5. Avoid anchoring bias by not attributing every presentation to COVID-19 and considering other or additional diagnoses (take a "COVID-19 time out" to confirm diagnosis)
6. Place two intravenous (IVs), obtain laboratory work, electrocardiogaphy/ultrasound as needed, and begin fluid resuscitation if indicated during initial in-room evaluation to avoid repeat visits to the room
7. During initial resuscitation, many patients require fluid boluses; balanced crystalloids are preferred over unbalanced crystalloids; boluses should be given in 5–10 mL/kg rapid infusions with reassessment of hemodynamic perfusion parameters (inferior vena cava [IVC] collapse, end-tidal carbon dioxide response to passive leg raise, skin perfusion, change in heart rate, arterial lactate measurements) to assess for further fluid needs
8. Consider early vasopressor initiation, in conjunction with a maximum of 30 mL/kg fluid bolus, and begin with norepinephrine, which can be initiated via a peripheral IV
9. Tolerate relative hypotension with a target mean arterial pressure (MAP) of 60–65 mmHg (systolic blood pressure > 90 mmHg)
10. Place IV pumps and alarms outside of room connected by long tubing to minimize nursing visits to bedside
11. Use ultrasound to identify B-lines, a "ragged" thick discontinuous pleural line with peripheral infiltrates under it; use ultrasound probe covers as you do with central lines to help keep clean
12. In a cardiac arrest, don appropriate PPE before initiating cardiopulmonary resuscitation (CPR); prioritize defibrillation of shockable rhythms; use mechanical chest compression devices if available; prioritize airway management that minimizes aerosolization risk—either intubate using video laryngoscopy while wearing a powered, air purifying respirator (PAPR) and PPE, or place a laryngeal mask airway first with a High Efficiency Particulate Arrestance (HEPA) filter then start compressions (less aerosolization than bag-valve-mask [BVM]; if already intubated, place HEPA filter between endotracheal tube and [BVM])

Airway and intensive care unit considerations

1. Manage asthma by metered-dose inhalers (MDIs) and avoid nebulization
2. Follow a sequential oxygen escalation strategy if possible, from nasal cannula (NC) to facemask (FM) to NC + FM to high-flow NC (HFNC) to noninvasive positive pressure ventilation (NIPPV) to intubation
3. Put a surgical mask over HFNC or a large canopy on the bed to reduce aerosolization
4. Proning should be done both very early and frequently, regardless of intubation status; early on during the disease, the benefit of proning is short-lived (<4 h) upon return to a supine position; for more severe patients, the effect of proning becomes more durable
5. Proning of patients on continuous positive airway pressure (CPAP)/bilevel positive airway pressure (BiPAP) is feasible and effective; however, deterioration and endotracheal intubation should be prompt when patients on noninvasive ventilation show signs of deterioration (e.g., delays increase the risk of converting single-organ failure into multi-organ failure)
6. Avoid high positive end-expiratory pressure (PEEP) settings early on as this may be harmful and consider using a compliance-mediated PEEP strategy
7. Avoid spontaneous ventilator modes early in an ICU admission
8. There is some evidence for clinical effectiveness of airway pressure release ventilation (APRV) mode in hypoxemic patients, especially in hypercarbic patients, with potential advantages over CPAP
9. Institutions tend to evolve toward cohorting patients by phase of disease (e.g., early, late, extubation)
10. Extubation may be challenging, with high re-intubation rates reported; due to airway edema, checking a leak test before extubation is important; do not extubate if inflammatory markers are still elevated
11. Re-intubation may be more common than in comparable non-COVID patients; this may be due to airway edema and stridor
12. Consider establishing a COVID-19 specific extubation protocol, which should be followed strictly
13. It is important to maintain appropriate fluid balance; Most patients arrive in the ICU following a period of acutely febrile illness and hyperventilation, thus severely dehydrated
14. Avoid aggressive diuresis; this may lead to elevated rates of acute kidney injury and preventable extracorporeal renal replacement therapy (RRT)

