Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations

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As coronavirus disease 2019 (COVID-19) spreads across the world, the intensive care unit (ICU) community must prepare for the challenges associated with this pandemic. Streamlining of workflows for rapid diagnosis and isolation, clinical management, and infection prevention will matter not only to patients with COVID-19, but also to health-care workers and other patients who are at risk from nosocomial transmission. Management of acute respiratory failure and haemodynamics is key. ICU practitioners, hospital administrators, governments, and policy makers must prepare for a substantial increase in critical care bed capacity, with a focus not just on infrastructure and supplies, but also on staff management. Critical care triage to allow the rationing of scarce ICU resources might be needed. Researchers must address unanswered questions, including the role of repurposed and experimental therapies. Collaboration at the local, regional, national, and international level offers the best chance of survival for the critically ill.

Introduction

Coronavirus disease 2019 (COVID-19) is the third coronavirus infection in two decades that was originally described in Asia, after severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).[1] As the COVID-19 pandemic spreads worldwide, intensive care unit (ICU) practitioners, hospital administrators, governments, policy makers, and researchers must prepare for a surge in critically ill patients. Many lessons can be learnt from the cumulative experience of Asian ICUs dealing with the COVID-19, SARS, and MERS outbreaks. In this Review, we draw on the experience of Asian ICU practitioners from a variety of settings—and available literature on the management of critically ill patients with COVID-19 and related conditions—to provide an overview of the challenges the ICU community faces and recommendations for navigating these complexities. These challenges and recommendations are summarised in tables 1 and 2.

Epidemiology and clinical features of critically ill patients

The number of people diagnosed with COVID-19 worldwide crossed the one million mark on April 2, 2020; the case fatality rate across 204 countries and territories was 5·2%.[2] By comparison, the SARS epidemic infected 8096 people in 29 countries from November, 2002, to July, 2003, and had a case fatality rate of 9·6%,[3] whereas the MERS outbreak infected 2494 people in 27 countries from April, 2012, to November, 2019, and had a case fatality rate of 34·4%.[4] These fatality rates should be interpreted with caution, because they vary across regions, are higher in strained health-care systems, and do not account for undiagnosed patients with mild disease who do not contribute to the denominator.[5–7]

In a review by the WHO-China Joint Mission of 55 924 laboratory-confirmed cases in China, 6·1% were classified as critical (respiratory failure, shock, and multiple organ dysfunction or failure) and 13·8% as severe (dyspnoea, respiratory rate ≥30 breaths per min,

oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen [PaO_2/FiO_2] ratio <300 mm Hg, and increase in lung infiltrates >50% within 24–48 h).[8] Not all critical cases were admitted to the ICU. Indeed, ICU admissions are dependent on the severity of illness and the ICU capacity of the health-care system. In Italy, the country outside China with the most patients with COVID-19 until March 29, 2020, up to 12% of all positive cases required ICU admission.[9,10]

Critically ill patients with COVID-19 are older and have more comorbidities, including hypertension and

> **Key messages**
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> - Clinical features of coronavirus disease 2019 (COVID-19) are non-specific and do not easily distinguish it from other causes of severe community-acquired pneumonia
> - As the pandemic worsens, intensive care unit (ICU) practitioners should increasingly have a high index of suspicion and a low threshold for diagnostic testing for COVID-19
> - Many questions on clinical management remain unanswered, including the significance of myocardial dysfunction, and the role of non-invasive ventilation, high-flow nasal cannula, corticosteroids, and various repurposed and experimental therapies
> - ICU practitioners, hospital administrators, governments, and policy makers must prepare early for a substantial increase in critical care capacity, or risk being overwhelmed by the pandemic
> - Surge options include the addition of beds to a pre-existing ICU, provision of intensive care outside ICUs, and centralisation of intensive care in designated ICUs, while considering critical care triage and rationing of resources should surge efforts be insufficient
> - Preparations must focus not just on infrastructure and supplies, but also on staff, including protection from nosocomial transmission and promotion of mental wellbeing

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	Recommendations
Epidemiology and clinical features	
Prediction of disease trajectory from the time of symptom onset is difficult	Support research to develop and validate prognostic tools and biomarkers
Diagnosis	
Clinical features are non-specific; risk of missing a case early in a local outbreak is substantial	Adopt a low threshold for diagnostic testing, where available
Sensitivity of RT-PCR assays for critically ill patients is unknown	Repeat the sampling if necessary, preferably from lower respiratory tract
RT-PCR assays might not be available in many ICUs; if available, assays will take time to complete	Maintain a high index of suspicion for COVID-19
Management of acute respiratory failure	
Benefits of NIV and HFNC, and associated risks of viral transmission through aerosolisation, are unclear	Reserve for mild ARDS, with airborne precautions, preferably in single rooms, and a low threshold for intubation
Intubation poses a risk of viral transmission to health-care workers	Perform intubation drills; the most skilled operator should intubate with full PPE and limited bag-mask ventilation
ECMO is extremely resource-intensive, even if centralised at designated centres	Balance the needs of a larger number of patients with less severe disease against the (unproven) benefit to a few
Other intensive care management	
Patients often develop myocardial dysfunction in addition to acute respiratory failure	Administer fluids cautiously for hypovolaemia, preferably with assessments for pre-load responsiveness; detect myocardial involvement early with troponin and beta-natriuretic peptide measurements and echocardiography
Bacterial and influenza pneumonia or co-infection are difficult to distinguish from COVID-19 alone	Consider empirical broad-spectrum antibiotics and neuraminidase inhibitors at presentation and subsequent rapid de-escalation
Benefits and risks of systemic corticosteroids are unclear	Avoid routine use until more evidence is available
Transfer out of the ICU for investigations such as CT scans poses risk of viral transmission	Minimise transfers by using alternatives such as point-of-care ultrasound
Viral shedding in the upper respiratory tract continues beyond 10 days after symptom onset in severe COVID-19	De-isolate patients only after clinical recovery and two negative RT-PCR assays performed 24 h apart
Repurposed and experimental therapies that are not supported by strong evidence are being used	Seek expert guidance from local or international societies and enrol patients in clinical studies where possible

