ESSENTIAL MEDICINES LIST FOR THE MANAGEMENT OF PATIENTS ADMITTED TO INTENSIVE CARE UNITS WITH SUSPECTED OR CONFIRMED COVID-19 DIAGNOSIS

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BACKGROUND

During the COVID-19 pandemic, many low-, medium-, and high-income countries have depleted their reserves of the essential medicines required to manage patients with COVID-19 in intensive care units (ICUs). Countries' health emergency preparedness plans call for the inclusion of a list of essential medicines and other medical devices that are required in ICUs to confront health emergencies.

OBJECTIVES AND TARGET USERS OF THE LIST

The list of essential medicines for the management of patients admitted to ICUs with a suspected or confirmed diagnosis of COVID-19 is a core guidance document that provides assistance to countries' health systems in prioritizing those essential medicines that should be widely available and affordable for the management of patients in ICUs during health emergencies—in this case, for patients with a suspected or confirmed diagnosis of COVID-19.

This document is targeted to health officials and health system managers in the countries of the Region of the Americas.

METHODS, CRITERIA USED TO DEVELOP THE LIST, AND INFORMATION SEARCH STRATEGIES

This list basically includes the drugs that are considered indispensable for the management of the array of clinical signs and symptoms most often seen in patients admitted to the ICU as a result of SARS-CoV-2 infection.

The list does not include most of the drugs routinely kept in ICUs for the management of other conditions or comorbidities, or to stabilize patients (e.g., insulin or antihypertensives), except for those that may be needed to provide treatment or support (e.g., neuromuscular blockers or anesthetics) for conditions triggered by the infection.

Also not included in the list are drugs used specifically to treat SARS-CoV-2 infection, since no high-quality scientific evidence is available at present to support their use except in the context of controlled clinical trials.

A team of experts on the subject searched for information on the care of ICU patients during the COVID-19 pandemic using MEDLINE (through PubMed), Cochrane, Tripdatabase, Epistemonikos, and global search engines on the internet (Google). Also included were reviews and guidelines developed by the ministries of health of countries of the Region of the Americas, the World Health Organization (WHO), the Pan American Health Organization (PAHO), the National Institute of Health and Clinical Excellence (NICE) of the United Kingdom, the Centers for Disease Control and Prevention (CDC) of the United States of America, and the National Institutes of Health (NIH) of the United States.

The following were some of the strategies and key words used to conduct the search: ("Intensive Care Units"[Mesh]) AND "Drugs, Essential"[Mesh], (Therapy/Broad[filter]) AND (intensive care unit AND medicines AND COVID-19), (Therapy/Broad[filter]) AND (critically ill patients AND COVID-19), (Therapy/Broad[filter]) AND (clinical management AND COVID-19), (title:((title:(intensive care unit) OR abstract:(intensive care unit)) AND (title:(COVID-19) OR abstract:(COVID-19))) OR abstract:((title:(intensive care unit) OR abstract:(intensive care unit)) AND (title:(COVID-19) OR abstract:(COVID-19)))), (title:((title:(critically ill patients) OR abstract:(critically ill patients)) AND (title:(COVID-19) OR abstract:(COVID-19))) OR abstract:((title:(critically ill patients) OR abstract:(critically ill patients)) AND (title:(COVID-19) OR abstract:(COVID-19))))

Evidence-based guidelines developed in accordance with the GRADE method were identified and prioritized. Randomized controlled trials (RCTs), systematic reviews, and meta-analyses were also identified, and any direct or indirect publication where the topic was mentioned was also taken into account[1-85].

For the research questions established, two reviewers selected the titles and abstracts retrieved through the biomedical databases used. For each PICO (patient, problem, or population; intervention; comparison; outcome) question, all studies that met the criteria were examined.

The most important clinical presentations, symptoms and managements in critically ill patients suffering from COVID-19 were identified, as prioritized in guidelines developed by WHO[3, 38], PAHO[61], and the Surviving Sepsis Campaign (SSC)[1].

Also considered were PAHO´s *Guidelines for care of critically ill adult patients with COVID-19 in the Americas: short version – v2*[61]; *Clinical care for severe acute respiratory infection: toolkit*, adapted for COVID-19 in 2020 by WHO[51]; NICE´s *Pneumonia (community acquired): antimicrobial prescribing*[59]; NICE´s *COVID-19 rapid guideline: antibiotics for pneumonia in adults in hospital*[64]; and reviews on the management of critically ill patients with COVID-19[65, 66].

The list is grounded in the evidence-based management recommendations presented in the above-mentioned guidelines, as well as systematic reviews and meta-analyses and the WHO Model List of Essential Medicines.

The following clinical scenarios were selected:

1. Management of patients with hypoxemic respiratory failure and respiratory distress syndrome.
2. Management of patients with hemodynamic compromise and septic shock.
3. Management of critically ill patients to prevent complications.

The quality of the evidence and the strength of each recommendation were based on analysis and on the recommendations in the prioritized guidelines[1,38], as appropriate.

In SSC guidelines[1], the GRADE method was used to assess the quality of the evidence, which was classified as high, moderate, low, or very low. The recommendations are based on the balance between benefits and risks, resources and costs, and on equity, acceptability, and feasibility. The recommendations can be strong or conditional or take the form of "best practices." The guidelines use the phrase "we recommend" for strong recommendations and "we suggest" for conditional or weak recommendations.

The WHO guideline development group[38] did not follow a formal process based on GRADE. The only time it makes a strong recommendation is when a declaration of good practice in favor of a given intervention is involved. It also establishes recommendations against interventions and makes conditional recommendations if special care is required in their implementation.

Medicines were selected by applying the WHO method, namely, on the basis of efficacy, safety, suitability, and cost criteria, with due consideration given to risk-benefit and cost-suitability trade-offs.

The generic name or international nonproprietary name (INN) of the medicines was used, and the inclusion of a single active ingredient was prioritized over fixed-dose combinations, except in situations in which using these is justified, based on evidence pointing to lower resistance or greater adherence to treatment. The active ingredients, their concentration, and dosage forms are included. Recommended pharmaceutical presentations may vary by country.