15. RRT circuits have a propensity toward thrombosis; some institutions transitioned to therapeutic anticoagulation, either with heparin or with low molecular weight heparin
16. There may be increased incidence of thromboembolic phenomena in critically ill COVID-19 patients, including both wedge infarcts and pulmonary thrombosis without apparent/detectable deep vein thrombosis
17. Some centers report positive effects of inhaled nitric oxide and prostacyclin therapy; durability of the beneficial effect(s) of such therapies requires further clinical investigation
18. Extracorporeal membrane oxygenation (ECMO) is not just a boutique therapy; its overuse will deleteriously affect resource use while not providing the desired outcome benefit; utilize extracorporeal life support organization (ELSO) recommendations in consultation with your ECMO team
19. Many patients are returning a week later after discharge from the ICU; there seems to be a bimodal road to recovery

Experience Speaks: Positive Clinical Signs

1. Observed reduction in respiratory rate without accompanying confusion, obtundation, or hypercarbia
2. Walking test without peripheral desaturation; absence of hypoxemia on arterial blood gas; resolution, of or no interstitial–alveolar involvement on CXR
3. Evidence of adequate peripheral perfusion of skin and extremities on clinical examination
4. Resolution of fevers and subjective patient reports of clinical improvement
5. Evidence of oxygen exchange improvement while on the same fraction of inspired oxygen (FiO_2) or during active PEEP reduction
6. Rapid weaning from CPAP/BiPAP while maintaining stable vital signs
7. Good response to proning, including patients on supplemental oxygen and noninvasive ventilation
8. Normal appearance of the pleural line on thoracic ultrasound; presence of B-lines without evidence of parenchymal consolidation
9. Progressive reduction of areas with interstitial and alveolar involvement on ultrasound
10. Preserved left and right ventricular systolic function on an echocardiogram.

Patient Clinical Red Flags

1. The presence of fevers and chills
2. Syncopal symptoms
3. New-onset atrial fibrillation or other tachyarrhythmias
4. Increase in highly sensitive troponins
5. Encephalopathy/confusion/altered level of consciousness
6. Evidence of skin and tissue hypoperfusion with livedo reticularis
7. "Silent hypoxia:" severe peripheral oxygen desaturation without dyspnea; patients tolerating low oxygen saturation (SpO_2) especially those who are young, with no tachycardia, and nonspecific fatigue
8. Reduction in SpO_2 saturations during administration of steady levels of FiO_2
9. Worsening of pulmonary ultrasound findings with extension of interstitial "B-lines" to the anterior and apical regions; appearance of new consolidation (s) or pleural effusion (s)
10. Worsening left or right ventricular function on echocardiography; progression from a hyperkinetic pattern with a relatively normal IVC to a hypokinetic pattern with plethoric IVC and depressed systolic function

Provider Safety

1. Ensure appropriately placed donning and doffing areas, and educate staff on correct PPE use
2. All providers in the resuscitation area should wear appropriate PPE with eye protection, N95 masks, gowns, and gloves
3. Intubator should ideally have a PAPR
4. Use video laryngoscopy to avoid proximity to a patient's mouth and to increase first pass success
5. Consider the use of a barrier enclosure during intubation
6. Consider implementing/offering self-isolation of HCWs to protect their families
7. Set up a counseling service for HCWs early on; the psychological stress, COVID-19-related PTSD, and burnout rates will be high

Shortage of Critical Resources

1. Limit clinical activities to essential tasks and procedures only
2. Keep detailed inventory of critical supplies (e.g., oxygen, resuscitation supplies, intubation supplies, sedatives, analgesics,

paralytic medications, ventilators, PPE) in real time and replenish stocks aggressively
3. Utilize only what is needed, optimizing use of disposable materials and limiting any waste

Humanitarian Considerations

1. Establish a well-functioning and efficient system of patient family notification, with a focus on optimizing the quality and frequency of communications
2. Have a smartphone or tablet with various video calling apps so that a volunteer can call family for patients and patients can see their family members
3. Establish protocols for remote grieving and pastoral care

Credit

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