Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Severe SARS-CoV-2 infection in critical care

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Contents

1. Introduction

The world recalls with great sadness the last pandemic which resulted in more than 50 million deaths worldwide [1–3]. The influenza A H1N1 infection known as "*Spanish flu*" is estimated to have affected more than 500 million people. Once again, the planet is facing a viral infection of enormous proportions. In December

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Acronyms and abbreviations

ARDS	acute respiratory distress syndrome
RCT	Randomized Control Trial
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
ICU	intensive care unit
WHO	The World Health Organization

2019, in Wuhan, China, SARS-CoV-2 (*severe acute respiratory syndrome coronavirus 2*) was detected, affecting 80,000 people in that country and expected to affect millions around the world [4]. The World Health Organization (WHO) recommends the need to implement early detection strategies for the infection, fostering isolation measures for confirmed cases, and strengthening healthcare systems for a quick and timely treatment of the most severe cases [5]. As this infection develops, 205 countries worldwide have reported positive cases, with mortality rates ranging from 4% to 11%, especially in the adult population [6,7]. In this review, we seek to describe the most important aspects of this severe infection, attempting to condense them in a single document, which will allow the reader to have a global view of the problem.

2. Methodology

Search strategy and article selection: A systematic review literature in all languages was performed through PUBMED, EMBASE (OVID) and Google scholar using the MeSH terms "*SARS-CoV-2*", "*Covid-19*", "*coronavirus*", "*infection*", "*sepsis*", "*ARDS*", "*mechanical ventilation and covid-19*", "*hydroxychloroquine*" and "*covid-19 treatment*", "*critical care*" between December 2019 and April 2020. The descriptors were validated in DecS (descriptors in health science) and MeSH (medical subject headings).

3. Results

The researchers found 6975 articles and selected the ones that were the most relevant: articles that discussed the basic science of the SARS-Cov-2 infection and the clinical aspects related to severity, pathophysiology, and therapeutic options described and studied.

We included articles written in different languages, and all studies in humans and preclinical studies related to the SARS-CoV-2 virus infection.

4. Discussion

4.1. Epidemiology

The first phase of viral dissemination began in December 2019 with a group of patients diagnosed with pneumonia of unknown etiology [5,6]. They all had a history of exposure to seafood and exotic animals at the local market in Wuhan, Hubei Province, China [1,2]. The first case in this city was reported on December 12, and in the following weeks, five cases of respiratory failure secondary to acute respiratory distress syndrome (ARDS) were reported [3]. The next country to have infected patients was Thailand on January 13, 2019 [2], and by the end of that month there were already more than 846 confirmed cases in 29 Chinese provinces and six nearby countries [2,8]. Due to its rapid transmissibility, severity and lethality, WHO declared the novel coronavirus (*SARS- CoV-2 or coronavirus disease-19 or COVID-19*) to be a *Public Health Emergency of International Concern (PHEIC)*, instituting contingency and isolation measures in all countries around the world [5].

The phylogenetic analysis of the virus suggests that bats could be the primary hosts [9]. It has therefore been considered to be a zoonotic disease. However, an animal sold in the seafood market in Wuhan could be an intermediate host that facilitated the appearance of the virus in humans. The pangolin, an exotic animal traditionally eaten in China, has been linked as the probable intermediate host [2,3].

As of Jun 29, 2020, WHO had reported 10,021,401 COVID-19 cases worldwide, with 499,913 fatalities [5]. The United States (US) population has been the most affected, with 2,496,628 infected people and more than 125,318 deaths, to date; New York City being the most affected [10]. The US has surpassed the number of cases reported in Brazil, the Russian Federation and India as the other countries with the highest number of cases worldwide. China, Italy, and Spain: as the countries with the highest number of cases worldwide at that time [5,10,11].

According to the disease's natural history, 81% of patients infected with COVID-19 have a mild illness and do not require hospitalization [7,8], as opposed to 19% of the infected population who have moderate or serious illness and require hospital care [10,11]. An average of 10 days may pass from the onset of symptoms to admission to an intensive care unit (ICU), and an average of two to eight weeks from the beginning of symptoms to a fatal outcome [6,7]. As of March 12, 2020 in the US, 53% of ICU admissions and 80% of COVID-19 related deaths were of patients over the age of 65, with more severe outcomes in the population over the age of 85 [12–14]. The high transmission rate has not just affected the general population, but also a significant percentage of healthcare workers (29% in China, 20% in Italy and 15% in Spain) [8].

The behavior of the disease in children is very different than in adults [11,12,15]. Xiaoxia Lu et al. stated that, according to a China CDC report, in a review of 72,314 cases, fewer than 1% were children under the age of 10 [16]. The median age was seven years, with 18% of cases occurring in children under one year of age and 23% in children between one and five years old. Fever was present in only 42% of children at any time during the illness. Close to 16% may be asymptomatic. In this description, less than 2% of the cases required pediatric intensive care, generally for associated sepsis or ARDS. The risk groups according to this description are patients with comorbidities, especially immunosuppression [11,12,16].