In the case of drugs with the same site and mechanism of action, the one costing less was selected in most countries of the Region of the Americas in order to improve affordability. If an option other than the proposed one is available in a given country at a lower cost, its use may be considered. The list was organized and classified by therapeutic class. Priority was given to including drugs and pharmaceutical forms contained in the 21st edition of the WHO Model List of Essential Medicines, published in 2019.

This list will be updated as new evidence becomes available.

SCIENTIFIC BASIS FOR KEY DRUGS IN THIS LIST. EVIDENCE LEVEL AND STRENGTH OF THE RECOMMENDATION

Drugs used specifically for the treatment of SARS-CoV-2 infection

More than 1,000 randomized trials involving drugs for the treatment of patients with COVID-19 are currently registered[81].

The Solidarity and Recovery trials have suspended the use of hydroxychloroquine and of lopinavir and ritonavir in patients hospitalized with this disease in view of the lack of benefit in reducing mortality in these patients[78-80, 85].

Preliminary data from the Adaptive COVID-19 Treatment Trial (ACTT)[72] suggest that in patients treated with remdesivir, time to recovery was a statistically significant four days faster, on average, than in patients who received placebo. However, the difference in mortality rates was not statistically significant[72, 73].

The rapid review conducted by PAHO[74] before this list was updated presents a meta-analysis of two randomized clinical trials, and the significant benefit in terms of mortality varies in accordance with the statistical method used. The certainty of the evidence was regarded as moderate primarily because of imprecision (small number of events, small sample, wide confidence intervals) and inconsistency (high I^2)[74].

Some low-quality studies suggest that tocilizumab can significantly reduce the risk of invasive mechanical ventilation or death in patients with severe pneumonia from COVID-19[76-77]. In the last review conducted by PAHO[74], which included meta-analysis of the available data, no benefits deriving from the use of tocilizumab are indicated. The panel of experts for NIH guidelines[43] regards the available data as still not sufficient to issue a recommendation for or against the use of interleukin-6 inhibitors (such as tocilizumab) for the management of COVID-19.

As a result, these medicines are not included in the current list, given the lack of high-quality evidence in favor of using them at the time of this update.

1. *Management of patients with hypoxemic respiratory failure and respiratory distress syndrome*

Drugs for the management of sedation, analgesia, delirium, and muscle relaxation in critically ill patients on mechanical ventilation in the intensive care unit

Sedation, analgesia, delirium management, and muscle relaxation are integral parts of the management of critically ill patients in ICUs and are particularly important in patients on mechanical ventilation. A large number of patients with COVID-19 will need mechanical

ventilation because of respiratory failure. An expert panel has recently recommended that patients diagnosed with coronavirus infection be managed the same way as any other patient on mechanical ventilation[1].

The first clinical practice guidelines recommended (with a low level of evidence) the use of diazepam or midazolam for rapid sedation in agitated patients; of lorazepam for the management of most patients requiring sedation; and of propofol as the preferred sedative when rapid awakening is required (neurological assessment or patient who will be extubated). Similarly, they recommended haloperidol as the drug of choice in the treatment of delirium, a condition that is frequent among critical care patients[29].

Benzodiazepines and haloperidol have been and continue to be, in many ICUs, the drugs most often used when sedation or treatment for delirium are required, respectively. However, more recent clinical practice guidelines suggest the use of propofol or dexmedetomidine over that of benzodiazepines for managing sedation in critically ill adults on mechanical ventilation[30-31], and they suggest not using haloperidol or atypical antipsychotics routinely for the treatment of delirium, with the clarification that both classes of antipsychotics can be used for short periods in selected patients. Dexmedetomidine is not among the medicines included in the WHO Model List of Essential Medicines for 2019. For this reason, consideration was given to including the other therapeutic options, despite limited evidence.

The use of neuromuscular relaxants in patients on mechanical ventilation is associated with improved oxygenation, prevents ventilator dyssynchrony, and reduces airway pressures, potential pulmonary lesions and barotrauma. Different guidelines agree on the need to use neuromuscular blocking agents in the management of adult patients with acute respiratory distress syndrome (ARDS)[1,32]. In adults with COVID-19 and mild to moderate ARDS, the most recent guidelines suggest using boluses of muscle relaxants on demand instead of continuous infusion and suggest reserving intravenous (IV) infusion, lasting no more than 48 hours, for the following cases: patients with persistent ventilator dyssynchrony; patients requiring very deep sedation; patients being ventilated in the prone position; and patients with a persistently high plateau pressure in the airways[1]. The most important clinical trial underpinning the recommendations was conducted with cisatracurium[33]. Atracurium is a muscle relaxant closely resembling cisatracurium structurally and with similar pharmacodynamic and pharmacokinetic properties, but less costly. Both cisatracurium and atracurium are metabolized through plasma mechanisms independent of the liver and their clearance is not affected by renal function. Vecuronium, which is considered an alternative option, can undergo more pharmacokinetic alterations in patients with impaired liver and kidney function[34]. Since they are currently options, given their inclusion in the WHO Model List of Essential Medicines, atracurium and vecuronium will be included.

Succinylcholine, a short-acting depolarizing relaxant, is reserved for cases requiring emergency orotracheal intubation in the ICU[35].

Opioids continue to be a cornerstone of pain management and sedoanalgesia in patients on mechanical ventilation. The opioids that are most highly rated and most often recommended in clinical practice guidelines for the management of critically ill patients are morphine and fentanyl[1, 29, 30].

On the basis of the aforementioned evidence, a list of essential medicines for the management of sedation, analgesia, delirium, and muscle relaxation in critically ill patients in the ICU should include the following: under benzodiazepine sedatives, midazolam and lorazepam; under non-benzodiazepine sedatives, propofol; under antipsychotics, haloperidol; under neuromuscular relaxants, succinylcholine, atracurium, or vecuronium; under opioids, morphine and fentanyl.

It is important to note that Surviving Sepsis Campaign[1] guidelines suggest using, as necessary, intermittent boluses of neuromuscular blocking agents instead of continuous infusion to facilitate lung-protective ventilation (evidence of low quality, weak recommendation).