ARDS=acute respiratory distress syndrome. COVID-19=coronavirus disease 2019. ECMO=extracorporeal membrane oxygenation. HFNC=high-flow nasal cannula. ICU=intensive care unit. NIV=non-invasive ventilation. PPE=personal protective equipment.

Table 1: Challenges in clinical management

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diabetes, than do non-critically ill patients.[11,12] The most common symptoms are non-specific: fever, cough, fatigue, and dyspnoea.[11–16] The median time from symptom onset to the development of pneumonia is approximately 5 days,[12,15] and the median time from symptom onset to severe hypoxaemia and ICU admission is approximately 7–12 days.[8,13,15,17,18] Most patients have bilateral opacities on chest radiograph and CT.[11–14,16] Common CT findings are ground glass opacities and consolidation.[19,20] Acute hypoxaemic respiratory failure—sometimes with severe hypercapnia—from acute respiratory distress syndrome (ARDS) is the most common complication (in 60–70% of patients admitted to the ICU), followed by shock (30%), myocardial dysfunction (20–30%), and acute kidney injury (10–30%).[11,13,15,16] Elderly patients might develop hypoxaemia without respiratory distress.[5] In one study, arrhythmia was noted in 44% of ICU patients.[11]

In a large report, 49% of all 2087 critically ill patients with COVID-19 in China died.[21,22] Small, single-ICU studies found mortality rates of 62% (in Wuhan, China) and 52% (in Washington, DC, USA), but these figures had not accounted for many who were still in the ICU.[15,16] Although 97% of patients on invasive mechanical ventilation died in a multicentre study conducted early in the Wuhan outbreak, mortality is affected by local practices, and larger studies are awaited.[23] The same study reported that 53% of deaths were related to respiratory failure, 7% to shock (presumably from fulminant myocarditis), 33% to both, and 7% to unclear mechanisms.[23] Mortality is associated with older age, comorbidities (including hypertension, diabetes, cardio-vascular disease, chronic lung disease, and cancer), higher severity of illness scores, worse respiratory failure, higher d-dimer and C-reactive protein concentrations, lower lymphocyte counts, and secondary infections.[5,8,12,15,18,21–24] Although patients older than 60 years account for more than 80% of deaths, younger patients are not spared.[21,22] The median time from symptom onset to death is 2–8 weeks, whereas the median time from symptom onset to clinical recovery is 6–8 weeks.[8,18] Prediction of the trajectory of illness from symptom onset is difficult, and prognostic tools and biomarkers are urgently needed.[5]

Diagnosis

Figure 1 suggests an initial approach for ICU practitioners who are called to assess a patient with suspected COVID-19 infection. The non-specific clinical features do not easily distinguish severe COVID-19 from other causes of severe community-acquired pneumonia.[25] WHO suggests that COVID-19 be suspected in patients with acute respiratory illness and fever, plus travel to or residence in a location reporting community transmission, or contact with a confirmed or probable COVID-19 case in the 14 days before symptom onset; and in patients with severe acute respiratory illness who require hospitalisation without an alternative diagnosis that fully explains the clinical presentation.[26] Given the exponential rise in the number of areas with community transmission worldwide and the substantial risk of missing cases early in a local outbreak,[9] ICU practitioners should increasingly have a high index of suspicion and a low threshold for diagnostic testing for any patient with severe acute respiratory infection, where available.

Diagnosis is based on RT-PCR assays for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Patients with pneumonia might have falsely negative upper respiratory tract samples.[20] Although sampling from the lower respiratory tract is recommended by WHO, such as with sputum and endotracheal aspirates,[26] this procedures potentially generate aerosol and must be performed with strict airborne precautions.[8,27] Although the diagnostic yield of bronchoalveolar lavage for COVID-19 might be high,[28] bronchoscopy should generally be avoided to minimise exposure of health-care workers to

SARS-CoV-2.[29,30] The sensitivity of RT-PCR assays for the critically ill is currently unknown. Repeated sampling might be required when initial tests are negative despite suspicious clinical features.[31] Importantly, RT-PCR assays might be unavailable in many ICUs, and where available still take time to run. Meanwhile, serological assays are being developed.[32]

Management of acute respiratory failure

Specific data on supportive ICU care for COVID-19 are lacking, and current recommendations are based on existing evidence from other viral respiratory infections and general intensive care management (figure 2).[33]