In a retrospective study, Maldonado YA et al. [17] developed the epidemiological profile of 2143 pediatric patients infected with COVID-19 in China. The most serious patients were under one year old and only one death was recorded in this cohort (a 14-year-old boy). The cases of serious illness made up 5% of all infected children, and 0.6% of this population progressed to ARDS and/or multiple organ failure.

In the adult population, WHO has established the following to be factors associated with a worse disease prognosis: age >60 years and comorbidities such as arterial hypertension (HTN), diabetes mellitus, cardiovascular disease, chronic respiratory disease and conditions which cause immunodeficiency. Recently, Guo G et al. [11] described the clinical progression of adults affected by COVID-19. Research in adults has shown that the morbidity (OR 1.12; 95%CI 1.01–1.25), severity (OR 1.63,95%CI 1.28–2.06) and mortality (OR 1.71, 95%CI 1.51–1.93) of males are significantly higher than those of females. This same author confirms the WHO description in which age greater than 60, hypertension, asthma, diabetes and other comorbidities increase the risk of infection. It has been shown that 36.8% of COVID-19 patients have comorbidities. The presence of two or more comorbidities in patients over the age of 60 increases the risk of dying from SARS-CoV-2 infection (OR 3.4, 95% CI 2.63–4.01) [11–14]. Recent studies have found that patients with

type A blood have a higher risk of severe respiratory infection (OR 1.45, 95% CI 1.20, 1.75), and patients with type O blood may have a genetic protective factor (OR 0.65; 95%CI 0.53, 0.79) [15].

Lei et al. in a retrospective study suggest asymptomatic patients receiving elective surgeries during incubation period may accelerate and exacerbate disease progression of COVID-19. Probably because surgery may not only cause immediate impairment immune function, but also induce early systemic inflammatory response, and the subsequent need for intensive care management [12].

The virus's high transmissibility may be analyzed using what is known as the "*basic reproduction number*" or *R0* [18]. The RO is the number of cases in which an infected individual may transit the infection directly in the general population [4,5]. The transmission dynamics have shown that the *R0* of COVID-19 is estimated to be between 1.4 and 3.9 (90% CI 1.4–3.8) [2,8]. For the influenza A H1N1 virus the *R0* index is 1.2 and for SARS it may be 1.3 [5]. However, each country has a specific *R0*, depending directly on the behavior of the virus and the population's isolation measures. Social distancing, preventive isolation of infected cases and the use of personal protective equipment (PPE) for healthcare personnel may contribute to mitigating viral dissemination and reducing the *R0* [5].

4.2. Pathophysiology

Coronaviruses are large viruses with a positive single-stranded RNA genome which contains several constituent proteins interspersed in its lipid layer (Fig. 1) [19–21]. This viral infection is considered to be a zoonotic disease, as previously mentioned, and may cause respiratory, gastrointestinal or neurological symptoms [21]. The SARS-CoV-2 virus is part of the *Coronaviridae* family, which infects humans, and belongs to the *BetaCoronaviruses* (as do SARS-CoV and MERS-CoV) which have an approximately 80% similarity to the SARS-CoV-1 nucleotides [2,22].

Similarities have been found between the "*spike*" proteins (receptor-binding domains) of SARS-CoV-1 and SARS-CoV-2 (Fig. 1) [23–25]. These proteins are essential for invading the cell through their receptor, angiotensin-converting enzyme 2 (ACE2) [14,16,26]. The *S* protein is a trimeric type I transmembrane protein with an N-glycosylation ectodomain that has 60 to 90 carbohydrates per trimer, a transmembrane region and a cytoplasmic tail with a group of S-acylation cysteine residues. This protein has a three-dimensional structure very similar to the *S* protein present in other coronavirus families [2,27,28].

The ACE2 receptor is a type I membrane protein which is expressed in the kidney, heart and gastrointestinal cells, blood vessels and the alveolar epithelium (type 2 pneumocyte – AT2) [29–31]. SARS-CoV-2 infection fosters ACE2 downregulation, causing increased production of angiotensin II, as angiotensin converting enzyme (ACE) generates high angiotensin II type 1a receptor stimulation [31]. The main consequence of this bond is increased pulmonary vascular permeability due to type 2 pneumocyte injury, endothelial compromise and non-cardiogenic pulmonary edema [25].

There are two phases in the immune response clinically induced by SARS-CoV-2 [9]. Initially, there is an innate immune response during the incubation period and in the first stage of the infection which seeks to eliminate the virus and thus avoid progression (Fig. 2) [14,22,31]. To achieve this protective immune response, the

