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ARTICLE OF REVISION

Guidelines on the Diagnosis, Treatment and Isolation of Patients with COVID-19

Orientações sobre Diagnóstico, Tratamento e Isolamento de Pacientes com COVID-19

Directrices sobre diagnóstico, tratamiento y aislamiento de pacientes con COVID-19

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This document was developed aiming to present a collection of the knowledge acquired to date, which can guide the diagnostic approach of COVID-19, as well as information on the isolation of patients and health professionals, in addition to comments on what evidence there is about treatment until now.

This document was prepared with the effective collaboration of the scientific societies mentioned above.

SUMMARY

Executive summary on the consensus among the experts collaborating on this document:

- To assist both in the diagnostic suspicion of COVID-19 and in the differential diagnosis, it is necessary to have knowledge about viral etiologies of Pneumonia / SARS (Severe Acute Respiratory Syndrome), as well as epidemiological data. If available, the ideal situation would be to perform the viral panel in all cases of SARS, including SARS-CoV-2 screening.
- It is possible to have SARS-CoV-2 and other respiratory virus co-infection. It is possible for SARS to be caused by viruses other than SARS-CoV-2.
- It is a consensus among the specialists participating in this document not using chest computed tomography exclusively for the diagnosis of COVID-19, nor using this test as a parameter to remove the patient from isolation. It is neces-

sary to adequately contextualize the tomographic findings with the clinical picture and molecular and / or serological tests, when available.

- To define a diagnosis of COVID19, it is necessary to be guided by the clinical-epidemiological information + RT-PCR and/or serological tests, when available and validated + computed tomography, which must be carefully considered in order to establish the diagnosis.
- The appropriate interpretation of diagnostic tests requires knowledge of symptom onset, as well as the pre-analytical test conditions, methodology used and the time of collection in relation to symptom onset.
- If the pre-analytical conditions are optimal, as well as the timing of the test, RT-PCR is considered the gold standard method.
- The RT-PCR test has a sensitivity of around 63%, when collected with a nasal / oropharynx swab. Therefore, a negative RT-PCR result does not rule out the diagnosis of COVID-19. Taking into account the clinical criteria, consider repeating it and / or performing a serological test, the latter from the 2nd week of symptom onset.
- Serological tests can help but are more sensitive after 7-9 days from symptom onset. To date, there are no validated tests that can be safely used. Disclosure of this information to the general population who will have access to the test is mandatory.
- Precaution and isolation measures for suspected or confirmed in-hospital cases must be maintained until hospital discharge. If it is necessary to discontinue the isolation before discharge, a strategy based on two negative RT-PCR tests, with an interval of at least 24 hours between them, associated with the resolution of fever and respiratory symptoms can be used. In the absence of the test, a strategy based on the resolution of fever in the last 72 hours without the use of antipyretic drugs can be used, in addition to improvement in respiratory symptoms, considering the respiratory isolation period of 14 days after symptom onset.
- All patients with a cold or "flu-like syndrome" should remain in respiratory isolation for 14 days, as COVID-19 should be suspected. Those in contact with these patients must also remain in respiratory isolation for 14 days. If another virus is diagnosed in the laboratory (example, positive result for influenza and negative for COVID-19), respiratory isolation should be carried out according to the isolated virus.
- Regarding treatment, there is no drug available to date that has demonstrated efficacy and safety in the treatment of patients with SARS-CoV-2 infection. Studies are ongoing and any medications used for the purpose of treatment must be administered under a clinical protocol through the application of the free and informed consent form.
- Caution should be exercised when using chloroquine or hydroxychloroquine in combination with azithromycin, as it may increase the risk of cardiac complications, probably due to the synergistic effect of QT-interval prolongation.

I - Considerations on the Etiological Diagnosis of Viral Pneumonias and SARS (Severe Acute Respiratory Syndrome)

(Dr. Clóvis Arns da Cunha)

Etiology of Community-Acquired Pneumonias

The last 10 to 15 years have taught us that respiratory viruses are "not only" the causes of upper airway infections (pharyngitis, rhinosinusitis, laryngitis), but also of lower airway infections, including bronchiolitis, bronchitis, pneumonia and even SARS, which correspond to cases of severe pneumonia that lead to respiratory failure, requiring mechanical ventilation and showing high lethality.[1,2] In addition to the coronavirus epidemics, the influenza viruses, highlighting the H1N1 virus in 2009, are the main respiratory viruses that cause SARS. Other respiratory viruses, such as RSV – Respiratory Syncytial Virus – and rhinoviruses also cause community-acquired viral pneumonia.[1]

It is important to emphasize that, even using the most up-to-date diagnostic tests of Modern Microbiology, with a primary focus on viral and bacterial screening, a study showed that it was not possible to define the etiological diagnosis in 62% of 2,259 hospitalized American patients with community-acquired pneumonia. In 38%, one pathogen was isolated. It is noteworthy that, in 23% of the total number, one or more viruses were isolated; in 11% of cases a bacterium was isolated; 3% had a virus + bacteria co-infection; and 1% had a fungal or mycobacterial infection. Among the most frequently isolated pathogens, the following stand out: Rhinovirus in 11% of all patients, influenza virus in 6%, and Streptococcus pneumoniae (pneumococcus) in 5%.[2]

This study is very important considering the current pandemic of the new coronavirus (SARS-CoV-2), as we have to expect that it will not be possible to define the etiological diagnosis in many cases of pneumonia and SARS.

Several coronaviruses, first discovered in poultry in the 1930s, cause respiratory, gastrointestinal, liver and neurological disease in animals. To date, seven coronaviruses have been found to cause disease in humans.[3]

Four of these seven coronaviruses most commonly cause symptoms of the common cold. Coronaviruses 229E and OC43 cause the common cold; two new serotypes, NL63 and HUK1, have also been associated with the common cold. Rarely, severe infection of the lower respiratory tract occurs, such as pneumonia, especially in children, the elderly and immunocompromised patients.

However, three of the seven coronaviruses are related to much more severe respiratory infections in humans, which are sometimes fatal, and have caused / are causing major outbreaks of fatal pneumonia in the 21st century, namely:[4]

SARS-CoV-2 is the new coronavirus identified as the etiological agent of the disease caused by the coronavirus 2019 (COVID-19), which started in Wuhan, China, in late 2019 and has since then spread worldwide. Until April 5, 2020, a total of 1,237,420 cases have been confirmed in the world, with 67,260 deaths (5.43% case-fatality rate), with 10,361 cases in Brazil, with 447 deaths (4.31% case-fatality rate). It should be noted that the case-fatality rate is lower than that previously seen in countries that test less severe patients (patients with a cold and "flu-like syndrome", without pneumonia).[4,5]

Mers-CoV The Middle East Respiratory Syndrome was initially identified in April 2012 in Saudi Arabia, and later in other countries in the Middle East - Qatar, United Arab Emirates and Jordan. Other cases identified outside the Arabian Peninsula, including some cases in Europe and Africa, had a history of travel or recent contact with travelers from countries in the Middle East. As of May 22, 2014, when the number of cases decreased substantially, 681 cases had been confirmed in laboratories by the WHO (World Health Organization) with 204 deaths (case-fatality rate of approximately 30%). No cases were reported in Brazil.[4]

SARS-CoV was first identified in China in late 2002 as the cause of an outbreak of severe acute respiratory syndrome (SARS). Between 2002 and 2003, 8,000 cases were reported (mostly in China), with approximately 800 deaths (10% case-fatality rate). No cases were reported in Brazil.[4]

II - Considerations about the Clinical Diagnosis

(Dra. Cláudia Fernanda de Lacerda Vidal, Dra. Cláudia Maio Carrilho, Dr. Ricardo Martins, Dr. Rogean Rodrigues Nunes, Dr. Luis Antonio dos Santos Diego, Dr. Clóvis Arns da Cunha)

Executive summary on clinical diagnosis:

- The incubation period is up to 14 days, with an average of 4 to 5 days.
- Signs and symptoms include fever (83% -99%), coughing (59-82%), asthenia (44-70%), anorexia (40%), myalgia (11-35%), dyspnea (31-40%), respiratory secretion (27%), loss of taste and / or smell (more than 80%). Dyspnea should be a warning sign, and digital oximetry should be checked and, if altered, arterial blood gases should be collected.
- The mean age of pneumonia cases is between 47 and 59 years.
- The clinical presentation can vary from mild to moderate disease, which includes "flu-like syndrome" and mild, without the need for oxygen therapy or hospitalization and may represent approximately 80% of symptomatic cases; severe illness occurs in approximately 15% of cases, which include patients with pneumonia and hypoxemia, and require hospitalization; critical illness with respiratory failure (need for mechanical ventilation - MV), septic shock and multiple organ dysfunction occurs in 5%.

- **Clinical Classification of COVID-19**
  - **Asymptomatic:** only serological tests, mainly IgG, performed in a large part of the population will allow us to say what percentage of the population has been infected, without becoming ill. These tests are currently being validated in Brazil.
  - **Moderate to mild disease:** characterized by a clinical picture of a common cold, flu-like syndrome or mild pneumonia, without the need for oxygen therapy or hospitalization. They represent about 80% of symptomatic patients and vase fatality is around 0.1%, when it occurs in young individuals without risk factors for complications. Depending on the age group (elderly) and comorbidities (heart disease, diabetes, neoplasia, pneumopathy) the risk of progressing to severe illness increases.
  - **Severe disease:**
    - *In adults:* fever and / or respiratory infection, plus respiratory rate of 23 breaths per minute, dyspnea and / or oxygen saturation <93% in ambient air;
    - *In children:* coughing or difficulty breathing, plus central cyanosis or SatO2 <90% or severe dyspnea (moaning and / or intercostal retraction)*. These patients require hospital oxygen therapy and often have underlying disease decompensation and / or persistent fever, but without the need for intensive care. They represent about 15% of symptomatic patients. *One should pay attention to the warning signs in infants and children: difficulties in breastfeeding or when drinking fluids, lethargy or reduced level of consciousness, or seizures. Also pay attention to other signs of pneumonia, such as tachypnea (<2 months: ≥60bpm; 2-11 months: ≥50bpm; 1-5 years: ≥40bpm).
  - **Critical illness:** these are patients with severe respiratory failure due to hypoxemia who require mechanical ventilation (ARDS, acute respiratory distress syndrome) and / or patients in septic shock. They represent about 5% of symptomatic cases and case fatality, depending on age and comorbidities, can reach 50%.
    - *In adults:*
    - Mild ARDS: PaO_2 >200mmHg and ≤300mmHg
    - Moderate ARDS: PaO_2 >100mmHg and ≤200mmHg
    - Severe ARDS: PaO_2 ≤100mmHg
    - When PaO2 is not available, SpO_2/FiO_2≤315 suggests ARDS
    - *In children:*
    - NIV or CPAP: PaO_2 ≤300mmHg or SpO_2/FiO_2≤264
    - Mild ARDS: OI*≥4 e <8 or OSI*≥5 and <7.5
    - Moderate ARDS: OI≥8 and <16 or OSI≥7.5 and <12.3
    - Severe ARDS: OI≥16 or OSI≥12.3
    - * OI: Oxygenation Index and OSI: Oxygenation Index using $SatO_2$. Use OI whenever PaO_2 is available. If using OSI, adjust FiO_2 to $SatO_2$≤97% to calculate SpO_2 / FiO_2.