Reports suggest that non-invasive ventilation (NIV) and high-flow nasal cannula (HFNC) were used in between one-third and two-thirds of critically ill patients with COVID-19 in China.[11–13,15] Minimal data exist to confirm or refute safety concerns regarding the risk of aerosol generation by these devices. Epidemiological data suggest that NIV was associated with nosocomial transmission of SARS;[34] however, human laboratory data suggest that NIV does not generate aerosols.[35] Suggestions that HFNC might be safe are questionable: studies that might be taken to support the safety of HFNC were not designed to show whether or not HFNC is aerosol generating and did not examine the spread of viruses.[36,37] Moreover, although NIV might reduce intubation and mortality in mild ARDS,[38] it is associated with higher mortality in moderate-to-severe ARDS from multiple causes,[39] and a high risk of failure in MERS.[40] Although weak evidence suggests that HFNC might reduce intubation rates without affecting mortality in unselected patients with acute hypoxaemic respiratory failure,[41] delayed intubation as a consequence of its use might increase mortality.[42] Thus, NIV and HFNC should be reserved for patients with mild ARDS until further data are available, with close monitoring, airborne precautions, and preferably use of single rooms. Thresholds for intubation in the event of deterioration and the absence of single rooms should be kept low.

Extrapolating from SARS, intubation of patients with COVID-19 also poses a risk of viral transmission to health-care workers, and intubation drills are crucial.[34,43] The most skilled operator available should perform the task with full personal protective equipment (PPE) and the necessary preparation for difficult airways. The number of assistants should be limited to reduce exposure. Bag-mask ventilation, which generates aerosols, should be minimised by prolonged pre-oxygenation; a viral filter can be placed between the exhalation valve and the mask.[43] Rapid sequence induction with muscle relaxants will reduce coughing. End-tidal carbon dioxide detection and observation of chest rise should be used to confirm endotracheal tube placement. The use of closed suctioning systems post-intubation will reduce aerosolisation.

A major focus of mechanical ventilation for COVID-19 is the avoidance of ventilator-induced lung injury while facilitating gas exchange via lung-protective ventilation.[44,45]

	Recommendations
Infection prevention	
A global shortage of medical masks and respirators threatens efforts to prevent transmission	Consider reuse between patients and use beyond the manufacturer-designated shelf life
N95 respirators that do not fit facial contours might not provide the necessary protection	Conduct regular fit testing, preferably before outbreaks
Self-contamination often happens during removal of PPE	Train on both the donning and doffing of PPE
Viable virus on health-care workers' mobile phones and hospital equipment can cause nosocomial transmission	Conduct surface decontamination and consider wrapping mobile phones in disposable specimen bags
SARS-CoV-2 might be transmitted faecally	Practise immediate and proper disposal of soiled objects
ICU visits pose a risk of infection to visitors	Restrict or ban visits to minimise transmission; use video conferencing for communication between family members and patients or health-care workers
ICU infrastructure	
Airborne infection isolation rooms with negative pressure are not universally available, especially in resource-limited settings	Consider adequately ventilated single rooms without negative pressure or, if necessary, cohort cases in shared rooms with beds spaced apart
ICU capacity	
Surges in numbers of critically ill patients with COVID-19 can occur rapidly	Implement national and regional modelling of needs for intensive care
Low-income and middle-income countries have insufficient ICU beds in general, and even high-income countries will be put under strain in an outbreak like COVID-19	Consider whether increasing intensive care provision is an appropriate use of resources; if so, make plans for an increase in capacity, including providing intensive care in areas outside ICUs and centralising intensive care in designated ICUs
Increasing ICU capacity requires more equipment (eg, ventilators), consumables, and pharmaceuticals, which might be in short supply	Pay close attention to logistical support and the supply chain; reduce the inflow of patients who do not urgently require intensive care (eg, by postponing elective surgeries)
Ventilators are in short supply	Consider transport, operating theatre, and military ventilators
ICU staffing	
Increasing ICU bed numbers and workload without increasing staff could result in increased mortality	Make plans for augmentation of staff from other ICUs or non-ICU areas, and provision of appropriate training (eg, with standardised short courses)
Risk of loss of staff to illness, medical leave, or quarantine after unprotected exposure to COVID-19, with a potentially devastating effect on morale, is high	Minimise risk of infection; consider segregation of teams and physical distancing to limit unprotected exposure of multiple team members, and travel restrictions to limit exposure to COVID-19, which is now global
Staff are especially vulnerable to mental health problems such as depression and anxiety during outbreaks	Reassure staff through infection prevention measures, clear communication, limitation of shift hours, provision of rest areas, and mental health support
ICU triage	
ICUs can become overwhelmed as surge strategies might not be sufficient in an emerging pandemic like COVID-19	Consider implementing a triage policy that prioritises patients for intensive care and rations scarce resources
ICU research	
The traditional pace of research might not match the pace of the outbreak	Use and adapt pre-approved research plans and platforms
Studies are often single-centre and underpowered	Collaborate through international research networks and platforms
Rapid conduct and sharing of research might compromise scientific quality and ethical integrity	Cautiously analyse the study methodology when interpreting the literature

COVID-19=coronavirus disease 2019. ICU=intensive care unit. PPE=personal protective equipment.