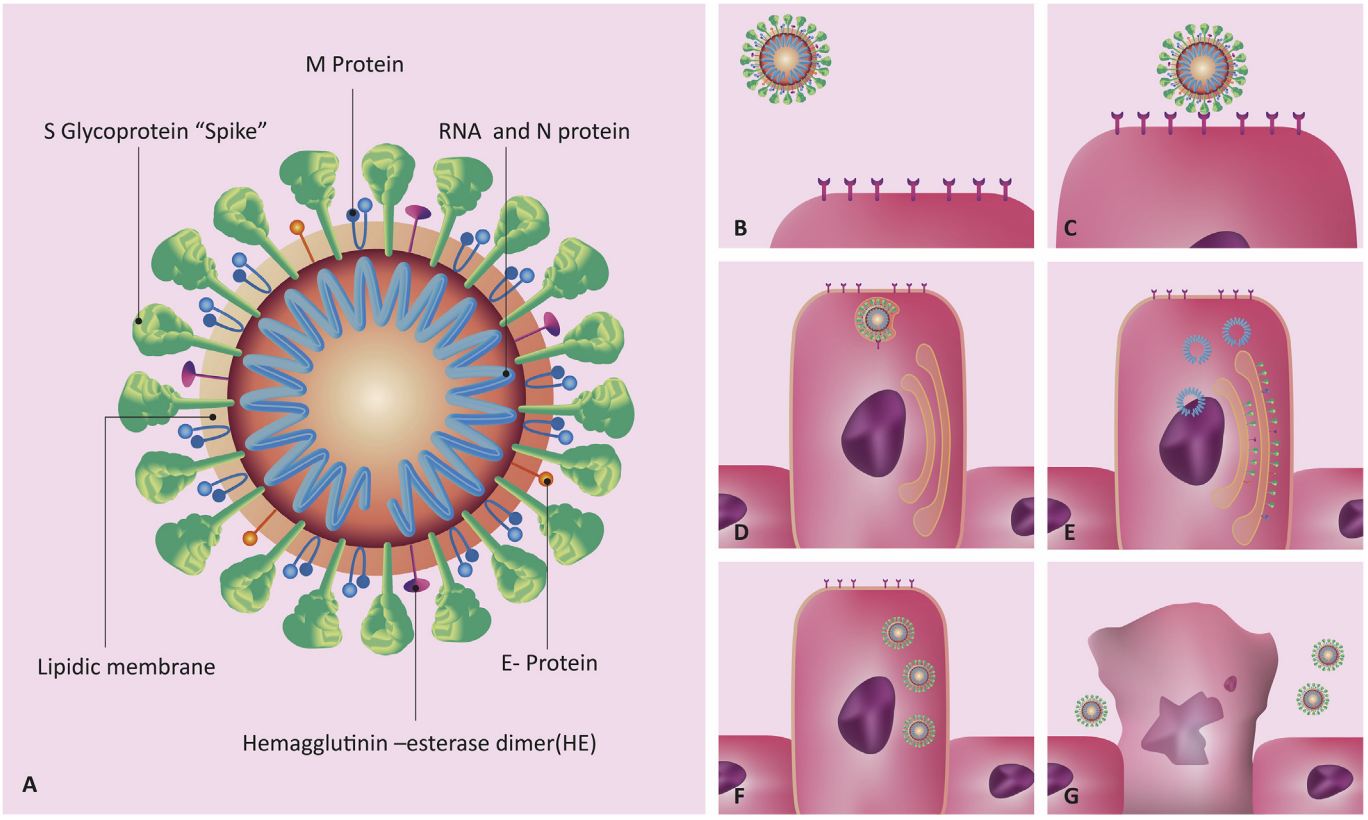

Fig. 1. Structural characteristics and pathophysiology of SARS-CoV-2 viral invasion. A: Structure of the virus. B: Locating the ACE2 receptor, C: Binding to the ACE2 receptor, D: Entering a type II pneumocyte, D: Detaching from the nucleocapsid, E: Using ribosomes to assemble more viruses, F: Newly assembled viruses, G: Exiting to the circulation and host cell destruction.