- **Complications of severe COVID-19 disease**
  - **Sepsis:** signs of organ dysfunction such as altered mental status, respiratory failure and hypoxia, renal failure, arterial hypotension, laboratory evidence of coagulopathy, thrombocytopenia, acidosis, hyperlactatemia, hyperbilirubinemia.
  - **Septic Shock:** persistent hypotension regardless of volume resuscitation, requiring vasopressors to maintain mean arterial pressure (MAP) ≥ 65 mmHg and serum lactate >2 mmol / L.
- Risk factors for severe disease: elderly individuals, cardiovascular disease, diabetes mellitus, SAH, chronic pulmonary disease, chronic kidney disease, neoplasms.
- The hospitalization rate is of 19%.
- Among the laboratory findings, lymphocytopenia is present in 83.2% of patients, thrombocytopenia in 36.2% and leukopenia in 33.7%.
- In children, symptomatic infection seems uncommon, and usually occurs with mild clinical pictures.
- 30 to 50% of SARS-CoV-2 transmissions occur from pre-symptomatic or oligosymptomatic individuals; the magnitude of asymptomatic transmission is uncertain.
- Pneumonia represents the most severe manifestation of the infection, with dyspnea occurring between the 5th and 10th day of illness.
- The elderly and individuals with comorbidities may develop fever and respiratory symptoms later and should be monitored.
- Worse clinical outcomes are related to the progression of lymphopenia, increase in the levels of transaminase, C-reactive protein, ferritin, D-dimer >1mcg / mL, elevation of troponin, creatine phosphokinase (CPK), and changes in renal function.
- The case-fatality rate for symptomatic patients is around 2.3%, and it can reach 49% in critically-ill patients.
- Case fatality may vary according to the number of cases being tested. In countries where patients with mild to moderate cases are tested, the case-fatality rate is lower (less than 2%). On the other hand, in countries where only severe and critically-ill cases are tested, case fatality rates increase to 10-12%.
- The interval during which the individual with COVID-19 remains infected is uncertain, but RNA levels seem to be higher soon after symptom onset, with a greater likelihood of transmission in the initial period of the disease.
- The viral load decreases over time and becomes negative between the 9th and 14th day of illness, except in critically-ill patients.
- Patient recovery can range from two weeks for mild cases to three to six weeks for severely-ill patients.

Introduction

In early December 2019, the first cases of pneumonia of an unknown etiology were identified in the city of Wuhan, in the Hubei province, in China. The pathogen was identified as a new enveloped RNA virus, classified as a beta coronavirus, currently called "Severe Acute Respiratory Syndrome-Related Coronavirus 2 (SARS-CoV-2)", with phylogenetic similarity to SARS-CoV. Cases of respiratory infections have been documented in hospitals and in the community. The disease caused by SARS-CoV-2 was then called Coronavirus Disease 19 (COVID-19) and declared by the World Health Organization (WHO) as an International Public Health Emergency.[6] Considering the rapid spread of the virus observed in China and the increase in the number of cases, a cohort was organized to identify the clinical characteristics, aiming to support the clinical diagnosis of the infection.

Incubation Period

Data from the first 425 confirmed cases of Pneumonia by SARS-CoV-2 show an average incubation period of 5.2 days, which can extend up to 12.5 days. Subsequent studies have shown an incubation period of up to 14 days following exposure, with the majority occurring between 4 and 5 days .[7,8]

Based on a modeling study on transmission data, it was estimated that symptoms develop in 2.5% of infected individuals within 2.2 days, and in 97.5% of infected individuals within 11.5 days. The mean incubation period was 5.1 days.[9]

There is evidence of transmission during the incubation period, in which the disease is mild or non-specific.[6,10]

Four possible sources of transmission have been described, either by droplets, contact spread or aerosol:[8]

1. Transmission by symptomatic individuals;
2. Pré-symptomatic transmission;
3. Asymptomatic transmission;
4. Transmission through contaminated surfaces.

It is suggested that between 30 to 50% of transmissions occur from individuals during the pre-symptomatic period (48% in Singapore, 62% in Tianjin, China and 44% in other countries). When transmission occurs before symptom onset, it becomes difficult to control the epidemic by isolating the symptomatic individuals only. Transmission by asymptomatic individuals and the one mediated by a contaminated environment remains uncertain.[11]

The rate of transmission from a symptomatic individual varies according to the location and respective measures for infection control, ranging from 1% to 5% among the thousands of intimate contacts of confirmed cases in China, or attack rate of 0.45% in the USA.[8,12,13]

Epidemiological Characteristics

Data from the first 425 confirmed cases of Pneumonia by SARS-CoV-2 showed a mean age of 59 years, ranging from 15 to 89 years and a predominance of the male gender (56%).[5,8,12,14,15]

Análise publicada posteriormente, referente a um total de 1099 pacientes com COVID-19 confirmados laboratorialmente, provenientes de 552 hospitais em 30 Províncias da China apontaram média de idade de 47 anos, variando de 35 a 58 anos, e 0,9% abaixo de 15 anos de idade, com 41,9% dos pacientes do sexo feminino.[7,8,16]

A subsequently published analysis, referring to a total of 1,099 laboratory-confirmed COVID-19 patients from 552 hospitals in 30 provinces of China showed a mean age of 47 years, ranging from 35 to 58 years, with 0.9% younger than 15 years old, with 41.9% of female patients.[7,8,16] Of all the patients, 23.7% had at least one pre-existing disease (SAH and COPD).[9,17] Around 3.5% were health professionals.[18] The infection in children seems to be less frequent and, when it occurs, it should develop with mild symptoms.[19]

Clinical Characteristics

The clinical picture of the infection ranges from oligo / asymptomatic cases to severe pneumonia, including Severe Acute Respiratory Syndrome (SARS) and Shock.

The frequency of asymptomatic infections is not known, which may still have clinical changes such as atypical pulmonary infiltrate pattern on chest computed tomography (20%) or ground-glass opacity pattern infiltrates (50%).[2,9]

A study evaluating 131 patients with flu-like syndrome in an emergency center in California, United States, identified 7 patients positive for SARS-CoV-2, which represented 5.3%, with a mean age of 38 years, mean symptom duration of 4 days6, which included fever, myalgia and coughing; all patients had mild disease and had negative tests (PCR-GeneXpert) for influenza and respiratory syncytial virus.

For the symptomatic clinical forms, of 1,099 patients with laboratory-confirmed COVID-19 from 552 hospitals in 30 provinces of China, fever was present in 43.8% of patients on admission, but developed in 88.7% of them during hospitalization. The second most common symptom was cough (67.8%); nausea or vomiting (5.0%) and diarrhea (3.8%) were less common. Other less common symptoms include headache, sore throat and rhinorrhea.[5]

Disorders of olfaction and taste, such as anosmia and dysgeusia, have been reported in 19% of cases of COVID-19, but there are no subsidies to consider them a particular characteristic of the disease.[7,9]

Pneumonia represents the most severe clinical manifestation of the infection, characterized by fever, cough, dyspnea and pulmonary infiltrates present bilaterally on imaging studies. Patients with pneumonia develop dyspnea after an average of 5 days from symptom onset, which can reach up to 8 days. There are no specific signs or symptoms that can differentiate COVID-19 from other viral respiratory infections.[20]

The most frequent signs and symptoms are described, recorded among 138 patients infected with pneumonia: fever (99%), asthenia (70%), dry cough (59%), anorexia (40%), myalgia (35%), dyspnea (31%) and respiratory secretion (27%). Fever may not be present in all cases.[7]

Atypical presentations have been described in elderly individuals and with comorbidities, which may show a delay in the presentation of fever and respiratory symptoms.[6]

The mean age of hospitalized adults ranged from 49 to 56 years in Wuhan, while in China, 87% of those hospitalized were between 30 and 79 years old.

The patient's physical examination may show no alterations. The presence of tachydyspnea (respiratory rate above 20 breaths per minute), crackles on respiratory auscultation, tachycardia and cyanosis are warning signs that can raise the possibility of a more severe clinical condition, such as Pneumonia or Severe Acute Respiratory Syndrome (SARS).[20]

Other signs of severity are arterial hypotension and oxygen saturation levels < 95%. This reassessment should be made initially by telephone contact, if possible, as a way to prevent the patient from leaving the home isolation period. It is worth noting the dissociation observed between the dyspnea complaint and the measured oxygenation. Most of the time, the hypoxia is greater than that perceived by the patient, making it important to use oximetry as an objective follow-up measurement.[20]

Children

The presence of symptomatic infection seems uncommon, and children usually have mild clinical conditions, although a severe form has been reported. About 2 to 6.3% of infected patients are under 20 years of age. Data from children hospitalized in China showed mild clinical conditions, characterized by fever, coughing and sore throat, and occasionally mild viral pneumonia. 94% of the children had asymptomatic, mild or moderate forms of the disease; 5% had the severe form and <1% had a critical clinical condition.[4,19]

Suspected Case

Clinical suspicion should be raised for cases of fever and/or respiratory tract symptoms in individuals that live in or are coming from areas with community transmission or close contact with a suspected or confirmed case for COVID-19. This is true also for cases of patients with severe respiratory disease when no other etiological agent has been identified.

Clinical categorization

Of a total of 1,099 patients with COVID-19, the clinical categorization at admission showed that 926 (84%) patients had the mild form of the disease, while the severe form was observed in 173 (16%) patients. Patients with more severe forms were at least 7 years older when compared to those who developed the milder forms of the disease (38.7% x 21%). The hospitalization rate is 19%.[7]

The severity spectrum of COVID-19 ranges from mild clinical conditions (in most cases) to severe forms requiring intensive care. According to data from the Chinese Center for Disease Control and Prevention, which included 44,500 confirmed infections, we can have mild disease without or with mild pneumonia in 81% of cases; severe disease in 14% of cases that require hospitalization and critical illness with respiratory failure (need for mechanical ventilation - MV), shock and multiple organ dysfunction in 5% of cases.[9]

Risk factors for severe disease include cardiovascular disease, diabetes mellitus, SAH, chronic pulmonary disease, chronic kidney disease, neoplasms. Individuals from any age group can have Severe Acute Respiratory Syndrome due to coronavirus 2 (SARS-CoV-2), although it is more common in middle-aged and elderly adults. Age is an important risk factor for severe illness, complications and death.[7,17]

Therefore, the clinical syndromes associated with COVID-19 can be classified as follows.[2,9,21]

Clinical Classification of COVID-19

- **Asymptomatic:** only serological tests, mainly IgG, performed in a large part of the population will allow us to say what percentage of the population has been infected, without becoming ill. These tests are currently being validated in Brazil.
- **Mild to moderate disease:** characterized by a clinical picture of the common cold, flu-like syndrome or mild pneumonia, without the need for oxygen therapy or hospitalization. They represent about 80% of symptomatic patients and the case fatality rate is around 0.1% in young individuals without risk factors for complications. Depending on the age group (elderly) and comorbidities (heart disease, diabetes, neoplasia, pneumopathy) the risk of progressing to severe illness increases.
- **Severe Disease:**
  - *In adults:* fever and/or respiratory infection, plus respiratory rate of 23 breaths per minute, dyspnea and / or oxygen saturation <93% in ambient air;
  - *In children:* coughing or difficulty breathing plus central cyanosis or SatO2 <90% or severe dyspnea (moaning and / or intercostal retraction) *. These patients require hospital oxygen therapy and often have underlying disease decompensation and/or persistent fever, but without the need for intensive care. They represent about 15% of symptomatic patients. *One should pay attention to the warning signs in infants and children: difficulties in breastfeeding or when drinking fluids, lethargy or reduced level of consciousness, or seizures. Also pay attention to other signs of pneumonia, such as tachypnea (<2 months: ≥60bpm; 2-11 months: ≥50bpm; 1-5 years: ≥40bpm).