Use of corticosteroids. Acute respiratory distress syndrome (ARDS-COVID-19).

a- In adult patients with COVID-19

No data are available on the use of corticosteroids in patients with COVID-19 and shock. However, indirect evidence from critically ill patients in shock, based on comparisons of low-dose corticosteroid therapy versus no corticosteroid therapy, showed no significant differences in short-term mortality (relative risk [RR]: 0.96; 95% confidence interval [CI]: 0.91–1.02) or long-term mortality (RR: 0.96; 95% CI: 0.90–1.02), although the time to shock resolution and hospital stay were shorter when corticosteroids were administered[21-23].

In a multicentric randomized controlled trial conducted in 17 ICUs in Spain in patients with moderate to severe ARDS, **early administration of dexamethasone was shown to reduce the duration of mechanical ventilation and overall mortality[36].**

In March 2020, a systematic review[67] on the use of systemic corticosteroids in this type of patients was published. It included a meta-analysis of the results of the last 2019 Cochrane review[23] and those of the aforementioned multicentric clinical trial[36]. **The results obtained suggest that systemic corticosteroids may improve mortality, duration of mechanical ventilation, and number of days without mechanical ventilation.** On the other hand, hyperglycemia was observed, along with an unclear effect on muscle weakness.

A PAHO systematic review looked at the efficacy and safety of the use of corticosteroids; it included meta-analysis of 8 RCTs in patients with COVID-19 and ARDS. Results showed a decrease in mortality among patients who received corticosteroids (RR: 0.74; 95% CI: 0.63–0.86; 1858 patients). In subgroup analyses, the effect remained robust among patients who received dexamethasone (RR: 0.70; 95% CI: 0.59–0.83; 1284 patients), but not among those who received hydrocortisone or budesonide. According to another meta-analysis of 8 observational studies with 1898 patients, no differences in adverse events were noted

between patients treated with corticosteroids and those who received no steroids (RR: 2.08; 95% CI: 0.97–4.46), I^2: 85%). The quality of the evidence is low due to the risk of bias and imprecision[61].

Another systematic review and meta-analysis reported that in patients with COVID-19 and ARDS, corticosteroids may significantly reduce mortality (one cohort study with 84 patients; hazards ratio [HR] = 0.41; 95% CI: 0.20–0.83; evidence of very low quality). This reduction was also seen in patients with ARDS without COVID-19 (7 RCTs with 851 patients; RR = 0.72; 95% CI: 0.55–0.93; low-quality evidence). In patients with severe COVID-19 but without ARDS, direct evidence from two observational studies showed an increase in mortality with the use of corticosteroids (HR = 2.30; 95% CI: 1.00–5.29), but the evidence was of very low quality. Randomized controlled trials on community-acquired pneumonia suggest that corticosteroids may reduce mortality (RR = 0.70; 95% CI: 0.50–0.98; evidence of very low quality) and increase hyperglycemia. Overall, the quality of the evidence is low or very low owing to imprecision, inconsistency, and indirectness[82].

A systematic review of 23 studies (including one RCT and 22 cohort studies), with a total of 13 815 patients, found that in adults with COVID-19, the use of systemic glucocorticoids did not reduce mortality (RR = 2.00; 95% CI: 0.69–5.75; I^2 = 90.9%) or the duration of lung inflammation (mean weighted difference [MWD] = -1 day; 95% CI: -2.91 to 0.91], but a significant reduction in the duration of fever was noted (MWD = -3.23 days; 95% CI: -3.56 to -2.90). In patients with SARS, glucocorticoids did not reduce mortality (RR = 1.52; 95% CI: 0.89–2.60; I^2 = 84.6%), the duration of fever (MWD = 0.82 days; 95% CI: -2.88 to 4.52; I^2 = 97.9%) or the time to absorption of lung inflammation (MWD = 0.95 days; 95% CI: -7.57 to 9.48; I^2 = 94.6%) either. The use of systemic glucocorticoid therapy prolonged hospital stay in all patients (COVID-19, SARS, and Middle East respiratory syndrome [MERS])[83].

More recently, the published results of the Recovery RCT showed that in patients hospitalized with COVID-19, dexamethasone significantly reduced mortality at 28 days in those who required invasive mechanical ventilation (RR = 0.64; 95% CI: 0.51–0.81; p<0.001) or oxygen (RR = 0.82; 95% CI: 0.72–0.94; p = 0.002). No benefit was seen in patients who did not require assisted ventilation (RR = 1.19; 95% CI: 0.91–1.55; p = 0.14)[68-69, 84]. On the basis of these results, one death would be prevented by treating approximately eight ventilated patients or 34 patients requiring oxygen only.

Dexamethasone is a drug that has been included in the WHO Model List of Essential Medicines in multiple forms since 1977. It is currently off patent and available at an affordable price in most countries[70].

The most recent SSC guidelines[1] recommend the use of systemic glucocorticoids **only** in patients who have respiratory failure **with ARDS.**

In adult patients with COVID-19 and in shock who require the addition of a second vasopressor, **administering a low dose of corticosteroids is suggested. This is a conditional recommendation based on evidence of low quality[61].**

PAHO´s most recent *Guidelines for care of critically ill adult patients with COVID-19 in the Americas* **recommend administering corticosteroids at low doses to critically ill**

patients who are on supplementary oxygen or on a ventilator, in order to reduce mortality and progression to invasive mechanical ventilation (strong recommendation based on evidence of moderate quality)[61].

Given these results and recommendations, the critical importance of restricting volume in this type of patients, and the fact that other corticosteroids were already included in the first edition of this list, the current updated version includes dexamethasone instead of methylprednisolone for the treatment of critically ill patients with COVID-19 who require supplementary oxygen or assisted ventilation, and hydrocortisone for the treatment of patients with COVID-19 and refractory septic shock[43].

In adult patients with COVID-19

***Routine use of corticosteroids is not recommended for the treatment of viral pneumonia[38,6] in adults unless indicated for another reason, such as exacerbations of asthma or of chronic obstructive pulmonary disease* (COPD), septic shock or ARDS. A benefit-risk analysis should be conducted for each patient.**

The use of systemic glucocorticoids is only recommended in patients who have respiratory failure with ARDS[1].