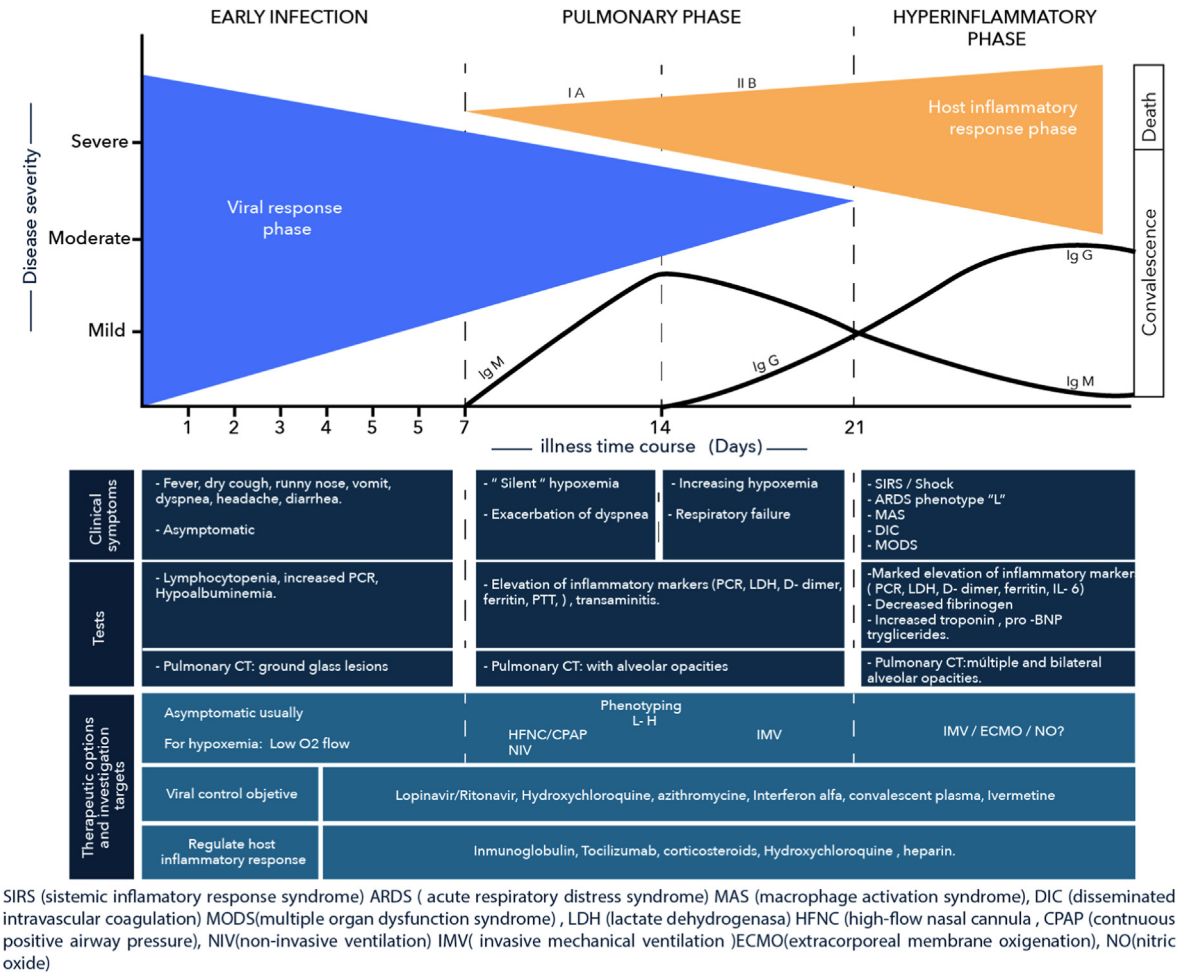

Fig. 2. Summary SARS-CoV-2 infection: diagnosis and treatment.
Abbreviations: SIRS (sistemic in_amatory response syndrome) ARDS (acute respiratory distress syndrome) MAS (macrophage activation syndrome), DIC (disseminatedintravascular coagulation) MODS (multiple organ dysfunction syndrome), LDH (lactate dehydrogenasa) HFNC (high-_ow nasal cannula), CPAP (contnuouspositive airway pressure), NIV(non-invasive ventilation) IMV(invasive mechanical ventilation)ECMO(extracorporeal membrane oxigenation), NO(nitric oxide).

Table 1
Described frequency of clinical manifestations and laboratory and imaging findings in adults vs children (2,12,17,32).

Clinical Manifestation	Adults Frequency	Children Frequency
Cough	57.6%	48.5%
Fever	88.7%	41.5%
Diarrhea	3.7%	8.8%
Rhinorrhea	5.5%	7.6%
Emesis	3.9%	6.4%
Dyspnea	45.6%	
Fatigue	44%	7.6%
Laboratory Tests		
Normal blood count	40%	69.2%
Neutrophilia	8.2%	4.6%
Lymphopenia	43.1%	3%
Elevated CRP	58.3%	13.6%
Elevated procalcitonin	5.5%	10.6%
Elevated LDH	57%	NI
Hypoalbuminemia	88.7%	NI
Viral panel Viral coinfection	6–22%	40%
Imaging		
Ground glass CT	68.5%	33%
CT consolidation with halo sign	NI	50%
Severity		
Mild/moderate	80%	90%
Severe	18.5%	5.2%

host must be immunocompetent and have an adequate genetic load. When there is an inadequate immune response, the virus will replicate, damaging all the tissues involved. A greater impact will be seen on organs with high ACE2 expression such as the lungs, intestine and kidneys [17,31].

An overexpression of proinflammatory cytokines and chemokines (cytokine release syndrome or CRS) has been found in cases which progress to ARDS, with a pattern similar to that of macrophage activation syndrome (MAS) [22,32–34]. In the description of the first cases in China by Nanschan Chen, 63% of the patients had increased ferritin and C-reactive protein (CRP), which are typical characteristics of MAS [18]. These biomarkers increase due to the viral infection stimulating *IL-1B* and *IL-18* which increase ferritin, and *IL-6* which stimulates hepatic synthesis of CRP [33].

Cytokine release syndrome affects patients who have severe pulmonary and systemic compromise, which tends to progress to lymphopenia; therefore, it has been suggested that CRS is mediated by leukocytes other than T cells [17,34]. A cytokine profile similar to that of MAS has been described in most of the serious forms of the disease, which includes high levels of *IL-1B, IL-2, IL-6, IL-7* and *IL-8* interleukins, tumor necrosis factor α (*TNF-α*), *CXC 10* chemokine ligand (*CXCL10*) and *CC2* chemokine ligand (*CCL2*); the modulation of this cytokine storm is one of the biggest challenges facing clinicians during this pandemic [33].