***Table 2*: Challenges in infection prevention, ICU infrastructure, capacity, staffing, triage, and research**

Prone positioning should be applied early, given its association with reduced mortality in other causes of severe ARDS. Although outcome data on prone
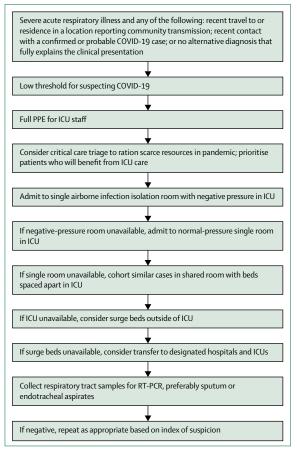
Figure 1: Initial approach to critically ill patients with suspected COVID-19
COVID-19=coronavirus disease 2019. ICU=intensive care unit. PPE=personal protective equipment.

positioning in COVID-19 (used in 12% of patients in one ICU study from Wuhan[15]) are currently lacking, the tendency for SARS-CoV-2 to affect the peripheral and dorsal areas of the lungs provides the ideal conditions for a positive oxygenation response to prone positioning. Veno-venous extracorporeal membrane oxygenation (ECMO) is reserved for the most severe of ARDS patients in view of evidence that it might improve survival, including in MERS.[46–48] However, the decision to provide very advanced care for fewer patients should be balanced against the requirement to provide less advanced care for more patients.[49] Preliminary data for COVID-19 are not encouraging.[11,13,15,17] In one report, out of 28 patients who received ECMO, 14 died, nine were still on ECMO, and only five were successfully weaned.[5]

Other intensive care management

Patients with COVID-19 might have hypovolaemia due to anorexia, vomiting, and diarrhoea.[11–15] Nevertheless, fluids should be administered cautiously, and preferably with assessments for pre-load responsiveness such as the passive leg raise test, given the high incidence of myocardial dysfunction in COVID-19.[11,13,15,16,23] This

incidence might be due to strong binding affinity of the SARS-CoV-2 spike protein to human angiotensin converting enzyme 2 (ACE2), a membrane-bound receptor crucial for host cell entry that is expressed in the heart and lungs, among other organs.[50,51] A conservative or de-resuscitative fluid strategy,[52] with early detection of myocardial involvement through the measurement of troponin and beta-natriuretic peptide concentrations and echocardiography,[53,54] and early use of vasopressors and inotropes are recommended (figure 2).

Most patients with COVID-19 in China were given empirical broad-spectrum antibiotics and many, oseltamivir, because laboratory diagnosis of COVID-19 takes time, and distinguishing the disease from other bacterial and viral pneumonias is often difficult.[11–15] One study of 201 patients with COVID-19 found only one co-infection with a different virus and none with bacteria.[24] Another study of 92 patients found six co-infections by other common respiratory viruses,[55] and a third study of 115 patients found five co-infections with influenza.[56] Any empirical antibiotic and anti-influenza therapy should be rapidly de-escalated based on microbiology test results and clinical response.

Chinese reports also show that systemic corticosteroids were administered to approximately half of patients with COVID-19 with severe or critical illness.[12–15,17] A retrospective study of 84 patients with ARDS associated with COVID-19 found lower mortality in those treated with methylprednisolone, but the findings are limited by the observational design of the study, small sample size, and possible confounders.[24] Because COVID-19 might be associated with a cytokine storm like that seen in other viral infections, immunosuppression has been proposed as an approach that might be beneficial for patients with signs of hyperinflammation, such as increasing ferritin concentrations.[57] Although the benefits of immunosuppression are unproven and the role of corticosteroids in COVID-19 remains unclear, a systematic review of observational studies of corticosteroids for SARS found no impact on mortality but possible harms, including avascular necrosis, psychosis, diabetes, and delayed viral clearance.[58] Similarly, an observational study found that corticosteroids for MERS did not affect mortality, but did delay viral clearance.[59] A systematic review of observational studies suggested that corticosteroids might increase mortality and secondary infections in influenza.[60] Until further data are available, the routine use of corticosteroids in viral severe acute respiratory infections, including COVID-19, is not recommended.[61]

Rapid liberation from invasive mechanical ventilation to reduce the incidence of ventilator-associated pneumonia and to create ICU capacity must be balanced against the risks of premature extubation (especially without facilitative post-extubation NIV and HFNC) and subsequent re-intubation (and the attendant risks of viral transmission to health-care workers). Transfer of patients out of the ICU for investigations such as CT scans risks

spreading SARS-CoV-2 and can be minimised with alternatives such as point-of-care ultrasound.[62] The latter was prioritised by some Chinese ICUs, and evidence of varying degrees of an interstitial pattern and consolidation on lung ultrasonography now exists for patients with COVID-19.[63,64] Finally, the median ICU length of stay for COVID-19 was 8 days in a Chinese report;[18] however, larger studies are needed to better understand the course of COVID-19 after admission to the ICU. WHO recommends that de-isolation of patients requires clinical recovery and two negative RT-PCR assays performed 24 h apart.[61] Viral shedding in the upper respiratory tract continues beyond 10 days after symptom onset in severe COVID-19.[65] This fact has significant implications for the use of isolation facilities.

Repurposed and experimental therapies

No proven therapy for COVID-19 exists, but several candidates—some previously used against SARS-CoV and MERS-CoV—have been used empirically and are undergoing investigation.[61,66] Table 3 summarises the evidence for some of the more prominent therapies: remdesivir,[67–70] lopinavir–ritonavir,[71–74] chloroquine,[75–77] hydroxychloroquine,[79,80] intravenous immunoglobulin,[81,82] convalescent plasma,[83–85] tocilizumab,[57,86] favipiravir,[87] and traditional Chinese medicines.[88,89]

Admittedly, therapies for which efficacy is not supported by strong evidence—not in COVID-19, and not even in SARS and MERS—are being administered in the hope of improving outcomes, before or in parallel with clinical studies. This enthusiasm to try new therapies during outbreaks must be balanced against ethical and scientific safeguards. During the Ebola outbreak, WHO experts concluded that due to "exceptional circumstances", it was "ethically acceptable to offer unproven interventions that have shown promising results in the laboratory and in animal models but have not yet been evaluated for safety and efficacy in humans as potential treatment or prevention".[90] During the SARS outbreak, however, ribavirin was widely used, but was subsequently found to be at best ineffective and at worst harmful.[58] Although expert guidance can be sought from local or international societies, patients treated with experimental therapies should be enrolled in a clinical study when possible.