Administering corticosteroids at low doses to critically ill patients who are on supplementary oxygen or on a ventilator is recommended to reduce mortality and progression to invasive mechanical ventilation (strong recommendation based on evidence of moderate quality)[61].

b- In children

To date, no high-quality studies are available in support of or against the routine use of adjuvant glucocorticoids to treat pediatric septic shock or another organic dysfunction associated with sepsis. One clinical trial is currently being developed to look at the potential risks and benefits of adjuvant hydrocortisone for treating septic shock that is refractory to fluid therapy and to vasoactive-inotropic agents in children.

Hydrocortisone can be prescribed at stress doses, with or without assessment of the adrenal axis[2,37], **only in situations in which a child with septic shock or another form of sepsis associated with organic dysfunction is known to have suffered acute or chronic exposure to corticosteroids; disorders of the hypothalamic-pituitary-adrenal axis, congenital adrenal hyperplasia, or other endocrinopathies related to corticosteroids; or to have recently been treated with ketoconazole or etomidate.**

In children with COVID-19

In the case of septic shock or other organic dysfunction, no good quality evidence is available that either supports or refutes the use of corticosteroids.

They should be used only if the child has previously suffered acute or chronic exposure to corticosteroids; disorders of the hypothalamic-pituitary-adrenal axis, congenital adrenal hyperplasia, or another endocrinopathy related to corticosteroids; or has recently been treated with ketoconazole or etomidate. In such cases, hydrocortisone can be prescribed at stress doses, with or without assessment of the adrenal axis[2].

Hydrocortisone is being conditionally included in this list, pending further evidence.

2. Management of patients with hemodynamic compromise and septic shock

The prevalence of shock in adult patients with COVID-19 varies considerably (from 1% to 35%). In hospitalized patients, its incidence can be as high as 20-35%[6], which explains the need to identify the best therapeutic options for its treatment.

Parenteral solutions

Cardiac dysfunction is common in patients with COVID-19 (7% to 23%)[7-10]. Fluid management in critically ill patients with COVID-19 admitted to ICUs (with or without septic shock) is a key, clinically significant element, both in terms of the quantity and the type of fluids that should be used in these cases.

The indirect evidence obtained on hemodynamic and fluid replacement management in critically ill patients included in 13 RCTs shows that appropriate fluid therapy can reduce mortality (RR = 0.59; 95% CI; 0.42–0.83) and hospital stay among critically ill patients in the ICU[11] (mean difference [MD] = -1.16 days; 95% CI: -1.97 to -0.36).

Appropriate fluid management has as much to do with the quantity as with the type of fluid administered. As concerns the first point (the amount of fluid that should be used in critically ill patients), the comparison between restricting fluids and administering fluids freely in patients with septic shock is arguably inconclusive with respect to mortality (RR = 0.87; 95% CI: 0.69–1.10) and serious adverse events (RR = 0.91; 95% CI: 0.78–1.05)[12]. However, all the results examined appear to favor conservative and restrictive fluid therapy with administration of low fluid volumes[13,38], and the avoidance of large fluid volumes, even in pediatric patients[14].

In conclusion, the recommendation concerning the volume of fluids that should be used in critically ill patients favors restrictive use. This recommendation is conditional and is based on evidence of low quality[1].

In reference to the type of fluids that should be used (crystalloids or colloids), there is one systematic review of 69 RCTs (*n* = 30 020 patients) in which[16] both types of fluids were compared in critically ill patients with COVID-19 and shock[16]; statistically significant differences in mortality were not found (RR = 0.97; 95% CI: 0.86–1.09) at 1 and 3 months.

However, the risk of kidney damage and the need for transfusion are higher with colloids (RR = 1.30; 95% CI: 1.14–1.48)[16]. By crystalloids we mean normal saline solution and Ringer´s lactate solution.

Considering that certain colloids are harmful, more expensive than crystalloids, and have limited availability in certain contexts (low- and middle-income countries), the SSC guideline[1] development panel recommends using crystalloid solutions as fluids to resuscitate patients with COVID-19 and shock.

In conclusion, the recommendation concerning the use of crystalloids versus colloids in critically ill patients with COVID-19 favors the use of crystalloids. This recommendation is strong and is based on evidence of moderate quality[1].

A breakdown of the data by type of colloid used in these comparative studies with crystalloids shows the following:

The use of albumin as a colloidal plasma volume expander in critically ill patients was addressed in 20 RCTs involving 13 047 patients. Trial results showed no benefits associated with albumin administration (weak recommendation, evidence of moderate quality)[16].

Additionally, no studies are available on the use of gelatins in patients with COVID-19. Indirect evidence from one systematic review of six RCTs involving 1,698 patients who were critically ill from other causes and in which the colloid given was a gelatin showed no mortality benefit at days 30 and 90, with disadvantages in terms of costs versus benefits. For this reason, the use of gelatins is not recommended (conditional recommendation, evidence of low quality)[16].

Nineteen RCTs with 4,736 enrolled patients compared using crystalloids with using a colloid such as dextran. No benefits favoring the latter were reported, whereas a disadvantage noted was an increase in red blood cell transfusion requirements (weak recommendation, evidence of low quality)[16].

More than 11,000 patients enrolled in 24 RCTs in which hydroxyethyl starch was used as the colloid in the comparison with crystalloids. The trials showed that, despite the lack of differences in mortality, starches pose a greater risk of needing red blood cell transfusions and renal replacement therapy than crystalloids (strong recommendation, evidence of moderate quality)[16].

The use of colloidal plasma expanders such as albumin, gelatins, dextran, or starches has shown lower cost-effectiveness than the use of crystalloids. This recommendation is conditional, and the quality of the evidence is low or moderate (an exception is starch, whose recommendation is strong and based on evidence of moderate quality)[1, 16].

The use of crystalloids for critically ill adult patients with COVID-19 is therefore recommended.