- **Critical illness:** these are patients with severe respiratory failure due to hypoxemia who require mechanical ventilation (SARS, severe acute respiratory syndrome) and / or patients in septic shock. They represent about 5% of symptomatic cases and case fatality, depending on age and comorbidities, can reach 50%.
  - *In adults:*
  - Mild ARDS: PaO2 >200mmHg and ≤300mmHg
  - Moderate ARDS: PaO2 >100mmHg and ≤200mmHg
  - Severe ARDS: PaO2 ≤100mmHg
  - When PaO2 is not available, SpO2/FiO2≤315 suggests ARDS
  - *In children:*
  - NIV or CPAP: PaO2 ≤300mmHg or SpO2/FiO2≤264
  - Mild ARDS: OI*≥4 e <8 or OSI*≥5 and <7.5
  - Moderate ARDS: OI≥8 and <16 or OSI≥7.5 and <12.3
  - Severe ARDS: OI≥16 or OSI≥12.3

  * OI: Oxygenation Index and OSI: Oxygenation Index using $SatO_2$. Use OI whenever PaO_2 is available. If using OSI, adjust FiO_2 to $SatO_2 \leq 97\%$ to calculate SpO_2 / FiO_2

- **Complications of severe COVID-19 disease**
  - **Sepsis:** signs of organ dysfunction, such as altered mental status, respiratory failure and hypoxia, renal failure, arterial hypotension, laboratory evidence of coagulopathy, thrombocytopenia, acidosis, hyperlactatemia, hyperbilirubinemia
  - **Septic Shock:** persistent hypotension regardless of volume resuscitation, requiring vasopressors to maintain mean arterial pressure (MAP) ≥ 65 mmHg and serum lactate >2 mmol / L.

In addition to SARS, other complications have been described following SARS-CoV-2 infection, such as arrhythmias (17%), acute myocarditis (7%) and shock (9%). Some patients may show an intense inflammatory response, similar to the cytokine release syndrome and persist with fever, elevation of inflammatory markers and pro-inflammatory cytokines, of which alterations have been associated with severe and fatal pictures of the disease.[9,22]

Laboratory Alterations

Upon hospital admission, lymphocytopenia is present in 83.2% of patients, thrombocytopenia in 36.2% and leukopenia in 33.7%, according to data from the cohort of 1,099 cases of COVID-19.[8]

Elevated levels of C-reactive protein have been verified in many patients, although elevated transaminases, CPK and D-dimer are less frequent. More severe patients have shown more important laboratory abnormalities (including leukopenia and lymphocytopenia), compared to those with less severe disease.

Some laboratory test patterns have progressed with worse clinical evolution, such as lymphopenia, elevated transaminases, C-reactive protein, ferritin, D-dimer>1mcg/mL, elevated troponin, CPK, altered kidney function, especially if there is progressive reduction of lymphocytes and progressive elevation of D-dimer.

Clinical Evolution

Regarding the clinical outcomes, of the 1,099 patients in the cohort in China, 5% were admitted to the Intensive Care Unit; 2.3% required mechanical ventilation and 1.4% died. Mechanical ventilation was implemented at greater proportion among critically-ill patients, with non-invasive ventilation in 32.4% and invasive ventilation in 14.5%.[8]

The mean duration of hospitalization was 12 days. On diagnosis at admission, 91.1% were diagnosed with pneumonia, followed by Acute Respiratory Distress Syndrome - ARDS (3.4%) and shock (1.1%). Severe illness occurred in 15.7% of patients after hospital admission.[8]

No radiological alterations were seen in 2.9% of patients at the initial presentation of the severely ill ones, and in 17.9% of the non-severely ill ones.[23,24]

The case fatality rate for symptomatic patients is around 2.3%, and among critically-ill patients, 49%. According to the WHO, the case fatality rate ranges from 0.7% to 5.8%, with many of the fatal cases occurring in the elderly or those with comorbidities. For patients aged 70-79 years, the case fatality rate was 8%-12%, while for those aged 80 and over, it was 15%-20%.[5,12,25,26]

The mean number of comorbidities is 2.7 among patients who progress to death, and the mortality rate is lower in patients without comorbidities (0.9%), when compared to 10.5% for cardiovascular disease, 7.3 % for diabetes mellitus and 6% for respiratory disease, SAH and malignant neoplasm.[3,7,17]

The proportion of severe cases and case fatality rates vary globally. In Italy, where the mean age of patients is 64 years, 12% of all patients with the infection and 16% of all hospitalized cases were admitted to the ICU, with an estimated case fatality rate of 7.2%.

In South Korea, with a mean age of 40 years for those affected by the virus, the case fatality rate is 0.9%. In the United States, 80% of the deaths occurred in patients aged ≥65 years.[9,20,22]

In the population of patients in long-term care facilities in the state of Washington, USA, the mean age was 83 years, and 94% had chronic diseases, with hospitalization and case fatality rates of 55% and 34%, respectively.[13]

Infection evolution

The interval during which the individual with COVID-19 remains infected is unclear, considering that studies were based on the positivity of PCR-RNA, of which positive result does not necessarily imply in the presence of the infecting virus.[27]

RNA levels seem to be higher soon after symptom onset, when compared to later periods, which suggests that transmission may be easier to occur in the initial period of the disease; however, this hypothesis needs to be proven.[14,28,29,30]

A series study of the first five cases in Europe showed three different types of clinical / biological evolution: **a) mild clinical picture**, with a diagnosis of high viral load in samples of the upper respiratory tract right at the beginning of symptom onset, suggesting the potential for high risk of transmissibility; **b) severe form**, with a biphasic pattern represented by a mild clinical condition initially, followed by worsening of the respiratory condition around the 10th day of symptom onset, despite the reduction or absence of viral load in nasopharyngeal samples at this time, which suggests that lung damage at this stage is more associated with immunopathological lesions; **c) critical clinical picture**, with rapid evolution to multiple-organ failure, with high and persistent viral elimination in samples from the upper and lower respiratory tracts, combined with systemic viral spread and detection of viremia, which indicates the capacity of the virus to evade the host's immune response.[14,22]

Viral load decreases over time and becomes negative between the 9th and 14th day of the disease, in most non-critical patients.[28]

After complete symptom resolution, the virus can still be detected in the upper respiratory tract for up to 30 days, but whether it still has an infectious capacity at this phase of absence of symptoms remains to be elucidated.

The duration of viral release (sharing) is variable and may depend on the disease severity. Studies with 21 patients with mild symptoms showed that 90% had repeated COVID-19-negative nasopharyngeal swabs for 10 days since symptom onset, while tests persisted positive for longer in patients with more severe clinical picture.[27,29]

Another study with 137 patients with COVID-19 and who survived, showed that the mean viral RNA isolation was 20 days, ranging from 8 to 37 days.[7,31]

Patient recovery can range from two weeks for mild cases up to three to six weeks for severe pictures of the disease.[14,32]

III- Considerations about Tomographic Findings

(Dr. Alair Sarmet Santos, Dr. Arthur Soares Souza Jr, César Araújo Neto, Dr. Dante Escuissato, Dr. Valdair Muglia)

Executive summary of tomographic scans

- High-resolution computed tomography (HRCT) of the chest should be used as a complementary exam to aid in the diagnosis of COVID-19 and should not be used alone, nor should it be performed for the screening of the disease.
- HRCT is mainly indicated for hospitalized, symptomatic patients with moderate or severe symptoms, especially to assess suspected complications such as pulmonary thromboembolism, overlapping bacterial infection, among others, in addition to help rule out other differential diagnoses.
- To date, there are no studies that support tomographic findings as predictors of clinical evolution
- HRCT should not be used as treatment control and has no high enough negative predictive value to remove suspected patients from isolation.
- The HRCT findings depend on the stage of the disease. Counted from symptom onset, the findings will be more frequent in the phases: intermediate (3 to 6 days) and late (after 7 days), with this being one of the factors that explain the sensitivity variability reported so far, between 60 and 96%.
- There is still insufficient scientific evidence to recommend the routine use of ultrasound to assess patients with COVID-19

Regarding the role of tomography as a complementary exam in the diagnosis of COVID-19, the Colégio Brasileiro de Radiologia developed a position that is described below.

Position on image examinations in COVID-19 by the Colégio Brasileiro de Radiologia (Brazilian College of Radiology)

High-resolution computed tomography (HRCT) of the chest should not be used alone for the diagnosis of COVID-19,

nor should it be performed alone to screen for the disease.[24]

To define a diagnosis of COVID-19, it is necessary to be guided by clinical-epidemiological information, associated with RT-PCR and / or serology tests when available and validated. The HRCT scan can help in this diagnostic definition, but it needs to be carefully correlated with clinical and laboratory data.[5,24,33]

No imaging exam should be recommended for asymptomatic or mild symptomatic patients.[9]

For moderate symptomatic patients who do not have access to laboratory tests or with a negative PCR result, the role of computed tomography is yet to be defined, but it can be performed according to clinical guidelines.[24]

In hospitalized, symptomatic patients with moderate or severe symptoms, computed tomography may be indicated, especially to assess suspected complications such as pulmonary thromboembolism, overlapping bacterial infection, among others, in addition to helping rule out other differential diagnoses.[34]

When indicated, the protocol consists of a high-resolution computed tomography (HRCT), preferably with a low-dose protocol. The use of intravenous contrast medium is not indicated, and should be reserved for specific situations, after evaluation by the radiologist.[24,35,36]

The findings of systematic HRCT examinations for patients with suspected COVID-19 infection or in confirmed cases do not influence the outcomes. To date, there are no studies that support tomographic findings as predictors of clinical evolution.[24,32]

HRCT should not be used as treatment control, except in suspected cases of complications, as mentioned above.

Both PCR and computed tomography do not have a high enough negative predictive value to remove suspected patients from isolation.[36]

It is suggested that the imaging exam reports include in their conclusion whether the findings are suggestive of an infectious process or not.

Finally, it is recommended that the imaging exam reports, in patients with suspected SARS-Cov-2 infection, show in their conclusion one of the following alternatives:[24]

- Findings suggestive of an infectious process of viral etiology;
- Indeterminate findings for an infectious process of viral etiology;
- Unusual findings in an infectious process of viral etiology.

Tomographic Findings

The HRCT findings depend on the stage of the disease. Counted from symptom onset, the findings will be more frequent in the phases: intermediate (3 to 6 days) and late (after 7 days), with this being one of the factors that explain the sensitivity variability reported so far, between 60 and 96%.[35,37] The main tomographic findings are summarized in the table 1.