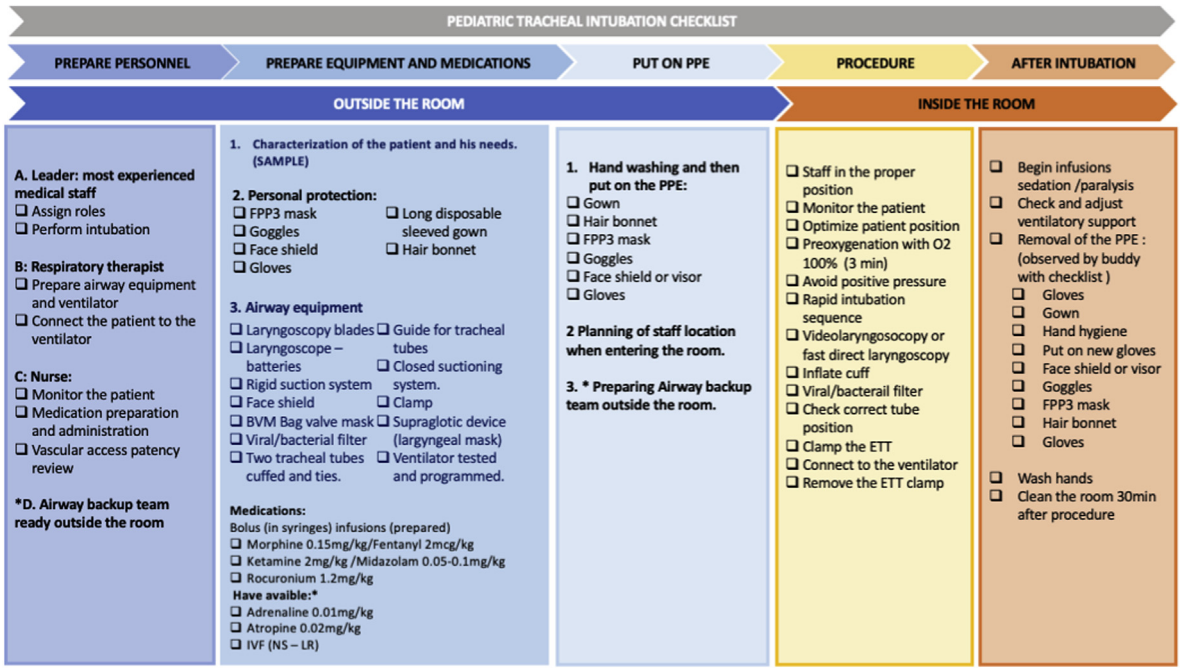

Fig. 3. Steps for oral-tracheal intubation in patients with suspected infection or infection with the SARS-CoV-2 virus.

4.3. Clinical manifestations and diagnosis

The SARS-CoV-2 incubation period is 2–14 days (Fig. 2). Its clinical manifestations are very broad, ranging from asymptomatic patients to those with ARDS and multiple organ failure (18). The initial symptoms may vary between adults and children, as described in Table 1 [12,14)].

The main comorbidities associated with more severe forms are [20,21]: prior cardiovascular disease (OR 3.42, 95% CI 1.88, 6.22), arterial hypertension (OR 2.36 95% CI 1.46, 3.83), elevated procalcitonin in patients admitted to ICU (OR 4.22 95% CI 2.88, 6.17) and diabetes mellitus (OR 2.07 95% CI 0.89, 4.82).

Laboratory findings include lymphopenia in up to 43.1% of patients, and lymphocyte counts lower than 1000/mm^3 are associated with greater severity (35). Acute phase reactants such as CRP and ESR tend to be elevated in 58.3% and 41.8%, respectively [36,37]. The combination of eosinopenia and elevated hs-CRP can effectively be used to facilitate rapid triage and identification of highly-suspected cases from mixed patients presenting with fever and respiratory symptoms, while limited medical resources for nucleic acid tests and radiographic examination [35].

As previously mentioned, elevated procalcitonin is associated with severe forms of the disease and suggests the presence of bacterial coinfection [38]. Complementary tests which explain multisystemic involvement, such as ASAT, ALAT, ferritin, LDH and D-dimer, should be considered [37]. An elevated D-dimer test has been considered to be an independent risk factor for mortality, and in the adult population, troponin elevation was much more frequent in patients who died compared to those who survived (51.2% vs 4.5% $p < 0.001$) [39,40].

Radiology exams are vitally important in the approach to early detection and management of patients with COVID-19 [20,26,29]. Conventional chest x-rays may show bilateral multifocal consolidations and pleural effusion [21,23]. The characteristic finding on chest computed tomography (CT) is the ground glass pattern with a bilateral peripheral distribution, predominantly in the lower lobes [23–25]. Computed tomography has been found to have a sensitivity of 97% and a specificity of 25% for predicting SARS-CoV-2

Table 2
Recommended initial parameters for invasive mechanical ventilation in patients with respiratory failure secondary to the SARS-CoV-2 virus (41,48).