To determine what type of crystalloids are most beneficial for replacing or expanding volume (balanced crystalloid solutions versus 0.9% saline solution)[1] when resuscitating critically ill patients, a Cochrane systematic review was conducted in 2019. It failed to show significant differences between treatments in terms of mortality (odds ratio [OR] = 0.91; 95% CI: 0.83–1.01) or acute renal injury (OR = 0.92; 95% CI: 0.84–1.00)[15]. However, the data did suggest a potential benefit of balanced crystalloid solutions for resuscitating patients with COVID-19 and shock.

One final systematic review with meta-analysis[39] found that in critically ill adult patients, although not specifically those with sepsis, mortality was lower at days 28-30 among those resuscitated with balanced crystalloid solutions than among those resuscitated with saline solution.

The SCC guidelines suggest that the use of buffered balanced crystalloids is superior to the use of unbalanced crystalloids. This evidence is of moderate quality, and the recommendation is conditional.

In conclusion, balanced crystalloid solutions such as Ringer´s lactate or, if unavailable, 0.9% sodium chloride solutions are recommended, with restrictive administration, to replace fluids in critically ill patients with COVID-19. Hypotonic solutions are not to be used. This is a conditional recommendation based on evidence of moderate quality[1].

In light of the limited availability of balanced crystalloid solutions[1], 0.9% sodium chloride solution continues to be a reasonable alternative.

Although in critically ill patients with COVID-19 recommendations are to use fluids sparingly, choose crystalloids and, within this category, balanced crystalloid solutions such as Ringer´s lactate, the mode and rate of administration of these fluids must be determined in accordance with the type of patient being treated[38].

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[1] Crystalloid solutions are defined as those containing water, electrolytes, and/or sugars in different proportions and osmolarities. With respect to plasma, they can be hypotonic, hypertonic, or isotonic. These solutions include 0.9% sodium chloride hydrosaline (sodium 154 mEq / osmolarity 308 mOsm/L), Ringer's (148 mEq sodium / osmolarity 310 mOsm/L), Ringer's lactate (sodium 130 mEq / lactate 28 mEq / osmolarity 272 mOsm/L), 5% dextrose in saline solution (glucose 50 g/ sodium 154 mEq / osmolarity 560 mOsm/L), and 5% dextrose in water (glucose 50 g / osmolarity 253 mOsm/L). Colloidal solutions such as dextran are plasma expanders containing high-molecular-weight particles in suspension that do not cross capillary membranes. Thus, they are capable of increasing plasma osmotic pressure and of retaining water in the intravascular space. Human albumin has also been used as a plasma expander at 5% or 25% in isotonic solution. Administration of albumin 25% solution increases intravascular volume by five times the albumin volume administered over 30 to 60 minutes.

Thus, in **adult patients** administering 250-500 ml of crystalloid fluid as a bolus over the first 15-30 minutes of resuscitation efforts for septic shock is recommended.[38]

In resuscitation for **septic shock in children**, administering 10-20 mL/kg of crystalloid fluid as a bolus over the first 30-60 minutes is recommended.[38]

Additional boluses may be needed (250-500 ml in adults; 10-20 ml/kg in children) depending on the clinical response and on improvements with respect to perfusion objectives; continuous vigilance for possible signs of fluid overload after each bolus is required. Perfusion objectives include achieving a mean arterial pressure >65 mmHg in adults, or an appropriate equivalent pressure depending on the age of the affected children; a urine output >0.5 ml/kg/h in adults or >1 ml/kg/ h in children; and improved skin and limb perfusion, heart rate, and level of consciousness[14, 38, 40].

Vasoactive drugs

Given the absence of direct evidence in patients with COVID-19 and shock, indirect evidence from critically ill patients in general can guide the therapeutic decision-making process in these cases.

In adults with COVID-19 and shock, norepinephrine is recommended as first choice (a comparison of norepinephrine with vasopressin or epinephrine in this type of patient showed no significant differences in mortality, although epinephrine was associated with more pronounced tachycardia and excess lactate production[1,17]). If norepinephrine is not available, vasopressin or adrenaline should be used as first choice.[1]

In adults with COVID-19 and shock who show signs of cardiac dysfunction and persistent hypoperfusion despite resuscitation with fluids and norepinephrine, the recommendation is to add dobutamine[1, 18, 19, 20] without first attempting to increase the dose of norepinephrine.

For children with COVID-19 and septic shock who have organ dysfunction, SSC guidelines[2] recommend both epinephrine and norepinephrine, which were assessed in comparison with dopamine. But since clinical trials comparing the two drugs with each other are not available, it is suggested that the decision to select one or the other as first choice be based on the patient's pathophysiological condition (preference for epinephrine to treat myocardial dysfunction and low cardiac output, and for norepinephrine to increase vascular resistance) and on local factors.

In light of the above, it is recommended to start with norepinephrine in critically ill patients with COVID-19 and cardiogenic or septic shock who require hemodynamic support. If norepinephrine is not available, vasopressin or adrenaline may be used. According to the most recent WHO guidelines[38], the recommendation in favor of this intervention is strong.

If there is evidence of cardiac dysfunction or persistent hypoperfusion, dobutamine may be used. This is a conditional recommendation, since it calls for special care[38].

In children, epinephrine is considered the first line of treatment, while norepinephrine is administered if shock persists despite an optimal dose of epinephrine[2].

On the basis of the evidence presented, this list includes dobutamine, vasopressin, and norepinephrine, despite their not being included in the 21st edition of the 2019 WHO Model List of Essential Medicines[50].

Management of septic shock. Use of antimicrobials

See the description in the following section.

3- Management of critically ill patients. Drugs to prevent complications

Antipyretic treatment

According to the findings of a population-based cohort study conducted in hospitalized patients with COVID-19, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) was associated with a significant increase in all-cause mortality, admissions to ICUs, the need for mechanical ventilation, and/or sepsis (primary composite variable analyzed, OR = 1.54; 95% CI: 1.13–2.11). No significant increase in cardiovascular or renal complications was observed (secondary variable, cardiovascular complications: OR = 1.54; 95% CI: 0.96–2.48, or acute renal failure OR = 1.45; 95% CI: 0.49–4.14). The conclusion stemming from the findings of this study is that NSAIDs should be used with caution in hospitalized patients with COVID-19, since the harms associated with their use can outweigh the benefits in this population[71].