Infection prevention

COVID-19 is extremely transmissible, with every case seeding more than two secondary cases.[10,91] In the WHO-China Joint Mission report, 2055 health-care workers accounted for 3·7% of cases with laboratory-confirmed COVID-19 in China.[8] WHO recommends that PPE for health-care workers providing direct care to patients with COVID-19 should include medical masks, gowns, gloves, and eye protection with goggles or face shields.[92] For aerosol-generating procedures (tracheal intubation, NIV, tracheostomy, cardiopulmonary resuscitation, bag-mask ventilation, and bronchoscopy), masks should
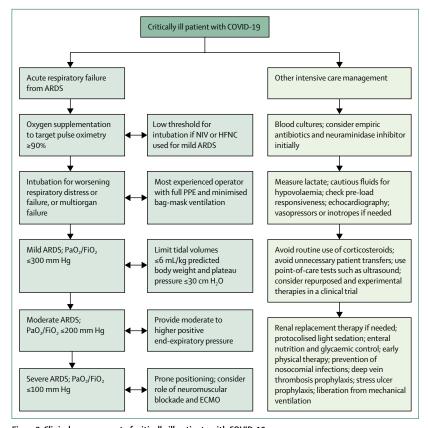

Figure 2: Clinical management of critically ill patients with COVID-19
ARDS=acute respiratory distress syndrome. COVID-19=coronavirus disease 2019. ECMO=extracorporeal membrane oxygenation. HFNC=high-flow nasal cannula. NIV=non-invasive ventilation. PaO_2/FiO_2=partial pressure of arterial oxygen to fraction of inspired oxygen. PPE=personal protective equipment.

be N95 or FFP2-equivalent respirators, and gowns or aprons should be fluid resistant. Although some clinicians have suggested the additional use of powered air-purifying respirators (PAPRs)—given accounts of health-care workers acquiring SARS despite wearing N95 respirators, and available albeit limited evidence that PAPRs result in less contamination of health-care workers[43]—their use comes with significant logistical challenges.[93]

There are several pitfalls related to PPE. Close attention to the supply chain is needed given the global shortage of medical masks and respirators.[5,6,94] Reuse between patients and use beyond the manufacturer-designated shelf life might be required.[95] Fit testing—preferably done before outbreaks—is crucial and should be regularly performed as facial contours change with time.[96] Non-N95 reusable masks with high-efficiency particulate air (HEPA) filters that do not require fit testing might be considered.[96] Although health-care workers often focus on donning PPE, data suggest a substantial risk of self-contamination when doffing PPE.[97] Training on the specific steps of wearing and removing PPE, together with hand cleansing, is crucial, and references for these procedures are widely available.[98]