Note 1. *During the evolution of COVID-19, some patients have shown a pattern of organizing pneumonia with a reversed halo sign.*

Note 2. *Some findings are very rare in pulmonary HRCT of patients with COVID-19 and, when present, alternative diagnoses become more likely: excavated lung lesions; mediastinal lymph node enlargement; tomographic pattern of lobar pneumonia, centrilobular nodules and "tree-in-bud" opacities. Pleural effusion, initially described as rare in COVID-19, has appeared more frequently in studies conducted in Western countries.*[37,38]

Note 3. *Pulmonary changes may persist later. Overall, the resolution of the findings is completed by the 26th day.*[32,35,37,38]

Note 4. *HRCT should not be used as a treatment control, except in suspected cases of complications.*

IV. Considerations about RT-PCR and Rapid Serological Tests

(Dra. Sílvia Figueiredo Costa, Dra. Mirian de Freitas Dal Ben Corradi, Dr. Alberto Chebabo)

Executive summary on molecular or serological tests

- SARS-CoV-2 infection can be divided into three stages: stage I, asymptomatic incubation period with or without detectable virus; stage II, non-severe symptomatic period with the presence of virus; stage III, severe respiratory symptomatic stage with high viral load. RT-PCR (Reverse-transcription polymerase chain reaction) is considered the gold standard method in clinical practice for the diagnosis of SARS-CoV-2.
- The specificity of RT-PCR is close to 100%; however, the sensitivity varies from 63% to 93%, according to symptom onset, viral dynamics and the clinical specimen collected.

Table 1. Tomographic findings in the different phases of COVID-19.

Initial phase (1-2 days)	Intermediate phase (3-6 days)	Late phase (7-14 days)
- Can be normal in 40 to 50% of cases - Focal ground-glass opacities or consolidations in about 17% of cases; - Bilateral multifocal opacities (about 28%); - Lung lesions have peripheral distribution in about 22% of cases.	- CT can be normal in 10 to 25% of cases; - Consolidation in about 55% of cases; - Involvement is bilateral, mostly (about 76%), with peripheral distribution (64%); - Reticular opacities in approximately 9% of cases	- CT can be normal in up to 5% of cases; - Consolidation occurs in up to 60% of cases; - The involvement is bilateral in about 88%, with peripheral distribution in 72%; - Reticular opacities in 20-48%. - Crazy paving pattern in 5 to 35% of cases

Source: Table constructed based on references.[32,35,37,38]

- Patients with COVID-19 seem to have decreased viral excretion in the first three days of symptoms, with an increase in RT-PCR positivity from 4th to the 6th day after symptom onset.
- The positivity of RT-PCR ranges from 63% in nasopharyngeal swab, 72% in sputum, 93% in lavage and only 29% in stool and 1% in blood.
- Other methods that can be used in the diagnosis of SARS-CoV-2 are methods to detect IgA-, IgM- and IgG-class antibodies using the ELISA technique (enzyme-linked immunosorbent assay) and immunochromatographic methods.
- The detection of acute phase antibodies (IgA and IgM) seems to start around the 5th day of symptom onset and may show cross-positivity due to infection by other viruses or vaccination against influenza.
- IgG class antibodies appear 10-18 days after symptom onset and have a positivity of 67 to 78%.
- Rapid immunochromatographic tests need to be validated and have a sensitivity that range from 20 to 87% and specificity of 91%.

The laboratory diagnosis of COVID-19 in clinical practice can be attained with the aid of the following tests:

RT- PCR (*Reverse transcription polymerase chain reaction*)

This method involves detecting SARS-CoV-2 by amplifying conserved virus sequences. The test is based on the protocol of the Charité Hospital of Berlin and recommended by the World Health Organization (WHO). Other protocols are also available, such as the one developed by the CDC, USA. Their specificity is close to 100%, but sensitivity depends on the collected sample and the period of the disease in which the patient is and varies from 63 to 92%. Some alterations in the Hospital Charité protocol can be implemented to improve test sensitivity, modifying the targets, such as the replacement of RdRP2 by HKU or by the N gene, which has a higher performance to confirm the detection of the E gene, used for screening.[39,40]

Nasopharyngeal swab samples show less sensitivity than sputum and bronchoalveolar lavage samples. (1) Wang et al. found 63% positivity in nasopharyngeal swabs, 72% in sputum and 93% in bronchoalveolar lavage samples. RT-PCR detected SARS-CoV-2 in only 29% of stool samples and 1% of blood samples.[41]

To ensure the best performance of the RT-PCR, attention should be paid to the sample collection technique, with adequate material and packaging for immediate transport to the technical area, not leaving the sample at room temperature.[33]

The viral kinetics in COVID-19 also has an impact on test performance: patients with COVID-19 seem to have decreased viral excretion in the first three days of symptoms, with an increase in test positivity on the 4-6th days of symptoms.[33] A detectable RT-PCR is observed in the nasopharynx for periods of 6 to 30 days.[7,42] Children can maintain PCR in positive stools for more than 30 days. No cross amplifications were observed with other endemic coronaviruses (HCoV-229E, -NL63, -OC43, -HKU1).[21]

Automated RT-PCR and 'Point of Care' methodologies are being introduced by several companies and will soon be available for use.

Sorology

It is the detection of IgA, IgM and IgG-class antibodies against SARS-CoV2 utilizing the ELISA (enzyme-linked immunosorbent assay) technique.

The detection of the IgA-class antibody seems to be more sensitive than that of IgM in cases of COVID-19, with 92.7% and 85.4% of positivity, respectively. The detection of these acute-phase antibodies seem to start around the 5th day of symptoms and may be cross-positive due to infection by other viruses or vaccination against influenza.[21,43]

The IgG antibody appears after 10-18 days of symptoms and has a 67-78% of positivity43–45. A Chinese rapid test (immunochromatographic) capable of detecting antibodies of the IgM and IgG classes, showed sensitivity of 87% and specificity of 91%46. Another rapid test, VivaDiagTM COVID-19 IgM/IgG Rapid test lateral flow (LFIA) used in Italy, did not show cross-reactivity with other coronaviruses, but showed a sensitivity of less than 20% when tested in patients with positive PCR result.[47]

Serological tests with conventional methodologies such as ELISA and Chemo or electroluminescence and rapid immunochromatographic methods need to be validated regarding their clinical applicability, in addition to defining the time of their greatest sensitivity to be recommended in clinical practice. The tests show in their initial validation a high positive predictive value, but with a low negative predictive value in the acute phase of the disease (first 7 days of symptoms) and cannot be used to exclude the disease in symptomatic patients. There are still no data to indicate the use of these tests for early diagnosis, and they can be used for late diagnosis in individuals with a respiratory clinical picture without confirmed etiology. The presence of positive IgG can be used as a confirmation of previous COVID-19 disease.

SARS-CoV-2 infection can be divided into three stages (Figure 1): stage I, an asymptomatic incubation period with or without a detectable virus; stage II, non-severe symptomatic period with the presence of virus; stage III, severe respiratory symptomatic stage with high viral load. For the development of an endogenous protective immune response in the incubation and non-severe stages, the host must be in good general health and with an appropriate genetic background (for example, HLA) that elicits specific antiviral immunity. During the acute phase of the infection, neutralizing antibodies are not detected. This type of antibody is seroconverted between days 4 and 9 of the infection, with a specific IgM peak on day 9 after the onset of the disease and the change to IgG in the second week. Taken together, the findings of this review suggest that patients with COVID-19 develop IgG and IgM responses to SARS-CoV-2 proteins, especially NP and S-RBD, and also suggest that infected patients can maintain their IgG levels for at least two weeks. Whether the kinetic/titer of specific antibody correlates with the severity of the disease, it has not yet been investigated.

Note 1. *For conceptual complementation regarding the interpretation of sensitivity/specificity, the following definitions can be of help:*[47]

Sensitivity *is the capacity of the test to correctly identify individuals with the investigated disease. An exam with 100% sensitivity has no false-negative results.*

Specificity *is the capacity of the test to identify true-negative results in healthy individuals. An exam with 100% specificity has no false-positive results.*

Positive predictive value *(PPV) is the probability of illness in a patient with a positive test.*

Negative predictive value *(NPV) is the probability that the patient does not have the disease if the test result is negative.*

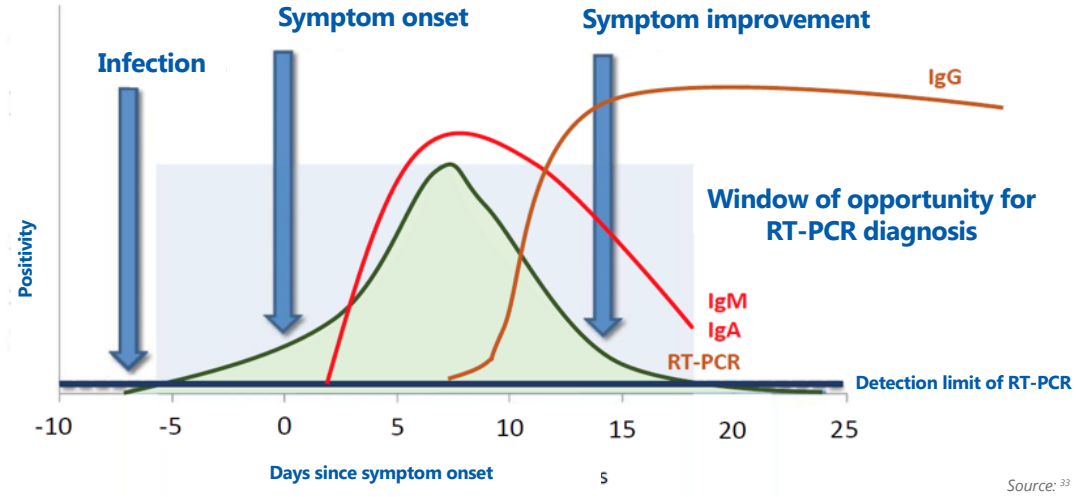

Figure 1. Result of diagnostic methods in the stages of SARS-CoV2 infection.