In view of the evidence available to date and the aforementioned data, and on the basis of the precautionary principle, this list includes paracetamol, rather than an NSAID, as an antipyretic.

Antimicrobial treatment

The prevalence of coinfections, or concomitant secondary infections, in cases of COVID-19 has not been precisely determined yet, although it appears to be low and to depend on local and endemic factors[38, 75].

Symptoms of secondary bacterial infection in patients with COVID-19 can be similar to those of the underlying viral infection, which hinders its diagnosis. This is indirectly reflected in the high rates of administration of IV antimicrobials in Wuhan: 53% of non-severe cases and >90% of patients who were hospitalized or in the ICU[1, 7-8].

With respect to patients with COVID-19 who experience a secondary bacterial infection, a recent systematic review of hospitalized patients with COVID-19 found that only 8% were reported to have a bacterial or fungal coinfection while in the hospital[8].

As a result, recommendations are based on data extrapolated from other viral pneumonias with potential for bacterial superinfection, on evidence-based guidelines[26] and recommendations, and on other clinical scenarios involving this type of infection (viral pneumonias resulting from influenza[1], pneumonias associated with mechanical ventilation[3], sepsis).

In the presence of acute coinfections, empirical antimicrobial therapy in critically ill adults with COVID-19 who are in an ICU should be based on the clinical diagnosis, time elapsed since admission of the patient to the hospital, diagnosis of sepsis, and local epidemiological data on sensitivity to antimicrobials (community-acquired pneumonia, healthcare-associated pneumonia).

In light of these considerations, recommendations concerning the use of antimicrobials in critically ill patients with COVID-19 with suspected bacterial superinfection concomitant with this viral infection are as follows:

On the initiation of empirical antibiotic therapy:

- In patients with suspicion or diagnostic confirmation of **mild COVID-19**, the recommendation is NOT TO USE antibiotic therapy or prophylaxis (**strong recommendation against its use**)[38].
- In patients with suspicion or diagnostic confirmation of **moderate COVID-19**, the recommendation is not to use antimicrobial therapy unless bacterial infection is clinically suspected.
- In patients with suspicion or diagnostic confirmation of COVID-19 presenting clinically as **severe COVID-19**, the recommendation is to begin with early empirical use of antimicrobial agents to treat the probable pathogens, with reliance on clinical judgment, host-related factors, and local epidemiological trends (**strong recommendation in favor of the intervention**)[38].

On timing and timeliness in the use of antimicrobials and treatment length in seriously ill patients:

- With regard to the timing and timeliness with which antimicrobials should be administered to critically ill patients with COVID-19 and sepsis, empirical antimicrobials should be administered to treat the responsible pathogens **within the first hour** after they are diagnosed[3,5]. In general, the length of treatment with antimicrobials must be as short as possible, depending on clinical course: 5 to 7 days.

On the type of antimicrobial that should be used:

- In general, the majority of patients with severe sepsis and septic shock have some level of immunocompromise, which is grounds for considering initiating treatment with a broad-spectrum antimicrobial class such as carbapenems (e.g., meropenem,

imipenem/cilastatin) or a combination of broad-spectrum penicillins or ß-lactamase inhibitors (e.g., piperacillin/tazobactam). Third-generation (ceftriaxone) or fourth-generation cephalosporins may also be used, especially as part of a combination therapy regimen[26].

- Some patients may have risk factors leading to suspicion of invasive infections with *Candida* spp.[2] If the risk of sepsis from *Candida* spp. justifies empirical antifungal therapy, the choice of the specific agent should be in keeping with the severity of the disease, local patterns for the most common *Candida* species, and any recent exposure to antifungal agents. Empirical use of amphotericin B is a reasonable recommendation in these patients[26].

- On the other hand, in pediatric patients with COVID-19, an estimated 20% has coinfection with *Mycoplasma pneumoniae*, and although this percentage has not been clearly established yet[27], in this population as well as in adults a combination of a ß-lactam antibiotic such as ampicillin plus a macrolide has been used in community-based patients.

On the route of administration:

- **For COVID-19 patients with severe pneumonia**, antimicrobial therapy is administered intravenously[51].

Considerations concerning the treatment of severe pneumonia:

When a patient seeks medical care for suspected pneumonia, pneumonia from COVID-19 and bacterial pneumonia are difficult to tell apart on the basis of clinical features alone[64].

During the COVID-19 pandemic to date, most pneumonias have been viral. The evidence thus far suggests that bacterial coinfection occurs in fewer than 10% of patients with COVID-19. Nonetheless, patients in critical care are at higher risk of bacterial infection than patients in other hospital wards or settings[64].

From the data furnished by the experience of countries where the pandemic began at an earlier date, it can be concluded that, to a greater or lesser extent, up to 20% of the pediatric population and of adults may have coinfection with *Mycoplasma pneumoniae.* For this reason, it becomes necessary to include a macrolide in the therapeutic armamentarium for use in this scenario[27, 52].

In compliance with the WHO recommendation and the prioritized evidence-based guidelines[26, 38, 51, 61, 64], included in this list are antimicrobials for the empirical treatment of patients with severe pneumonia. Empirical treatment should be based on the clinical diagnosis (community-acquired pneumonia, hospital-acquired pneumonia), local

[2] These factors include immunocompromised states (neutropenia, chemotherapy, transplant, diabetes mellitus, chronic liver failure, chronic renal failure), long-term invasive vascular devices (hemodialysis catheters, central venous catheters), total parenteral nutrition, necrotizing pancreatitis, recent surgery (particularly abdominal), prolonged administration of broad-spectrum antimicrobials, prolonged admission to hospital/ICU, colonization.

epidemiological trends, and local bacterial susceptibility. Antibiotics having the lowest ecological impact should be selected in accordance with data and guidelines from one´s own institution, country, or region (choosing antibiotics from the ACCESS group in the WHO categorization is recommended)[38].