	Efficacy	Safety
Remdesivir (nucleotide analogue)		
Deemed to be the most promising candidate drug by experts convened in January, 2020, by WHO;[66] relevant studies include PALM, an RCT of remdesivir and different monoclonal antibodies in 681 patients with Ebola virus disease (primary outcome: death at 28 days);[67] study of remdesivir, lopinavir–ritonavir, and interferon beta in mice infected with MERS-CoV;[68] in-vitro studies of remdesivir on SARS-CoV-2, MERS-CoV, and SARS-CoV[69,70]	Not efficacious for Ebola virus disease compared with other investigational therapies;[67] superior activity compared with lopinavir–ritonavir in mice with MERS-CoV;[68] effectively inhibited SARS-CoV-2, MERS-CoV, and SARS-CoV in vitro[69,70]	No peer-reviewed, published safety data available for SARS-CoV-2; in the PALM trial, only 1 of 175 patients randomised to remdesivir had a potentially serious adverse event (hypotension during a loading dose followed by cardiac arrest, possibly due to remdesivir or to fulminant Ebola virus disease itself)[67]
Lopinavir–ritonavir (protease inhibitor)		
Second candidate identified for rapid implementation in clinical trials, alone or in combination with interferon beta, by WHO;[66] relevant studies include an RCT of lopinavir–ritonavir versus standard care in 199 hospitalised adults with SARS-CoV-2-associated pneumonia and hypoxaemia (primary outcome: time to clinical improvement);[71] MIRACLE, an ongoing RCT of lopinavir–ritonavir plus interferon beta versus placebo in patients with MERS-CoV infection (primary oucome: 90-day mortality);[72] case reports describing use of lopinavir–ritonavir plus interferon alfa in patients with MERS-CoV infection;[73] observational study of lopinavir–ritonavir in patients with SARS-CoV[74]	No significant difference in time to clinical improvement, reduction in viral load, or 28-day mortality with lopinavir–ritonavir compared with standard care in patients with severe COVID-19 (28-day mortality was numerically lower: 19·2% vs 25·0%), but median time to randomisation was 13 days after symptom onset, so effects of earlier treatment remain unknown;[71] efficacy unclear in case reports of patients with MERS-CoV;[73] associated with reduced viral load and mortality in an observational study of SARS-CoV[74]	Gastrointestinal side-effects, including diarrhoea, nausea, and vomiting[31,71]
Chloroquine (antimalarial)		
Studies ongoing in patients with COVID-19;[75] in vitro studies of chloroquine on SARS-CoV and SARS-CoV-2[76,77]	According to a news briefing,[75] chloroquine slowed the progression of pneumonia and accelerated SARS-CoV-2 clearance and recovery in >100 patients with COVID-19, but results have not been published in the peer-reviewed literature and caution is advised in interpreting these findings;[75] in-vitro antiviral effects reported for both SARS-CoV and SARS-CoV-2[76,77]	No peer-reviewed, published safety data available for SARS-CoV-2, but concerns include the possibility of QT prolongation[78]
Hydroxychloroquine (antimalarial)		
Open label, non-randomised trial in 36 patients with COVID-19 (endpoint: presence or absence of virus at 6 days);[79] in-vitro studies of hydroxychloroquine on SARS-CoV-2[80]	Reduced SARS-CoV-2 load in the nasopharynx of patients with COVID-19, especially when combined with azithromycin;[79] more potent than chloroquine in inhibiting SARS-CoV-2 in vitro[80]	No peer-reviewed, published safety data available for SARS-CoV-2, but concerns include the possibility of QT prolongation[78]
Intravenous immunoglobulin (immunotherapy)		
Phase 1 trial of human polyclonal immunoglobulin G (SAB-301) in healthy participants;[81] study of human polyclonal immunoglobulin G (SAB-300) in a mouse model of MERS-CoV[82]	SAB-301 found to be safe and well tolerated;[81] SAB-300 reduced viral lung titres near or below the limit of detection in mice infected with MERS-CoV[82]	No peer-reviewed, published safety data available for the various types of interferon (alfa and beta) for SARS-CoV-2, but generally well tolerated[81]
Convalescent plasma (immunotherapy)		
Meta-analysis of 27 studies of treatment in patients with SARS-CoV infection;[83] use has been protocolised for MERS-CoV;[84] uncontrolled case series of 5 patients with SARS-CoV-2[85]	Might reduce mortality in severe acute respiratory infections due to SARS-CoV and influenza;[83] associated with reduction in viral load and improvement in fever, oxygenation, and chest imaging in a case series, but study limited by small sample size, multiple possible confounders, and absence of controls[85]	No peer-reviewed, published safety data available for SARS-CoV-2, but studies of SARS-CoV have not reported serious adverse events[83]
Tocilizumab (monoclonal antibody against interleukin-6)		
Licensed for cytokine release syndrome; hypothesised to work against cytokine storm with raised ferritin and interleukin-6 levels due to SARS-CoV-2[57,86]	No peer-reviewed, published efficacy data available for SARS-CoV-2	No peer-reviewed, published safety data available for SARS-CoV-2
Favipiravir (RNA-dependent RNA polymerase inhibitor)		
Hypothesised to have an antiviral action on SARS-CoV-2 (RNA virus); multiple clinical studies underway for SARS-CoV-2[87]	No peer-reviewed, published efficacy data available for SARS-CoV-2; preliminary, unpublished trial data suggest a more potent antiviral action with favipiravir compared with lopinavir–ritonavir, but caution is advised in interpreting these results[87]	No peer-reviewed, published safety data available for SARS-CoV-2; preliminary, unpublished trial data suggest fewer adverse events with favipiravir compared with lopinavir–ritonavir, but caution is advised in interpreting these results[87]
XueBiJing and others		
Traditional Chinese medicines, such as XueBiJing, suggested as candidates to treat SARS-CoV-2 infection are being studied[88]	No peer-reviewed, published efficacy data available for SARS-CoV-2, but XueBiJing reported to reduce mortality in patients with severe community-acquired pneumonia with mixed aetiologies[89]	No peer-reviewed, published safety data available for SARS-CoV-2

COVID-19=coronavirus disease 2019. MERS-CoV=Middle East respiratory syndrome coronavirus. MIRACLE=MERS-CoV Infection Treated with a Combination of Lopinavir/Ritonavir and Interferon-β1b. PALM=Pamoja Tulinde Maisha. RCT=randomised controlled trial. SARS-CoV=severe acute respiratory syndrome coronavirus. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Table 3: Evidence for the safety and potential benefits of repurposed and experimental therapies

Building a safety culture and encouraging staff to point out protocol errors were useful to reduce nosocomial SARS transmission.[99]

Surface decontamination is also key to infection prevention. Viable SARS-CoV-2 persists on inanimate surfaces such as plastic and stainless steel for up to 72 h.[27] Because more than one-third of health-care workers' mobile phones might be contaminated with common viral pathogens,[100] these should be cleaned regularly or wrapped with specimen bags that are discarded after contact with patients or daily. Environmental contamination by SARS-CoV-2 was detected on furniture and equipment within a patient's room and toilet in Singapore.[101] During the MERS outbreak in South Korea, viable coronavirus was detected on doorknobs, bed guardrails, air exhaust dampers, and elevators.[102] Immediate and proper disposal of soiled objects is also warranted as SARS-CoV-2 might be transmitted faecally.[28,31,101]

Visits to the ICU should be restricted or banned to prevent further transmission, except perhaps for the imminently dying.[63,93] Where feasible, video conferencing via mobile phones or other interfaces can be used for communication between family members and patients or health-care workers.