V. Considerations about removal from isolation for patients and health professionals

(Dra. Viviane Maria de Carvalho Hessel Dias, Dr. Jaime Luis Lopes Rocha)

Executive summary of isolation removal recommendations for patients and professionals

- Preferably maintain the **suspected/confirmed** patient with COVID-19 in isolation/contact and respiratory precautions throughout the hospitalization, due to the high risk of in-hospital transmission. However, if during hospitalization new information changes the suspicion to other diagnoses, the precautionary recommendation should be adapted to the updated diagnosis.
- If it is necessary to interrupt **precautions for suspected/confirmed patients** based on transmission while still in hospital, a test-based strategy or a non-test strategy can be used (i.e., time strategy since disease onset and time since recovery).
- **Test-based strategy for patients:**
  - Fever resolution without the use of antipyretics AND
  - Improvement of respiratory symptoms (example, coughing, shortness of breath) AND
  - Negative results of a COVID-19 molecular test certified in the country, for use in emergencies for the detection of SARS-CoV-2 RNA from at least two consecutive nasopharyngeal swab samples collected with an interval of ≥24 hours. This can be adjusted for a sample depending on the availability of resources
- **Non-test-based strategy for patients:**
  - At least 3 days (72 hours) have passed since recovery, defined as resolution of fever without the use of antipyretics and improvement of respiratory symptoms (for example, coughing, shortness of breath) AND
  - o At least 14 days have passed since the symptoms first appeared.
- Meeting the criteria for discontinuing transmission-based precautions is not a prerequisite for discharge.
- Post-discharge recommendations should be considered for both continuing treatment at home and in a long-term care or assisted living facility.
- For health professionals to return to work, a test-based strategy or a non-test-based strategy (that is, time since disease onset and time since recovery) can also be used.
  - **In the test-based strategy,** the professional should be absent from work until the fever has resolved without the use of antipyretics AND there has been an improvement in respiratory symptoms (for example, coughing, shortness of breath) AND the result of at least one molecular assay for COVID-19 in a nasopharyngeal swab sample is negative.
  - **In the non-test-based strategy,** the professional should be absent from work until at least 3 days (72 hours) have passed since recovery from fever without the use of antipyretics AND respiratory symptoms have improved (for example, coughing, shortness of breath) AND at least 14 days have passed since the symptoms first appeared.
  - **Note:** : In case of scarce labor, it should be considered evaluating the return to work **as of 7 days** after symptom onset, provided that the recommendation to improve fever and respiratory symptoms has been met. However, in this case, when returning, the professional must wear a surgical mask throughout their stay in the health service, until the period of 14 days since symptom onset has been met.

Hospitalized patients

The SARS-CoV-2 virus can be detected initially 1-2 days before symptom onset in the upper respiratory tract samples; and it can persist for 7 to 12 days in moderate cases and up to 2 weeks in severe cases. In stool, viral RNA has been detected in up to 30% of patients since day 5 after symptom onset and up to 4 to 5 weeks in moderate cases. The significance of the presence of the virus in stool for transmission has yet to be clarified.

Hospitalized patients may have longer SARS-CoV-2 RNA detection periods compared to patients with mild or moderate disease. Severely immunocompromised patients (for instance, those undergoing treatment with immunosuppressive drugs, bone marrow or solid organ transplant recipients, inherited immunodeficiency, poorly controlled HIV) may also have longer periods of SARS-CoV-2 RNA detection. These groups can also be contagious for longer periods than others. In addition, placing a patient in an environment where they will have close contact with individuals at risk for severe illness justifies a conservative approach. Therefore, it is justified

to maintain isolation and precautionary measures while the patient remains hospitalized.[9,26]

However, if it is necessary to discontinue precautionary/isolation measures while the patient remains hospitalized, it is recommended to use strategies that include RT-PCR testing (Table 2). However, if the test is not readily available, a strategy based on the resolution of fever and respiratory symptoms can be used, as well as on the time of transmission or extend the isolation period by analyzing case by case, by discussing it with the HICC (Hospital Infection Control Commission).[10,14,15,27,28,39]

In the absence of RT-PCR or in case of a negative result in a strongly suspected case, clinical judgment and suspected SARS-CoV-2 infection should guide the continuity or discontinuation of empirical precautions based on transmission.[49-51]

Patients can be discharged from the health service whenever clinically indicated and the discharge does not depend on the decision on the continuity or not of precautionary and isolation measures.

***Note 1**. The risk of transmission after recovery is probably much lower than that during the disease19,29.*

***Note 2.** Testing guidelines are based on limited information and are subject to change as more information becomes available.*

***Note 3.** Regarding serological tests, there is still no validation to guide the discontinuity of precautions and isolation using this methodology so far.[14,43,44,52]*

***Note 4.** If, during hospitalization, new information changes the suspicion to other diagnoses, the precautionary recommendation should be adapted to the updated diagnosis.*

Recommendations after discharge

If discharged to home[49]

Isolation should be maintained at home if the patient returns home before the transmission precautions are discontinued. The decision to send the patient home should be made after consulting with the care team and local or state public health departments.

It should include considerations about the suitability of the household and the patient's capacity to follow the recommendations for isolation at home.

To define the duration of isolation at home, adopt a non-test-based strategy, as of 14 days after symptom onset if there is fever resolution for more than 72 hours without antipyretics and improvement of respiratory symptoms.

If the patient is discharged to a long-term care service or assisted living facility[13,27,29,42]

Precautions based on transmission are still necessary and the patient must go to a facility that has the capacity to adhere to the prevention and infection control recommendations for the care of patients with COVID-19. Preferably, the patient should be placed in a designated place to care for the residents with COVID-19.

To define the duration of isolation, use the same recommendations for hospitalized patients.

Considerations for discharge from isolation for healthcare professionals

Decisions about returning to work for health professionals with confirmed or suspected COVID-19 should be made in the context of local circumstances. The options include a test-based strategy or a non-test-based strategy (i.e., time since disease onset and time since recovery strategy) as shown in table 3.[15,18,30]

***Note 1:** : From the onset of symptoms, the ideal time to collect the molecular test would be between the third and the seventh days. However, there is evidence that symptomatic patients already have a positive PCR, considering pre-analytical and analytical issues.[21,53,54]*

***Note 2:** In case of scarce labor, it should be considered evaluating the return to work 7 days after symptom onset, provided that the recommendations to improve fever and respiratory symptoms have been met. However, in this case, when returning, the professional must wear a surgical mask throughout their stay in the health service, until the 14-day period since symptom onset has been met.*

***Note 3:** Collection of molecular tests for asymptomatic professionals is not formally recommended.*

Table 2. Recommendations for interrupting precautionary and isolation measures in hospitalized patients.[49]

Situation	Duration	Comentários
Hospitalized patient, compatible clinical picture and positive initial RT-PCR Hospitalized patient, compatible clinical picture, but negative initial RT-PCR	Preferably maintain isolation/contact and respiratory precautions throughout the hospitalization, due to the high risk of in-hospital transmission. If necessary, define the end of isolation before discharge, adopt a strategy based on 2 negative RT-PCR tests with an interval of at least 24 hours, in addition to resolution of fever without antipyretics, as well as improving respiratory symptoms. If there is no test available, consider discontinuing isolation 14 days after symptom onset if the fever resolution persists for more than 72 hours without antipyretics and improvement of respiratory symptoms. Repeat RT-PCR if available in tracheal aspirate or, mini balloon if possible. Preferably keep isolation/precautions throughout the hospitalization, due to the high risk of in-hospital transmission. If necessary, define the end of the isolation before discharge, adopt a non-test-based strategy, as of 14 days after the symptom onset if there is fever resolution for more than 72 hours without antipyretics and improvement of respiratory symptoms.	Hospitalized patients with moderate/severe and/or immunocompromised cases may have longer periods of detection of SARS-CoV-2 RNA Attention: The following factors may interfere with the test positivity: - Pre-analytical questions; - Type of sample: oronasopharynx <nasopharynx aspirate <bronchoalveolar lavage; - Moment of ideal collection in relation to symptom onset

Additional considerations

In the context of sustained widespread transmission with increasing pressure on healthcare systems or when healthcare facilities are already overloaded and laboratory capacity is limited, alternative algorithms for discharging patients with COVID-19 may be recommended.

Although the oral-fecal route does not seem to be a transmission factor, its significance has not yet been determined. Discharged patients should be advised to strictly follow personal hygiene precautions in order to protect household contacts. This applies to all patients in convalescence, but particularly convalescent children.[48]

Table 3. Strategies to guide the return to work for health professionals.

Test-based strategy	Non-test-based strategy
The professional must be absent from work until: - fever resolution without the use of antipyretics AND - improvement in respiratory symptoms has occurred (for example, coughing, shortness of breath) AND - the result of at least one molecular test for COVID-19 in an oronasopharyngeal swab sample is negative.	**The professional** must be absent from work until: - at least 3 days (72 hours) have passed since recovery from fever without the use of antipyretics AND - improvement of respiratory symptoms has occurred (for example, coughing, shortness of breath) AND - at least 14 days have passed since the symptoms first appeared.

VI. Treatment considerations

(Dra. Lessandra Michelin, Dra. Silvia Figueiredo Costa, Dra. Priscila Rosalba D. Oliveira, Dra. Claudia Vidal, Dra. Mirian Dal Ben Corradi)

Executive summary of treatment considerations

- Until now, no medication has shown efficacy and safety results to justify recommendations for specific treatment of infection by SARS-CoV-2.
- The use of medications with therapeutic plausibility can be considered in the context of clinical studies by applying the informed consent form.
- Caution should be exercised when using chloroquine or hydroxychloroquine in combination with azithromycin, as it may increase the risk of cardiac complications, probably due to the synergistic effect of prolonging the QT interval.
- There are no studies to date that can recommend any drugs for the prophylaxis of SARS-CoV-2 disease.
- There is no scientific evidence to date that supports the prescription of anticoagulant therapy as treatment for infection by SARS-CoV-2.
- **Note: Some of the references mentioned in this document are not Currently indexed and should be considered with caution.**

Medications evaluated for treatment – COVID-19

A identificação urgente de possíveis estratégias de tratamento da infecção por SARS-CoV-2 é uma prioridade. Até o The urgent identification of possible treatment strategies for SARS-CoV-2 infection is a priority. To date, there is no consensus on the best pharmacological treatment for patients with COVID-19. Ongoing research of therapies include new and old available agents, being researched in clinical trials or through compassionate use 55. Pharmacological targets and the main classes of studied therapeutic drugs are described below:

Pharmacological targets

SARS-COV-2 expresses viral proteins on its outer surface that facilitate binding to host cells through the angiotensin-converting enzyme 2 (ACE2). SARS-CoV-2 is a single-stranded RNA coronavirus that replicates by recruiting non-structural proteins, such as 3-chymotrypsin protease, papain type protease, papain type protease, helicase and RNA-dependent RNA polymerase56. Due to the structural similarity with other viruses, several antiviral therapies have been tested.