In cases of suspected community-acquired bacterial pneumonia, a combination of a ß-lactam antibiotic (ampicillin, amoxicillin-clavulanic acid) and a macrolide (clarithromycin), or of a cephalosporin such as ceftriaxone and a macrolide, are the recommended treatments from among the therapeutic options included.

As an alternative to the use of macrolides, some guidelines suggest using doxycycline (to be avoided during pregnancy) or levofloxacin[51, 64] (which are not included in this list because they offered no additional benefit).

The use of macrolides may be associated with a prolonged QT interval and can intensify the effect of other drugs that might be used to treat infection with SARS-CoV-2. This was seen among patients with COVID-19 who were treated with azithromycin and hydroxychloroquine, since the group that received azithromycin had a longer QT interval (23 [10 to 40] milliseconds) than patients who received hydroxychloroquine only (5.5 [-15.5 to 34.25] milliseconds; $p = 0.03$)[62].

Chorin et al.[63] reported in a prepublication distributed by medRxiv that with the use of hydroxychloroquine plus azithromycin, 30% of the patients showed a prolonged QTinterval, potentially in excess of 500 milliseconds in 11% of cases. It is worth noting that this is a non-peer-reviewed publication and that the study provides no other data that would indicate, for instance, whether patients' plasma levels of K+ were known[63].

Furthermore, of the clinical trials for COVID-19 that have been published to document the characteristics of patients admitted to the hospital for this disease and the prevalence of comorbidities and complications, among other things, very few mention the rate of occurrence of arrhythmias. According to a study from China, published in early February, involving 138 patients infected with the coronavirus who were hospitalized with pneumonia, 16.7% of them suffered arrhythmia as a complication, and 44.4% of these were in the ICU[8].

The WHO Model List of Essential Medicines[50] includes clarithromycin, in the macrolide class of drugs, for the treatment of severe pneumonia in adults and children over 5 when coverage for atypical microorganisms is considered necessary. It does not include azithromycin for this indication pursuant to a review by the expert committee that updated the WHO Model List of Essential Medicines for the year 2017[53], which determined that:

1. analysis of a Cochrane systematic review in patients with community-acquired pneumonia[54] revealed a significantly higher rate of adverse effects with azithromycin than with levofloxacin, and a significantly higher rate of adverse effects with erythromycin than with clarithromycin, but no data was reported for the comparison between clarithromycin and levofloxacin[54].

2. the Food and Drug Administration (FDA) of the United States issued a warning about fatal cardiovascular events (arrhythmias) with azithromycin[55].

It is important to note that in 2018, the FDA[56] also issued an alert on the use of clarithromycin in patients with heart disease, based on data from the CLARICOR clinical trial[57-58].

NICE guidelines on community-acquired pneumonia and the prescription of antimicrobials[59] make reference to the fact that the developing committee discussed the evidence on the effectiveness of azithromycin. However, it determined that because of its long half-life and the resulting greater likelihood of resistance, this drug was a less desirable option than other macrolides and made the decision not to include it among its recommendations.

With due regard to the recommendations and evidence previously presented, priority is given to the use of clarithromycin. This is because, owing to its shorter half-life, it would allow for better management in the treatment of severe pneumonia in cases of severe COVID-19 only when antimicrobial therapy for atypical microorganisms is considered necessary. EKG monitoring of the QT interval while using this drug is recommended.

Furthermore, since local circulation of seasonal influenza is continuous, neuraminidase inhibitor therapy should be considered for the treatment of flu patients who are at risk of becoming gravely ill from COVID-19[3,60].

For this reason, and considering that antimicrobial susceptibility patterns vary locally, it is recommended that the following antimicrobials be included in the list of medicines for the treatment of complications from superinfection in critically ill patients with COVID-19: amikacin, amoxicillin-clavulanate/ampicillin-sulbactam, clarithromycin, amphotericin B, ceftazidime, ceftriaxone, meropenem/imipenem-cilastatin, piperacillin-tazobactam, vancomycin, and oseltamivir[26,28].

Prevention of thromboembolism

Coagulopathy is common among patients with severe COVID-19 and with venous and arterial thromboembolism[38]. It has been associated with inflammation and a prothrombotic state, with increased fibrin, fibrin degradation products, fibrinogen and D-dimer[41-43]. These markers have been associated with less favorable clinical outcomes[43-45].

The incidence of these complications as a function of disease severity has not been completely determined. Among patients in the ICU, the incidence of thromboembolic disease associated with COVID-19 appears to be higher[43, 46-47].

In a prospective, multicentric French cohort study of 150 patients in the ICU, 16.7% developed pulmonary embolism despite prophylactic anticoagulation. Patients with COVID-19 and ARDS had a higher incidence of pulmonary embolism in comparison with patients who did not have ARDS in association with COVID-19[47]. A Dutch study of 184 patients in the ICU reported a cumulative incidence of venous thromboembolism of 27% (95% CI: 17%–32%), despite prophylaxis[48].

A study using routine ultrasound reported an incidence of venous thromboembolism of 69% among patients admitted to the ICU[46].

Pharmacological prophylaxis with low-molecular-weight heparin (such as enoxaparin)[61] is recommended, when not contraindicated, in hospitalized patients (adults and adolescents) with COVID-19 to prevent venous thromboembolism. For those who have contraindications, mechanical prophylaxis (intermittent pneumatic compression devices) is recommended. According to WHO guidelines[38], the recommendation in favor of this intervention is strong.

This guideline also recommends monitoring patients with COVID-19 for signs or symptoms suggestive of thromboembolism, such as stroke, deep vein thrombosis, pulmonary embolism, or acute coronary syndrome. If these are suspected on clinical grounds, appropriate diagnostic and management pathways should be set in motion right away. The recommendation in favor of this intervention is strong[38].