Ventilatory mode	Volume control (VC) or pressure-regulated volume control (PRVC)
Tidal volume (TV)	4–8 ml/kg Monitor the plateau pressure: If > 30 cm H_20, decrease TV.
Respiratory rate	Children from 1 m to 2 years: 22 to 30 bpm Children from 2 to 4 years: 18 to 24 bpm Children over 8 years old: 14 to 20 bpm Adults: 12–20 bpm
Inspiration/expiration ratio (I:E ratio)	1:2
End-expiratory pressure (PEEP)	Optimal according to the patient Initial: 5–8 cm H20 Titrate according to oxygenation, chest x-ray and arterial gases Increase by 2 cm H_20 increments
Fraction of inspired O2 (FiO2)	Begin at 100% and rapidly decrease to less than 60% in the first 2–6 h
Alarms	10% above and below the parameters. Plateau pressure <30 cm H_20, driving pressure <15 cm H20

Table 3
Main specific treatments described for controlling SARS-CoV-2 infection.

TREATMENT	MECHANISM OF ACTION	AUTHOR	DESIGN	PATIENTS	PRIMARY OUTCOMES	CONCLUSION	REGISTERED STUDIES IN CLINICAL TRIALS (50)
LOPINAVIR/ RITONAVIR	Viral protease inhibitor.	Han Zhong, Yan Wang, Zai-Li Zhang et al. [51]	Meta-analysis	5 studies 1 trial Lopinavir/ritonavir 4 trials lopinavir/ritonavir and combinations	Evaluating the efficacy and safety of current option of therapies	Lopinavir/ritonavir combinations might observe better virological eradication capability than other anti-coronavirus agents	*Sung-Han Kim, Asan Medical Center Et al: Comparison of Lopinavir/ Ritonavir or Hydroxychloroquine in Patients With Mild Coronavirus Disease (COVID-19). Seoul Korea. Republic of, 138-736 **Qin Ning, Tongji Hospital Et al:AProspective/ Retrospective, Randomized Controlled Clinical Study of Antiviral Therapy in the 2019-nCoV Pneumonia. Seoul Korea. Wuhan, Hubei, China, 430030. ***Ivan FN Hung, MD FRCP Et al: Lopinavir/Ritonavir, Ribavirin and IFN-beta Combination for nCoV Treatment. The University of Hong Kong
HYDROXY-CHLOROQUINE	• Changes pH endosoma • Stops nucleic acid replication. • Prevents viral entry • via ACE2 binding • Reduction of viral • infectivity • Immunomodulator	Sarma P, Kaur H, Kumar H et al. [52]	Systematic review & Meta-analysis	7 studies (3 studies for meta-analysis)	Presence or absence of the virus on Day 6 of treatment.	Five studies reported either the safety or efficacy. HCQ seems to be promising in terms of less number of cases with radiological progression with a comparable safety profile to control/conventional treatment.	*Pere Domingo, MD, PhD Et al: Clinical Trial of Combined Use of Hydroxychloroquine, Azithromycin, and Tocilizumab for the Treatment of COVID-19 (TOCOVID). Hospital de la Santa Creu i Sant Pau. Barcelona, Spain. **Henrique Fonseca, PhD Et al: Safety and Efficacy of Hydroxychloroquine Associated With Azithromycin in SARS-CoV2 Virus (Coalition Covid-19 Brasil II). ARO-HIAE Academic Research Organization HIAE. Multicenter, Brazil *** Effectiveness and Safety of Medical Treatment for SARS-CoV-2 (COVID-19) in Colombia NCT04359095. Bogotá, Colombia

(*continued on next page*)

Table 3 (*continued*)