Nucleoside analogues available for HIV and respiratory viruses may have a therapeutic role in blocking RNA synthesis, targeting the RNA-dependent RNA polymerase found in SARS-CoV-2. Moreover, the currently available HIV protease inhibitors exhibited some in vitro activity against the 3-chymotrypsin-like protease found in SARS.[57,58]

Other non-structural or accessory proteins have a role in possible developing therapeutic targets59. Unlike leading to direct viral replication, other therapeutic approaches aim to modulate the innate immune system to attack the virus or inhibit cytokines that are upregulated during viral replication, aiming to attenuate the physiological response to the disease.[55,59]

Therapeutic classes

Antivirals

Nucleoside Analogues

Ribavirin

Ribavirin is a purine nucleoside analogue that causes its antiviral effect by inhibiting viral RNA synthesis. RNA is ubiquitous in many viruses, which is why ribavirin has been studied in several viral diseases, including hepatitis B, C and respiratory syncytial virus.[57] Due to the lack of data and the important toxicity and side effects of the medication, its use should be considered with caution. In vivo data suggest that the serum concentrations of ribavirin necessary to effectively reduce viral replication are higher than those that are safely achievable in humans, and many studies have questioned its effectiveness.[56,57]

Favipiravir

Favipiravir, a drug licensed in Japan for the treatment of influenza, is another potential agent due to its activity against a broad spectrum of RNA viruses, including coronavirus. Several studies are underway to evaluate favipiravir for the treatment of COVID-19.[55,58]

Neuraminidase inhibitors

Oseltamivir

Oseltamivir is unlikely to be active against SARS-CoV-2 based on previous studies with SARS-CoV. To date, there are no studies that support its effectiveness against SARS-Cov-2.[55,61]

Protease inhibitors

Lopinavir/Ritonavir (Table 4 in the Annex)

Lopinavir is an aspartic acid protease inhibitor developed for the treatment of HIV. The rationale of the therapy with lopinavir and ritonavir (LPV/r) for COVID-19 arises from in vitro studies that demonstrate inhibition of the 3-chymotrypsin-like protease found in new coronaviruses. However, LPV was specifically designed to match the structure of the C2 catalytic site in the HIV aspartic acid protease. The SARS-CoV-2 protease is a cysteine protease family and is structurally different, as it does not have a catalytic site at C2.[58,62 16,31,55] The literature available to date for LPV/r in the treatment of COVID-19 stems from a series of descriptive cases of five patients in Singapore who received 200-100 mg of LPV/r twice daily for 14 days. Three patients had reductions in ventilation requirements in the three days following the start of treatment, while two had progressive respiratory failure.[23] A Chinese retrospective cohort study evaluated the use of LPV/r and arbidol, showing improvement in viral clearance and clinical picture with the combined therapy.[62] In a recent randomized, controlled and open clinical trial, including patients hospitalized with SARS-CoV-2 infection, patients who received 400 to 100 mg of LPV/r twice daily for 14 days versus a control group without antiviral drugs, showed no benefit regarding the use of LPV/r, not even a difference in viral load.[16] There are several ongoing studies evaluating the clinical effectiveness of LPV/r as monotherapy and in combination with other therapies such as arbidol, ribavirin and interferon (IFN).[62,63,64,16]

Adenosine analogue

Remdesivir

Remdesivir is an adenosine analogue, initially used for Ebola, which has been considered a promising antiviral against a wide variety of RNA viruses, including SARS-CoV-2, as it has shown a decrease in viral replication.[55] In vitro studies in human airway epithelial cell cultures as a lung model found activity against coronaviruses.[65] Studies that evaluated the potency of Remdesivir were effective in decreasing coronavirus in epithelial cells of human airways.[55,65,66] Recently, a cohort of critically-ill patients hospitalized for COVID-19 has been published, who were treated with Remdesivir in compassionate use, with clinical improvement in 36 of the 53 patients (68%).[67] Certainly, evidence of efficacy still awaits data from randomized, placebo-controlled studies.[68,69]

Immunomodulators

Corticosteroids

Clinical data to date have shown no benefit of corticosteroid use in the treatment of SARS, MERS or COVID-19, but have shown evidence of an increased risk of damage, including prolonged mechanical ventilation, avascular necrosis, delayed viral clearance and secondary infections.[31,70] The lack of benefits on survival was further supported by a systematic review of corticosteroids in patients with SARS, where they showed an increased risk of psychosis, avascular necrosis, prolonged viremia and hyperglycemia while undergoing treatment with corticosteroids. At the moment, it is indicated in severe cases with a weak level of evidence.[65,70-73]

Interferon

Interferon (INF) are endogenous signaling proteins released by host cells during the response to infections or inflammation. The positive regulation of IFNs stimulates the immune system to attenuate viral replication and eradicate offending pathogens. There are two IFNs that mediate the host's immune responses, alpha and beta. IFN-alpha causes a potent host-mediated immune cell response that has generated interest in the treatment of viral diseases such as hepatitis B and C. IFN-beta has been used mainly in the treatment of multiple sclerosis.[30,55] In vitro studies have shown a reduction in viral replication of SARS and MERS-CoV with Interferon-alpha and-beta. Patients with MERS-CoV who were treated with a combination of ribavirin and INF-alpha had better survival, but there is no evidence yet to support the use for SARS-COV-2 infection.[55,74] This has not diminished the potential application of this therapy and the researchers await the results of ongoing studies evaluating the efficacy of IFN-alpha 2b as part of the combined therapy with ribavirin for COVID-19 in order to further elucidate any benefit of IFN treatment.[75,76]

Intravenous Human Immunoglobulin

There is no evidence that IVIG has any benefit in treating the infection by the new Coronavirus.[30]

Monoclonal Antibodies

Convalescent individuals' serum (Table 4 - annex)

The proposed mechanism for the benefit of convalescent human plasma derived from coronavirus survivors is the transfer of passive immunity in an effort to restore the immune system during critical illnesses and neutralize the virus to suppress the viremia. In a retrospective review of 40 SARS patients who failed treatment with methylprednisolone and ribavirin in 3 days, 74% of patients who received convalescent plasma were discharged on day 22 compared to only 19% of patients who received high doses of corticosteroids ($p<0.001$). For the greatest benefit of treatment with convalescent plasma, the study suggests using it at the beginning of the disease (before the 16th day).[55,77] Preliminary data on convalescent plasma therapy in the outbreak of COVID-19 suggest improvement in clinical symptoms with no sign of adverse effects. Two series of cases, one with 5 patients and the other with 4 patients, showed evident clinical improvement and mechanical ventilation weaning (3 patients) after the transfusion.[78] Tested in 5 patients, it showed evident clinical improvement and weaning from mechanical ventilation (3 patients) 12 days after the transfusion.[79,80]

Tocilizumab

Tocilizumab is a monoclonal antibody with approval for T cell-induced cytokine release syndrome (CRS), giant cell arteritis, rheumatoid arthritis and polyarticular or systemic juvenile idiopathic arthritis. Publications suggest that patients with severe COVID-19 suffer significant lung injury secondary to an increase in inflammatory cytokines, resulting in a cytokine storm. Viral replication activates the innate immune system to secrete several signaling proteins, such as interleukins (ILs), which result in hyperinflammation and further damage to the lungs. IL-6 is an essential inflammatory protein involved in this pathway. Tocilizumab binds to IL-6 receptors, thereby decreasing cell signaling and effectively regulating excess inflammatory response.[81] Wuhan's data in critically-ill patients with COVID-19 also found increased levels of cytokines, including IL-6 and granulocyte-colony stimulating factor (G-CSF). IL-6 may be a key factor in the robust inflammatory response in the lungs of ICU patients with COVID-19. Recently published data from Wuhan indicate that tocilizumab added to lopinavir, methylprednisolone and oxygen therapy in 20 patients with severe COVID-19 resulted in rapid reductions in fever in all patients, improved oxygenation by 75% and hospital discharge in 95% of patients.[55,82,83] Clinical trials are testing the medication for COVID-19.[84,85]

Outhers

Chloroquine and Hydroxychloroquine (Table 4 - annex)

The potential antiviral effect of chloroquine is known for a wide variety of viruses, including SARS-CoV. Chloroquine analogues are weak bases that, in their non-protonated form, penetrate and concentrate in acidic intracellular organelles, such as endosomes and lysosomes. Once present intracellularly, chloroquine analogues become protonated and increase intravesicular pH. Chloroquine-mediated pH changes may result in early inhibition of viral replication by interference with endosome-mediated viral entry or delayed transport of the involved virus60,86.This mechanism translates into the potential role of chloroquine analogues in the treatment of COVID-19, and also seems to interfere with the terminal glycosylation of ACE2 receptor expression, which prevents binding to the SARS-CoV-2 receptor and the subsequent spread of the infection. There is evidence that chloroquine has an in vitro effect against COVID-19. Clinical studies and case series have shown that hydroxychloroquine has a similar effect, decreasing viral load; some studies suggest some benefit when used in combination with other medications, such as azithromycin.[87] Clinical studies are evaluating hydroxychloroquine as a safe and effective drug for COVID-19.[88]

Note: *Caution should be exercised when using chloroquine or hydroxychloroquine in combination with azithromycin, as it may increase the risk of cardiac complications, probably due to the synergistic effect of prolonging the QT interval.*[89]

Nitazoxanide

Nitazoxanide is a 2-(acetyloxy)-N-(5-nitro-2-thiazolyl) benzamide with an antiprotozoal indication. Nitazoxanide is metabolized to its active metabolite tizoxanide, which selectively blocks the maturation and intracellular movement of post-translational influenza viral hemagglutinin, in addition to blocking the implantation of proteins on the plasma membrane. Nitazoxanide can potentiate the production of type-1 IFNs produced by the host cell, which can potentiate antiviral activity through hemagglutinin inhibition. In vitro studies of canine coronavirus have found that the use of nitazoxanide inhibited viral replication. Based on these in vitro animal data, it is believed that nitazoxanide may have activity against SARS-CoV-2. The haff260 data in patients with respiratory syndrome, the subgroup analysis showed 5 coronavirus positive patients, but these did not show any difference in the primary outcome of days of hospitalization. Other studies are being awaited with the drug results to evaluate its effectiveness in the treatment of COVID-1990.[90,91]

Arbidol

Arbidol, a drug used for the prophylaxis and treatment of influenza and respiratory viral infections, works by preventing viral fusion to reach the cell membrane. It has demonstrated activity against several viruses, including SARS, and is currently being evaluated for the treatment of COVID-19 in several studies in China.[55]

Heparin

Coagulopathy in SARS-Cov-2 infection is associated with high mortality, and the elevation of D-dimer is considered an important marker of this state of hypercoagulability.[93] Severe pulmonary inflammation and difficulty in gas exchange in COVID-19 has been suggested to be related to the over-regulation of pro-inflammatory cytokines, with the elevation of D-dimer being a reflection of intense inflammation stimulating intrinsic fibrinolysis in the lungs.[94]

Based on the immunothrombotic model, thrombin blocking by heparin can reduce the inflammatory response. Therefore, one of the properties of heparin is its anti-inflammatory function by binding to cytokines, inhibition of neutrophil chemotaxis and leukocyte migration, neutralization of complement factor C5a and sequestration of proteins in the acute phase.

Severe Acute Respiratory Syndrome (SARS) is one of the most common complications in COVID-19, with high plasma concentrations of tissue factor and plasminogen activator inhibitor-1 (PAI-1), which contributes to pulmonary coagulopathy through the production of thrombin mediated by tissue factor and decreased fibrinolysis mediated by the bronchoalveolar plasminogen activator, through the increase in PAI-1.

Heparin treatment can help mitigate pulmonary coagulopathy. Another property of heparin is the antagonistic action against histones, released from endothelial dysfunction caused by the invasion of the pathogenic microorganism, with reduction of edema and pulmonary vascular injury secondary to the injury caused by lipopolysaccharides. Heparin can impact microcirculatory dysfunction and reduce damage to target organs, demonstrating a reduction in myocardial inflammation and collagen deposition in an animal model of myocarditis.[93]

This effect of heparin is under investigation in COVID-19 patients. Another concept is the antiviral property of heparin, assessed in experimental models, through its polyanionic nature, binding to several proteins and inhibiting viral adhesion.