LIST OF ESSENTIAL MEDICINES FOR THE TREATMENT OF PATIENTS ADMITTED TO INTENSIVE CARE UNITS WITH A SUSPECTED OR CONFIRMED DIAGNOSIS OF COVID-19

MEDICINE	DOSAGE FORM AND CONCENTRATION
DRUGS FOR FEVER	
Paracetamol	Injection: 10-ml ampoule with 10 mg/ml or vial containing 50-100 ml
MEDICINAL GASES	
Oxygen	Inhalation. For use in the management of hypoxemia
DRUGS FOR ANALGESIA	
Fentanyl	*Injectable: 5-ml ampoule with 50 µg/ml*
Morphine	Injection: 1-ml ampoule with 10 mg (of sulfate or chlorhydrate)
DRUGS FOR SEDATION	
Haloperidol	Injection: 1-ml ampoule with 5 mg
Lorazepam	Parenteral formulation: 1-ml ampoule with 2 mg/ml; 1-ml ampoule with 4 mg/ml
Midazolam	Injection: 1 mg/ml and 5 mg/ml
Propofol	Injection: ampoule with 10 mg/ml, 20 mg/ml
MUSCLE RELAXANTS	
Atracurium*	Injection: ampoule with 10 mg/ml (besilate) *Vecuronium powder for injection: 10 mg (bromide) in vial, as an option depending on local availability
Succinylcholine	Injection: 2-ml ampoule with 50 mg (chloride)/ml
ADJUVANTS FOR SEDATION	
Atropine	Injection: 1-ml ampoule with 1 mg (sulfate)
ANTIMICROBIALS **(Used to treat coinfections. See note regarding use in accordance with local guidelines.)**	
Amikacin	Injection: 2-ml vial with 250 mg (sulfate)/ml
Amoxicillin + clavulanic acid*	Powder for injection: 500 mg (sodium) + 100 mg (as potassium salt); 1000 mg (sodium) + 200 mg (as potassium salt) in vial. **Ampicillin sulbactam* 1.5 g (ampicillin 1 g, sulbactam 0.5 g); 3 g (ampicillin 2 g, sulbactam 1 g) as an alternative depending on local availability
Amphotericin B	Powder for injection: 50 mg in vial (as sodium deoxycholate or liposomal complex)
Clarithromycin	Powder for injection: 500 mg in vial
Ceftazidime	Powder for injection: 250 mg or 1 g (as pentahydrate) in vial
Ceftriaxone	Powder for injection: 250 mg; 500 mg; 1 g in vial

MEDICINE	DOSAGE FORM AND CONCENTRATION
Meropenem*	Powder for injection: 500 mg (as trihydrate); 1 g (as trihydrate) in vial *Optionally: imipenem + cilastatin 250 mg/250 mg, 500 mg/500 mg, as alternatives depending on local availability
Piperacillin + tazobactam	Powder for injection: 2 g (as sodium salt) + 250 mg (as sodium salt); 4 g (as sodium salt) + 500 mg (as sodium salt) in vial
Vancomycin	Powder for injection: 250 mg (as chlorhydrate) in vial
GLUCOCORTICOIDS	
Hydrocortisone* *Conditional. For specific uses detailed at the bottom of the table	Powder for injection: 100 mg (as sodium succinate) in vial
**Dexamethasone **For specific uses detailed at the bottom of the table	1-ml ampoule with 4 mg/ml (as disodium phosphate)
VASOACTIVE DRUGS	
Dobutamine	Injection: 20-ml ampoule with 5, 10, 25, 50 and 100 mg (as chlorhydrate)
Epinephrine* (adrenaline)	Injection: 1-ml ampoule with 1 mg (as chlorhydrate or tartrate). Injection: 10-ml ampoule with 100 µ/ml (as tartrate or chlorhydrate) First one in children **Vasopressin solution for injection: 20 units/ml as alternative depending on local availability*
Norepinephrine (noradrenaline)*	Injection: 4-ml ampoule with 1 mg/ml *As first choice
VOLUME EXPANDERS (CRYSTALLOIDS)	
Ringer's lactate	Ringer´s with sodium lactate, compound solution. Injectable
Normal saline	Injectable solution: isotonic (0.9%) (equivalent to 154 mmol/L of Na+ and 154 mmol/L of Cl-)
DRUGS FOR COINFECTION WITH INFLUENZA VIRUS	
Oseltamivir*	Capsule: 30 mg; 45 mg; 75 mg (as phosphate). Oral powder: 12 mg/ml *Reserved for severe illness caused by suspected or confirmed coinfection with influenza virus in critically ill hospitalized patients.
ANTICOAGULANTS	
Enoxaparin	Injection: ampoule or prefilled syringe with 20 mg/0.2 ml; 40 mg/0.4 ml; 60 mg/0.6 ml; 80 mg/0.8 ml; 100 mg/1 ml; 120 mg/0.8 ml; 150 mg/1 ml *Alternatives are limited to nadroparin and dalteparin.

MEDICINE	DOSAGE FORM AND CONCENTRATION
ANTACIDS	
Omeprazole	Powder for injection: 40 mg in vial
Ranitidine	Injection: 2-ml ampoule with 25 mg/ml (as chlorhydrate)
ANTIEMETICS	
Metoclopramide	Injection: 2-ml ampoule with 5 mg (chlorhydrate)/ml
Ondansetron	Injection: 2-ml ampoule with 2 mg/ml (as chlorhydrate)
ANTISEPTICS AND DISINFECTANTS	
Alcohol for hands	Solution: contains 75% isopropyl alcohol (isopropanol) or 80% ethanol, volume/volume
Chlorhexidine	Solution: 5% (digluconate)
Iodopovidone	Solution: 10% (equivalent to 1% available iodine)
BRONCHODILATORS	
Ipratropium bromide	Inhalation (aerosol): 20 micrograms/dose
Salbutamol	Inhalation (aerosol): 100 micrograms (sulfate) per dose Injection: 5-ml ampoule with 50 micrograms (sulfate) per ml

- *The drugs or presentations in italics are not part of the WHO Model List of Essential Medicines but were included on the basis of the evidence and recommendations presented herein.*
- **Use of hydrocortisone limited to patients with: (a) respiratory failure and ARDS; (b) COVID-19, in shock and before adding a second vasopressor; (c) COVID-19 and viral pneumonia, only if experiencing exacerbation of asthma or chronic obstructive pulmonary disease (COPD), septic shock or ARDS.*
- ***Dexamethasone: use with proof of efficacy only in critically ill patients with COVID-19 who require supplementary oxygen or assisted ventilation.*

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