ICU infrastructure

To protect other patients and health-care workers, critically ill patients with suspected or confirmed COVID-19 should ideally be admitted to an airborne infection isolation room (AIIR) that is at negative pressure relative to surrounding areas, with accessible sinks and alcohol hand gel dispensers (figure 1), especially if aerosol-generating procedures are done.[103] However, a survey of 335 ICUs across 20 Asian countries showed that only 12% of ICU rooms were AIIRs, and 37% of ICUs had no AIIRs. During the SARS outbreak in Singapore, negative pressure ventilation was created by mounting industrial exhaust fans.[93]

If AIIRs are unavailable, patients can be placed in adequately ventilated single rooms with the doors closed, as recommended by WHO.[104] In the same Asian survey, only 37% of ICU rooms were single rooms, and 13% of ICUs had no single rooms.[105] The number of single rooms and AIIRs was generally lowest in low-income countries.

Where single ICU rooms are unavailable, cohorting of cases in shared rooms with dedicated staff is an alternative, with beds spaced apart.[104] Although the current evidence points towards droplet rather than airborne transmission of COVID-19,[8] concerns of nosocomial transmission in shared rooms remain, especially when aerosol-generating procedures are performed. Thus, PPE should be considered for patients in shared rooms. Oxygen masks with HEPA filters might provide some protection for non-intubated patients.[106]

ICU capacity

Controlling the community spread of COVID-19 is difficult but possible,[107] and crucial for the preservation of ICU capacity. National and regional modelling of needs for intensive care is crucial.[9,10] Many countries might not have enough ICU beds in the first place, let alone isolation or single rooms. The median number of critical care beds per 100 000 population was 2·3 in ten low-income and lower-middle-income countries, 4·6 in five upper-middle-income countries, and 12·3 in eight high-income countries in Asia in one analysis,[108] and 9·6 in 28 high-income countries in Europe in a 2012 report.[109] China, an upper-middle-income country, has 3·6 critical care beds per 100 000 population,[108] and Wuhan was initially overwhelmed by COVID-19.[5,6,15] Italy, a high-income country with 12·5 critical care beds per 100 000 population,[109] continues to struggle with the outbreak.[9,10,110] By contrast, a low-income country such as Uganda has only 0·1 critical care bed per 100 000 population.[108,111] This raises serious concerns about the ability of resource-limited settings to manage critically ill patients with COVID-19.[112]

Most countries cannot match China's feat of rapidly building new hospitals and ICUs during the COVID-19 outbreak in Wuhan.[15] Surges in the number of critically ill patients with COVID-19 can occur rapidly. Thus, ICU practitioners, hospital administrators, governments, and policy makers must plan in advance for a substantial increase in critical care bed capacity.[9,10,113] Adding beds into a pre-existing ICU is a possibility, but space constraints and nosocomial transmission from crowding limit this option.[6] Other options include the provision of intensive care outside ICUs, such as in high-dependency units, remodelled general wards, post-anaesthesia care units, emergency departments, or deployable field units (figure 1).[6,113] Another option is the transfer of patients to designated hospitals and ICUs. Although the centralisation of expertise and resources might improve outcomes and efficiency, these benefits must be weighed against the risks of inter-hospital transfer.[6,9] The sustainability of depending on a few centres, or scarcity thereof, even as the outbreak worsens must be considered.

A substantial increase in ICU capacity involves increases not only in bed numbers, but also in equipment (eg, ventilators), consumables, pharmaceuticals, and staffing.[6,10,93,113] Although focusing on bed numbers without ensuring the availability of necessary equipment is unsafe, such equipment might be in short supply. Use of transport, operating theatre, and military ventilators might be required. To reduce strain on ICUs, elective surgeries should be postponed, and lower-acuity patients discharged to other areas, including designated de-escalation wards for recovering ICU patients with COVID-19 who might still require isolation.

ICU staffing

High ICU workload-to-staffing ratios are associated with an increase in patient mortality.[114] Augmentation of staff with colleagues from other ICUs or even non-ICU areas might be required.[6] Training of these external staff on

general intensive care management and specific COVID-19 protocols is crucial.[6,93,113] Standardised short courses exist,[115] such as the BASIC course, which incorporates a mobile app for access to course material while caring for patients. Incredibly, more than 40 000 health-care workers were deployed from other parts of China to Wuhan.[8] However, as the pandemic spreads, support from other sectors of a hospital or a country might increasingly be scarce as every area starts to become overwhelmed.

Staffing of ICUs must take into account the risk that health-care workers might become infected with SARS-CoV-2.[6,93] Minimising the risk of infection is essential, not only because of the direct loss of manpower but because of the potentially devastating effect of staff infection on morale, which might result in absenteeism. Where possible, rostering of staff should consider segregation of teams to limit unprotected exposure of all team members to infected patients or colleagues, and the resultant loss of staff to illness, medical leave, or quarantine.[116] Physical distancing of staff, including having meals separately, is important. Travel restrictions to limit exposure to COVID-19 are being implemented and should be considered worldwide.[117]

Health-care workers in ICUs are especially vulnerable to mental health problems, including depression and anxiety, during outbreaks like COVID-19, because of the constant fear of being infected and the demanding workload.[118] Staff who worked in high-risk SARS units continued to suffer from post-traumatic stress disorder years later.[119] Measures to prevent such problems include a focus on infection prevention to reassure staff, clear communication from hospital and ICU leadership, limitation of shift hours and provision of rest areas where feasible, and mental health support through multi-disciplinary teams, including psychiatrists, psychologists, and counsellors.[117,118]