TREATMENT	MECHANISM OF ACTION	AUTHOR	DESIGN	PATIENTS	PRIMARY OUTCOMES	CONCLUSION	REGISTERED STUDIES IN CLINICAL TRIALS (50)
IVERMECTIN	Affinity for glutamate-gated chloride ion channels Greater membrane permeability and cellular hyperpolarization.	Leon Caly, Julian D. Druce, Mike G Catton [53]	Preclinical study.	Vero/hSLAM infection with SARS CoV2	Greater than 5000 times in vitro reduction of viral RNA at 24 and 48 h.	Significant reduction of viral RNA in vitro. No clinical studies.	* Max Ivermectin- COVID 19 Study Versus Standard of Care Treatment for COVID 19 Cases. A Pilot Study. NCT04373824. New Dheli, India ** Ivermectin Effect on SARS-CoV-2 Replication in Patients With COVID-19. NCT04381884. Buenos Aires, Argentina
TOCILIZUMAB	IL-6 receptor antagonist, leading to a reduction in cytokine production.	Saeed K.Alzghari, Valerie S.Acuña [54]	Systematic review.	6 studies 4 case-reports papers 2 retrospective papers	Evaluate outcomes associated with TCZ treatment in patients with COVID-19.	Tocilizumab, an IL-6 inhibitor, is a potential supportive treatment for COVID-19. Preliminary investigations are showing benefits with tocilizumab for COVID-19.	*Francesco Perrone, MD, PhD Et al: Tocilizumab in COVID-19 Pneumonia (TOCIVID-19). Multicenter, Italy. **Yikai Yu, M.D. China, Hubei Et al: Tocilizumab vs CRRT in Management of Cytokine Release Syndrome (CRS) in COVID-19 (TACOS). Tongji Hospital. ***Pere Domingo, MD, PhD. Spain Et al: Clinical Trial of Combined Use of Hydroxychloroquine, Azithromycin, and Tocilizumab for the Treatment of COVID-19 (TOCOVID). Hospital de la Santa Creu i Sant Pau - Barcelona, Spain.
CONVALESCENT PLASMA	Neutralizing Antibodies	Rajen K, Krishnasamy N, Rangarajan J et al. [55]	Systematic review	5 studies one pilot study, one preliminary co mmunication, one novel report, o ne case report, one descriptive study one pilot study, one preliminary co mmunication, one novel report, o ne case report, one descriptive study 1 pilot study, 1 preliminary communication, 1 novel report, 1 case report, 1 descriptive study	evaluate the effectiveness of CPT therapy in COVID-19 patients	CPT therapy in COVID-19 patients appears safe, clinically effective, and reduces mortality	*Shanghai, Shanghai, China, 201508 Et al: Anti-SARS-CoV-2 Inactivated Convalescent Plasma in the Treatment of COVID-19. China, Shanghai Shanghai Public Health Clinical Center ** Convalescent Plasma for Patients With COVID-19: A Pilot Study (CP-COVID-19) NCT04332380. Bogotá, Colombia *** Convalescent Plasma for Patients With COVID-19: A Randomized, Open Label, Parallel, Controlled

REMDESIVIR	nucleotide analogue prodrug that inhibits viral RNA polymerases	Jonathan Grein, Norio Ohmagari, Daniel Shin et al. [59]	Cohort compassionate-use	61 adult patients	describe outcomes in a cohort of patients hospitalized for severe Covid-19 who were treated with remdesivir on a compassionate-use basis	clinical improvement was observed

Clinical Study (CP-COVID-19) NCT04332835. Bogotá, Colombia
*Multicenter, Retrospective Study of the Effects of Remdesivir in the Treatment of Severe Covid-19 Infections (REMDECO-19) NCT04365725 – Paris, France
** Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19) NCT04292899. California – USA
*** Treatments for COVID-19: Canadian Arm of the SOLIDARITY Trial (CATCO) NCT04330690. Canada

infection [26] (Fig. 2).

Reverse transcription polymerase chain reaction (RT-PCR) is considered to be the gold standard for detecting SARS-CoV-2. This test may be obtained from different samples with variable sensitivity. The one with the highest yield tends to be bronchoalveolar lavage (93%), followed by bronchial aspiration (72%), sputum samples (63%), nasal swabs and pharyngeal swabs (32%) [27–29]. For diagnostic stratification, a second RT-PCR test is recommended 72 h later in patients with an initially negative result [27,28].

4.4. Treatment

The initial treatment should be symptomatic, aimed at ensuring rest, adequate hydration, temperature control and optimal nutritional support [41,42]. Likewise, the use of the WHO-recommended PPE is essential, along with appropriate donning and doffing, especially when performing procedures which produce aerosols [5] (Fig. 3).

4.5. Nutritional support

Patients with COVID-19 infection need an adequate supply of macro and micronutrients to help strengthen their immune system [9]. B-complex, especially *vitamin B3,* has a significant inhibitory effect on pulmonary neutrophil infiltration and an antiinflammatory effect on the respiratory system [43]. *Vitamin C,* which is important in supporting immune function and antioxidant effects, may be useful in COVID-19 infection [43,44]. *Selenium* deficiency not only deteriorates the host immune response, but could also foster rapid viral mutation, increasing its virulence [43]. Zinc, in turn, is essential for maintaining and developing immune cells both in the innate as well as the adaptive response; thus, increasing intracellular zinc concentrations could efficiently interfere with the replication of a variety of RNA viruses [45].

4.6. Oxygen therapy and mechanical ventilation

Oxygen therapy is one of the pillars of treatment for patients with hypoxemia associated with COVID-19 infection [41]. Worsening hypoxemia is an important warning sign which must be strictly monitored [22]. Correction should be implemented promptly using high or low flow systems, according to each individual's needs [46].

Low-flow nasal cannulas are adequate, especially for individuals with mild hypoxemia [41]. High-flow nasal cannulas (HFNC) have been reported to be successful in COVID-19 patients with moderate to severe hypoxemia [46], since they provide higher FiO2s, high flows and mild positive end-expiratory pressures, which lead to adequate oxygenation and ventilation [41,46]. If this type of therapy is selected, the patient should be placed on an N95 (FF3) respirator to decrease the risk of dispersing contaminating aerosols. When using this therapy, it is important to closely evaluate clinical deterioration to advance with interventions. Persistent hypoxemia (Pa02/Fi02 < 200 or Sa/Fi < 264), increased need for oxygen or worsening tachypnea are indications for considering invasive mechanical ventilation in patients on HFNCs [41].