An in vitro study has shown that the SARS-Cov-2 S-1 protein-binding receptor interacts with heparin; however, the clinical benefit is yet to be determined. Thus, there are several mechanisms by which heparin can be beneficial for the treatment of COVID-19, depending also on the results of new clinical studies, including the definition of the correct dose of low-molecular weight heparin (LMWH), for which prophylactic doses may be suitable for many patients, although inappropriate for patients with high BMI.[95] In a retrospective study with 449 severe COVID-19 patients, of whom 99 (22%) received heparin, lower mortality was observed in 28 days in patients with SIC sepsis score ≥4, and 20% lower mortality if D--dimer >3.0 µg/mL.[96] Moreover, an experimental study aimed at evaluating the effect of nebulization with anti-thrombin (AT) associated or not with heparin, in an animal model of lung injury, showed a reduction in lung injury mediated by coagulation factors.[97]

References:

1. *Machado, A. A. Infecção pelo vírus Influenza A (H1N1) de origem suína: Como reconhecer, diagnosticar e prevenir. J. Bras. Pneumol. 35, 464–469 (2009).*
2. *Jain, S. et al. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. N. Engl. J. Med. 373, 415–427 (2015).*
3. *Bansal, M. Cardiovascular disease and COVID-19. Diabetes Metab. Syndr. 14, 247–250 (2020).*
4. *Xie, M. & Chen, Q. Insight into 2019 novel coronavirus - an updated intrim review and lessons from SARS-CoV and MERS-CoV. Int. J. Infect. Dis. (2020). doi:10.1016/j.ijid.2020.03.071*
5. *Huang, C. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395, 497–506 (2020).*
6. *Spellberg, B. et al. Community Prevalence of SARS-CoV-2 Among Patients With Influenzalike Illnesses Presenting to a Los Angeles Medical Center in March 2020. JAMA (2020). doi:10.1001/jama.2020.4958*
7. *Zhou, F. et al. Clinical course and risk factors for mortali-*

ty of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England) 395, 1054–1062 (2020).

8. *Fang, L. et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. Lancet Respir. Med. (2020). doi: 10.1056/NEJMoa2001316*
9. *Cascella, M., Rajnik, M., Cuomo, A., Dulebohn, S. C. & Di Napoli, R. Features, Evaluation and Treatment Coronavirus (COVID-19). in (2020).*
10. *Rothe, C. et al. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. The New England journal of medicine 382, 970–971 (2020).*
11. *Clinical management of severe acute respiratory infection when COVID-19 is suspected. Available at: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected. (Accessed: 13th April 2020)*
12. *Wang, D. et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA - J. Am. Med. Assoc. (2020). doi: 10.1001/jama.2020.1585*
13. *McMichael, T. M. et al. Epidemiology of Covid-19 in a Long-Term Care Facility in King County, Washington. N. Engl. J. Med. (2020). doi: 10.1056/NEJMoa2005412*
14. *Lescure, F.-X. et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. Lancet. Infect. Dis. (2020). doi: 10.1016/S1473-3099(20)30200-0*
15. *Ferretti, L. et al. Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing. Science (2020). doi: 10.1126/science.abb6936*
16. *Cao, B. et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N. Engl. J. Med. (2020). doi: 10.1056/NEJMoa2001282*
17. *Fang, L., Karakiulakis, G. & Roth, M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir. Med. (2020). doi: 10.1016/s2213-2600(20)30116-8*
18. *Return-to-Work Criteria for Healthcare Workers | CDC. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/return-to-work.html. (Accessed: 13th April 2020)*
19. *Milton, D. K. et al. Brief CommuniCation Respiratory virus shedding in exhaled breath and efficacy of face masks. doi: 10.1038/s41591-020-0843-2*
20. *Grasselli, G., Pesenti, A. & Cecconi, M. Critical Care Utilization for the COVID-19 Outbreak in Lombardy, Italy: Early Experience and Forecast During an Emergency Response. JAMA (2020). doi: 10.1001/jama.2020.4031*
21. *Corman, V. M. et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill. Bull. Eur. sur les Mal. Transm. = Eur. Commun. Dis. Bull. 25, (2020).*
22. *Onder, G., Rezza, G. & Brusaferro, S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA (2020). doi: 10.1001/jama.2020.4683*
23. *Young, B. E. et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. JAMA (2020). doi: 10.1001/jama.2020.3204*
24. *Rubin, G. D. et al. The Role of Chest Imaging in Patient Management during the COVID-19 Pandemic: A Multinational Consensus Statement from the Fleischner Society. Radiology 201365 (2020). doi: 10.1148/radiol.2020201365*
25. *Arabi, Y. M., Fowler, R. & Hayden, F. G. Critical care management of adults with community-acquired severe respiratory viral infection. Intensive Care Med. 46, 315–328 (2020).*
26. *Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) - United States, February 12-March 16, 2020. MMWR. Morb. Mortal. Wkly. Rep. 69, 343–346 (2020).*
27. *Liu, W. et al. Long-term SARS coronavirus excretion from patient cohort, China. Emerg. Infect. Dis. 10, 1841–1843 (2004).*
28. *Hung, I. F. N. et al. Viral loads in clinical specimens and SARS manifestations. Emerg. Infect. Dis. 10, 1550–1557 (2004).*
29. *Cheng, P. K. C. et al. Viral shedding patterns of coronavirus in patients with probable severe acute respiratory syndrome. Lancet (London, England) 363, 1699–1700 (2004).*
30. *Zhang, L. & Liu, Y. Potential interventions for novel coronavirus in China: A systematic review. J. Med. Virol. 92, 479–490 (2020).*
31. *Stockman, L. J., Bellamy, R. & Garner, P. SARS: systematic review of treatment effects. PLoS Med. 3, e343 (2006).*
32. *Pan, F. et al. Time Course of Lung Changes On Chest CT During Recovery From 2019 Novel Coronavirus (COVID-19) Pneumonia. Radiology 200370 (2020). doi: 10.1148/radiol.2020200370*
33. *Lippi, G., Simundic, A.-M. & Plebani, M. Potential preanalytical and analytical vulnerabilities in the laboratory diagnosis of coronavirus disease 2019 (COVID-19). Clin. Chem. Lab. Med. (2020). doi: 10.1515/cclm-2020-0285*
34. *Kim, H. Outbreak of novel coronavirus (COVID-19): What is the role of radiologists? European radiology (2020). doi: 10.1007/s00330-020-06748-2*
35. *Zhou, Z. et al. Coronavirus disease 2019: initial chest CT findings. Eur. Radiol. (2020). doi: 10.1007/s00330-020-06816-7*
36. *Ai, T. et al. Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology 200642 (2020). doi: 10.1148/radiol.2020200642*
37. *Bernheim, A. et al. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. Radiology 200463 (2020). doi: 10.1148/radiol.2020200463*
38. *Chate, R. C. et al. Presentation of pulmonary infection on CT in COVID-19 : initial experience in Brazil. 46, 4–7 (2020).*
39. *Liu, R. et al. Positive rate of RT-PCR detection of SARS-CoV-2 infection in 4880 cases from one hospital in Wuhan, China, from Jan to Feb 2020. Clin. Chim. Acta. 505, 172–175 (2020).*
40. *Vogels, C. B. F. et al. Analytical sensitivity and efficiency comparisons of SARS-COV-2 qRT-PCR assays. (2020).*
41. *Wang, W. et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA (2020). doi: 10.1001/jama.2020.3786*
42. *Ling, Y. et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. Chin. Med. J. (Engl). (2020). doi: 10.1097/CM9.0000000000000774*
43. *Guo, L. et al. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). Clin. Infect. Dis. (2020). doi: 10.1093/cid/ciaa310*
44. *Zhao, J. et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clin. Infect. Dis. (2020). doi: 10.1093/cid/ciaa344*
45. *Li, Z. et al. Development and Clinical Application of A Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis. J. Med. Virol. (2020). doi: 10.1002/jmv.25727*
46. *Williamson, Mary A. - Snyder, L. M. Interpretação de exames laboratoriais. (Guanabara Koogan, 2016).*

47. Santos Luiz Francisco, F. R. G.-M. Um guia para leitor de artigos científicos na área de saúde. (214AD).
48. (No Title). Available at: https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-Discharge-criteria.pdf. (Accessed: 13th April 2020)
49. Disposition of Non-Hospitalized Patients with COVID-19 | CDC. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-in-home-patients.html. (Accessed: 13th April 2020)
50. Discontinuation of Transmission-Based Precautions and Disposition of Patients with COVID-19 in Healthcare Settings (Interim Guidance) | CDC. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html. (Accessed: 13th April 2020)
51. Management of Patients with Confirmed 2019-nCoV | CDC. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html. (Accessed: 13th April 2020)
52. Shi, Y. et al. COVID-19 infection: the perspectives on immune responses. Cell death and differentiation (2020). doi: 10.1038/s41418-020-0530-3
53. Park, R. & Cancer, C. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. 1, 12–14 (2020).
54. Wölfel, R. et al. Virological assessment of hospitalized patients with COVID-2019. (2020). doi: 10.1038/s41586-020-2196-x
55. Barlow, A. et al. Review of Emerging Pharmacotherapy for the Treatment of Coronavirus Disease 2019. Pharmacotherapy (2020). doi: 10.1002/phar.2398
56. Li, G. & De Clercq, E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nature reviews. Drug discovery 19, 149–150 (2020).
57. Tan, E. L. C. et al. Inhibition of SARS coronavirus infection in vitro with clinically approved antiviral drugs. Emerg. Infect. Dis. 10, 581–586 (2004).
58. Jordan, P. C., Stevens, S. K. & Deval, J. Nucleosides for the treatment of respiratory RNA virus infections. Antivir. Chem. Chemother. 26, 2040206618764483 (2018).
59. Dong, L., Hu, S. & Gao, J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov. Ther. 14, 58–60 (2020).
60. Borba, M. et al. Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, phase IIb cl. medRxiv 2020.04.07.20056424 (2020). doi: 10.1101/2020.04.07.20056424
61. Zhu, N. et al. A novel coronavirus from patients with pneumonia in China, 2019. N. Engl. J. Med. (2020). doi: 10.1056/NEJMoa2001017
62. Deng, L. et al. Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study. J. Infect. (2020). doi: 10.1016/j.jinf.2020.03.002
63. The Efficacy of Lopinavir Plus Ritonavir and Arbidol Against Novel Coronavirus Infection - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04252885. (Accessed: 13th April 2020)
64. Huang, C. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England) 395, 497–506 (2020).
65. Sheahan, T. P. et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci. Transl. Med. 9, (2017).
66. Gordon, C. J., Tchesnokov, E. P., Feng, J. Y., Porter, D. P. & Gotte, M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J. Biol. Chem. 295, 4773–4779 (2020).
67. Grein, J. et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N. Engl. J. Med. (2020). doi: 10.1056/NEJMoa2007016
68. Severe 2019-nCoV Remdesivir RCT - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04257656. (Accessed: 13th April 2020)
69. Mild/Moderate 2019-nCoV Remdesivir RCT - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04252664. (Accessed: 13th April 2020)
70. Russell, C. D., Millar, J. E. & Baillie, J. K. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet (London, England) 395, 473–475 (2020).
71. Arabi, Y. M. et al. Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. Am. J. Respir. Crit. Care Med. 197, 757–767 (2018).
72. Alhazzani, W. et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med. (2020). doi: 10.1007/s00134-020-06022-5
73. Efficacy and Safety of Corticosteroids in COVID-19 - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04273321. (Accessed: 13th April 2020)
74. Haagmans, B. L. et al. Pegylated interferon-alpha protects type 1 pneumocytes against SARS coronavirus infection in macaques. Nat. Med. 10, 290–293 (2004).
75. Efficacy and Safety of IFN-α2β in the Treatment of Novel Coronavirus Patients - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04293887. (Accessed: 13th April 2020)
76. Lopinavir/ Ritonavir, Ribavirin and IFN-beta Combination for nCoV Treatment - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04276688. (Accessed: 13th April 2020)
77. Soo, Y. O. Y. et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. Clin. Microbiol. Infect. 10, 676–678 (2004).
78. Zhang, B. et al. Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection. Chest (2020). doi: 10.1016/j.chest.2020.03.039
79. Shen, C. et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA (2020). doi: 10.1001/jama.2020.4783
80. Anti-SARS-CoV-2 Inactivated Convalescent Plasma in the Treatment of COVID-19 - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04292340. (Accessed: 13th April 2020)
81. Mehta, P. et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet (London, England) 395, 1033–1034 (2020).
82. Ruan, Q., Yang, K., Wang, W., Jiang, L. & Song, J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive care medicine (2020). doi: 10.1007/s00134-020-06028-z
83. Ruan, Q., Yang, K., Wang, W., Jiang, L. & Song, J. Correction to: Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive care medicine (2020). doi: 10.1007/