ICU triage

Should ICUs become overwhelmed by COVID-19 despite surge strategies,[5,6,9,10,15] critical care triage that prioritises patients for intensive care and rations scarce resources will be required (figure 1).[110,120] This applies to patients with and without COVID-19, because both groups will be competing for the same ICU resources. Critical care triage is ethically complex and can be emotionally draining. It should ideally be coordinated at a regional or national health-care systems level, and some countries have now provided guidelines for COVID-19.[121,122] A triage policy implemented by clinicians trained in triage or senior ICU practitioners, complemented by clinical decision support systems, might identify patients with such a low probability of survival that they are unlikely to benefit from ICU care.[120] Although generic physiological outcome prediction scores might not accurately predict the course of illness,[5] older adults with comorbidities, higher d-dimer and C-reactive protein concentrations,

and lower lymphocyte counts do worse.[5,8,12,15,18,21–24] Rationing of resources also involves the withholding and withdrawal of life-sustaining treatments for existing ICU patients. To this end, it is noteworthy that a quarter of patients who died early in the Wuhan outbreak did not receive invasive ventilation.[5]

Research questions and methodology

A search of WHO's International Clinical Trials Registry Platform on March 31, 2020, revealed 667 registered trials on COVID-19. Although many are trials of repurposed or experimental therapeutic agents, other more basic questions that are equally crucial should be addressed through research. Some of these questions have been listed as potential challenges in tables 1 and 2. The short-term and long-term prognoses of critically ill patients have to be clarified. Data on the effectiveness of NIV and HFNC, and the associated risk of viral transmission, remain scarce.[34–37] The risk of nosocomial transmission in shared ICU rooms should be studied. More data on cardiac involvement and myocardial dysfunction are needed.[11,13,15,16,23] The role of ECMO is unclear.[49] The indications for corticosteroids should be crystallised, while considering interactions between different therapies.[61] For example, although limited by confounding from differences in baseline severities, a post-hoc analysis of a non-COVID-19 ARDS trial suggested that beta-interferon use was associated with higher mortality compared with placebo in patients receiving corticosteroids, but not in those who were not on corticosteroids.[123]

Multiple challenges to research exist during pandemics. First, the surge of disease often outpaces the traditional steps for research, including protocol design, securing of funding, and ethics approval, all amidst busy clinical work. Pre-approved adaptable plans drawn prior to an outbreak are useful. For example, several interventions against SARS-CoV-2 are being incorporated into the Randomized, Embedded, Multi-factorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP), a pre-approved platform trial for severe community-acquired pneumonia.

Second, many ongoing studies of COVID-19 are single-centre and underpowered to detect significant differences in meaningful outcomes between arms. To this end, pandemics provide a great opportunity for collaboration. Platforms such as the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) and the International Forum for Acute Care Trialists (InFACT)—formed during the 2009 H1N1 pandemic—enable large research networks to share common goals and standardise data collection globally.[124] WHO has also produced a master protocol for trials on experimental therapeutics for COVID-19.[125] Last, the pace of research and data sharing must be balanced with scientific quality and ethical integrity. China's rapid sharing of the SARS-CoV-2 genetic code had an

Search strategy and selection criteria

We identified the references for this Review through searches of PubMed for articles published between Jan 1, 1950, and March 22, 2020, using combinations of the terms "coronavirus", "COVID-19", "SARS-CoV-2", "nCoV", "severe acute respiratory syndrome", "SARS", "Middle East respiratory syndrome", "MERS", "outbreak", "epidemic", "pandemic", "acute respiratory distress syndrome", and "intensive care". We reviewed guidelines for the management of COVID-19 published by WHO and the US Centers for Disease Control and Prevention. We added articles through searches of the authors' personal files. We also reviewed relevant references cited in retrieved articles. Articles published in English and Chinese were included. The final reference list was generated on the basis of relevance to the topics covered in this Review, with the aim of highlighting the multiple challenges the intensive care community might face in the management of COVID-19, and providing recommendations for navigating these complexities.

immediate impact on case identification, isolation, and the spread of the virus.[126] The COVID-19 pandemic also saw a ballooning of the number of preprints (manuscripts openly posted online before peer review). During the Ebola and Zika outbreaks, the median time between preprints and peer-reviewed publication was 150 days.[127] Although preprints rapidly provide new knowledge, ICU practitioners should be aware of the potential compromise in data quality when the conventional peer-review process is bypassed. A systematic review also found that only 50% of Ebola intervention studies fully complied with frameworks for ethical trial conduct.[128]

Conclusion

As countries ramp up efforts to prevent or delay the spread of COVID-19, the world must prepare for the possibility that containment and mitigation measures might fail. Even if SARS-CoV-2 infects a small proportion of the 7·8 billion people on Earth, many thousands will still become critically ill and require ICU care. The ICU community must brace itself for this potentially overwhelming surge of patients and optimise workflows, in advance, for rapid diagnosis and isolation, clinical management, and infection prevention. Hospital administrators, governments, and policy makers must work with ICU practitioners to prepare for a substantial increase in critical care bed capacity. They must protect health-care workers from nosocomial transmission, physical exhaustion, and mental health issues that might be aggravated by the need to make ethically difficult decisions on the rationing of intensive care. Researchers must address key questions about what remains a poorly understood disease. Collaboration at the local, regional, national, and international level—with a focus on high-quality research, evidence-based practice, sharing of data

and resources, and ethical integrity in the face of unprecedented challenges—will be key to the success of these efforts.

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