Early invasive mechanical ventilation has been proposed to decrease respiratory effort, facilitate cardiovascular performance and optimize oxygen delivery to the tissues in patients with respiratory failure secondary to COVID-19 infection [47]. It is recommended that invasive ventilatory support not be delayed, since this delay has been associated with increased mortality [41]. Oral-tracheal intubation should be performed safely, using adequate PPE for the healthcare personnel, and preparing the airway equipment and medications beforehand, as described in Fig. 3.

Once an advanced airway has been achieved, protective mechanical ventilation should be initiated, which involves strategies aimed at decreasing ventilator-induced lung injury (VILI) [39,40]. Table 2 summarizes the recommended parameters for initiating mechanical ventilation in all age groups. It is important to emphasize that, given the virus's high transmissibility, inspiratory filters should be installed to avoid aerosol dispersion [41].

The PRONE position is a key part of treatment for patients with moderate to severe ARDS who need oxygen therapy or mechanical ventilation support [47,48]. It should be started in all patients with a Pa02/Fi02 less than 150 mm Hg, for periods of 12–16 h a day. According to the availability of equipment and PPE, some Spanish centers have established *"programmed protonation"* teams who go from patient to patient changing their position in order to optimize the strategy. This has been especially useful in adults and obese patients [41].

The hypothesis proposed by Gattinoni et al. [49] after observing multiple ventilated patients during this pandemic is that COVID-19 pneumonia is a specific entity, despite meeting the Berlin definition for ARDS. It has distinctive characteristics such as severe hypoxemia, often associated with an almost normal respiratory compliance in more than 50% of cases. They also describe a phenotype that depends on three elements: 1) the severity of the COVID-19 virus infection, the host response and comorbidities; 2) the ventilatory response of the hypoxemia; and 3) the time elapsed between the beginning of the infection and being seen at the healthcare center. Thus, the interaction of these three elements leads to the appearance of a time-related disease spectrum within two phenotypes: type **L** (low) and type **H** (high) (Fig. 2).

Initially, phenotype **L** is seen, in which the patient's lung elastance is low, compliance is close to normal, there is a low ventilation/perfusion ratio (due to a loss of perfusion and hypoxic vasoconstriction regulation), there is low lung weight (only ground glass densities may be visible on CT) and there is low lung recruitment (since there are few non-aerated areas) [49]. Subsequently, as the disease progresses, it transitions to the following phenotype, with predominance of increased progression of pulmonary permeability due to the growing inflammatory process leading to interstitial edema. This causes increased lung weight and superimposed pressure, and dependent atelectasias begin to be seen. This progression leads to decreased gas volume, giving way to the next phenotype, **H**. This phenotype develops as a result of the progression of the disease and the injury attributed to high ventilatory stress. The **H** phenotype is characterized by high elastance, a high right to left shunt, high lung weight and high capacity for lung recruitment.

4.7. Specific treatment

This treatment is aimed at preventing viral entry into the cell, limiting its replication or treating the inflammatory response and all the ongoing pathophysiological processes. The evidence is under construction and there are currently close to 400 registered *Randomized Clinical Trials* to evaluate different management alternatives [50]. Table 3 summarizes the main medications described, their mechanism of action and the studies in progress [51–55].

4.8. Prognosis and clinical outcomes

The reported mortality rate for COVID-19 infection ranges from 4 to 11% in adult patients and is 0.2% in children [8,56]. Eighty percent of the deaths in China occurred in patients over the age of 60, with only 0.1% in those under 19 years old [57]. In a retrospective study, Zhou et al. [58] found that the main factors associated with mortality were: a high SOFA (OR 6.14 95% CI 3.48, 10.85), coronary disease (OR 5.40 95% CI 0.96, 30.40), arterial hypertension (OR 3.05 95% CI 1.57, 5.92) and age over 65 years. The risk of dying increases for every year over the age of 65 (yearly increase OR 1.10 95% CI 1.03, 117). This same study found other factors associated with greater mortality, such as COPD (OR 5.40 95% CI 0.96, 30.40) and a history of smoking (OR 2.23 95% CI 0.65, 7.63), but conclusions could not be drawn due to a lack of precision in the studies [59–61].

5. Conclusions

SARS-CoV-2 virus infection is characterized by high transmissibility and lethality, especially in at-risk groups. Its widespread dissemination worldwide has overwhelmed most healthcare systems. The symptoms are predominantly respiratory, which in severe cases progress to hypoxemic respiratory failure. It is essential to use PPE when caring for these patients, and supportive care, including early initiation of invasive mechanical ventilation, is the pillar of treatment. Various medications are being studied to attack the virus at various stages of its invasion and modulate the inflammatory response it produces. An effective treatment must be quickly developed to control and modulate this terrible pandemic.

Ethical approval

Not required.

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Authors contributions

Drs. FS, LA, HM conceived the idea for the manuscript. Drs. JFS, LA, HM, SB, MS, ND, SC, ABQ, OM, AP and JUL carried out the systematic literature review and designed the figures that represent the virus. All the authors drafted the manuscript and contributed significantly to the article revision. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. None of the researchers have conflicts of interest to declare.

Declaration of competing interest

The authors have disclosed that they do not have any potential conflicts of interest.

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