s00134-020-06028-z

84. *Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019 - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04310228. (Accessed: 13th April 2020)*
85. *Tocilizumab vs CRRT in Management of Cytokine Release Syndrome (CRS) in COVID-19 - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04306705. (Accessed: 13th April 2020)*
86. *Huang, M. et al. Treating COVID-19 with Chloroquine. J. Mol. Cell Biol. (2020). doi: 10.1093/jmcb/mjaa014*
87. *Chen, Z. et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv 2020.03.22.20040758 (2020). doi: 10.1101/2020.03.22.20040758*
88. *Efficacy and Safety of Hydroxychloroquine for Treatment of COVID-19 - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04261517. (Accessed: 13th April 2020)*
89. *Chen, C. et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. medRxiv 2020.03.17.20037432 (2020). doi: 10.1101/2020.03.17.20037432*
90. *Haffizulla, J. et al. Effect of nitazoxanide in adults and adolescents with acute uncomplicated influenza: a double-blind, randomised, placebo-controlled, phase 2b/3 trial. Lancet. Infect. Dis. 14, 609–618 (2014).*
91. *Gamino-Arroyo, A. E. et al. Efficacy and Safety of Nitazoxanide in Addition to Standard of Care for the Treatment of Severe Acute Respiratory Illness. Clin. Infect. Dis. 69, 1903–1911 (2019).*
92. *Blaising, J., Polyak, S. J. & Pecheur, E.-I. Arbidol as a broad-spectrum antiviral: an update. Antiviral Res. 107, 84–94 (2014).*
93. *Tang, N., Li, D., Wang, X. & Sun, Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J. Thromb. Haemost. 18, 844–847 (2020).*
94. *Xiong, T.-Y., Redwood, S., Prendergast, B. & Chen, M. Coronaviruses and the cardiovascular system: acute and long-term implications. Eur. Heart J. (2020). doi: 10.1093/eurheartj/ehaa231*
95. *Thachil, J. The versatile heparin in COVID-19. J. Thromb. Haemost. (2020). doi: 10.1111/jth.14821*
96. *Tang, N. et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J. Thromb. Haemost. (2020). doi: 10.1111/jth.14817*
97. *Camprubi-Rimblas, M. et al. Effects of nebulized antithrombin and heparin on inflammatory and coagulation alterations in an acute lung injury model in rats. J. Thromb. Haemost. 18, 571–583 (2020).*
98. *Gautret P, Lagiera JC, Parolaa P, Hoanga VT, Meddeba L, Mailhea M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open label non-randomized clinical trial. International Journal of Antimicrobial Agents – In Press 17 March 2020. doi: 10.1016/j.ijantimicag.2020.105949*
99. *Molina JM et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Médecine et Maladies Infectieuses (2020). doi: 10.1016/j.medmal.2020.03.006*
100. *Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study. Preprint. https://www.mediterranee-infection.com/wp-content/uploads/2020/03/COVID-IHU-2-1.pdf?fbclid=IwAR0-uBG8W7rsx0YxGUfILvwlHr5uKs0VGyQEFqkhSL0pk3IvyQ7BF_KAwE*
101. *Chen J et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). Journal of Zhejiang University (Medical Sciences). 2020;49(1). doi:10.3785/j.issn.1008-9292.2020.03.03*
102. *Chen Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv 2020. doi: 10.1101/2020.03.22.20040758*

Annex 1

Table 4. Summary of studies available to date on drugs evaluated for the treatment of COVID-19..

Treatment	Reference	Country	Design/Intervention	Sample	Primary Outcome	Results
			Antivirals- Protease Inhibitors			
Lopinavir/ Ritonavir	Deng L et al. J Inf 2020	China	Retrospective cohort Lopinavir/R 400/100 mg 12/12 h + Arbidol 200mg every 8/8 h vs. Lopinavir/R 400/100 mg every 12 h	33 patients combination therapy group used less corticosteroids (1 / 6.2%) vs. monotherapy group (7/41.2%) 199 patients Support group vs. Support group + lopinavir/R 400/100 mg 12/12 h	Virus clearing Improvement/ worsening of viral PNM on treatment D7	Nasopharynx PCR negative on treatment D7 in (12/75%) in the combination therapy group and 6/35% in monotherapy. On D14 15/94% of the combination therapy group versus 9/53% had negative PCR.
Lopinavir/ Ritonavir	B et al. NEJM 2020	China	Prospective, randomized, controlled and open clinical trial	COVID-19 patients confirmed with RT-PCR and one of the following criteria: SatO2≤94% ambient air or O2 supplement needed Period from 25/Jan to 7/ March/2020	Clinical improvement time Clinical status (scale) on D7, D14 Mortality on D21 Duration of mechanical ventilation Length of hospitalization Treatment/death time	Chest CT improved 11/69% in combination therapy and 5/29% in monotherapy on treatment D7. No difference in the outcomes studied
			Antivirals - Adenosine Analogues			
Remdesivir	Grein J et al. NEJM , april 10, 2020	EUA	COVID-19 cohort of critically-ill patients, based on compassionate use of Remdesivir 200mg on day 1+100mg/day for 9 days.	COVID-19 patients confirmed with RT-PCR and one of the following criteria: SatO2≤94% ambient air or O2 supplement needed Period from 25/Jan to 7/ March/2020	Follow-up in 28 days, or until discharge or death. Parameters: Progression of the need for oxygen support. Adverse events Proportion of clinical improvement Discharge or death	Total of 53 patients analyzed: 68% improved with respiratory support 57% patients on MV were extubated 47% (25/53) were discharged until the last follow-up 84% achieved clinical improvement until D28 of follow-up; lower in patients with MV and the elderly (≥ 70 years old 13% (7/53) died: 6/34 (18%) with MV vs. 1/19 (5%) without invasive ventilation 60% had adverse events: increased liver enzymes, rash, diarrhea, altered kidney function, hypotension. 23% (12/53) had severe adverse events: multiple organ dysfunction, septic shock, hypotension, ARF, especially if under MV
			Nucleoside Analogues			
Favipiravir X Arbidol (Umifenovir)	Chen C. et al. 2020	China	Randomized clinical trial 1: 1 Favipiravir: 1600mg, 2x / day on the 1st day and 600mg 2x/day after the 2nd day Arbidol: 200mg 3 times a day, for 7-10 days	240 patients (120 in each group)	Clinical recovery (fever, respiratory rate, oxygen saturation, and cough) on D7 and at the end of treatment	Recovery after 7 days of treatment: 61.21% with Favipiravir vs. 51.67% with arbidol (p- = 0.01396). In the group of non-critically ill patients, 71.43% with favipiravir X 55.86% with arbidol (p =

						0.0199). Fever / cough duration: 4/8 days on Favipiravir X 7/10 days on Arbidol (p<0.0001)
Monoclonal Antibodies						
Convalescent serum	Zhang B et al. CHEST 2020	China	Case series	4 patients	There is no outcome, as it is a series of cases. The 4 treated patients were severely ill and did not respond to other treatments.	The 4 patients showed clinical improvement after the use of plasma. Three patients were discharged from the hospital and 1 was transferred to a non-COVID ICU to continue dialysis
Convalescent serum	Shen C et al. JAMA 2020	China	Case series	5 patients	There is no outcome, as it is a series of cases. The 5 treated patients were severely ill and did not respond to other treatments.	The 5 patients showed clinical improvement after receiving the transfusion (improvement in fever, improvement in the PaO2/ FiO2 ratio) and radiological improvement. Drop in SARS-CoV2 viral load was also observed
Antimalarials						
Chloroquine (CQ)	Antimaláricos Huang M et al. JMCB 2020	China	CQ Group 500mg 2x/ day for 10 days Lopinavir/Ritonovir Group (400mg/100mg 2x/ day for 10 days)	22 patients Moderate form Severe form (dyspnea and hypoxemia)	Virus clearing Chest CT Hospitalization time	Virus clearing faster in CQ group D9 PCR (-) CQ Group 6 (60%) Lopinavir/Ritonovir 3 group (25%) CQ Group: D14 Improvement CT (RR 2.21 - CI 0.81-6.67) Discharge CQ group 100% and Lopinavir/ Ritonavir 50%
Chloroquine (CQ)	Borba MGS, et al. MedRxiv 2020	Brazil	Randomized double-blind Oral CQ group or nasogastric tube (600 mg 2x/day for 10 days or total of 12g) Oral CQ group or nasogastric tube (450mg/ day 2x/ day on the first day and then 450mg/ day for 5 days or 2.7g total dose). All patients received ceftriaxone and azithromycin and underwent baseline ECG and during treatment.	81 patients Inclusion criteria: RR> 24 bpm and or HR> 125 bpm and or 90% saturation and or shock with suspected COVID-19	Adverse events death in 24 days duration of mechanical ventilation and hospitalization Virus detection on D0 and D4	No difference in outcomes. CQ group (high dose) increased case fatality rate 17% 2 patients had ventricular tachycardia and death. 1 patient developed rhabdomyolysis Many patients did not complete 10 days.
Hydroxychloroquine (HCQ)	Gautret P, et al. IJAA, 2020	France	Inclusion criteria: age> 12 years and PCR + for SARS-coronavirus-2 Exclusion: HCQ allergy, QT prolongation, G6DP deficiency, pregnant and postpartum women HCQ Group (600mg/ day for 10 days) vs. HCQ Group (600mg/ day for 10 days) + Azithromycin (500mg/ 1 day and 200mg from 2 to 5 days) vs. Control Group (no drugs- patients who	22 patients with high respiratory symptoms		HCQ Group (N = 20) (PCR negative 70%) Control group (N = 16) (PCR negative 12.5%) HCQ + Azitro Group (N = 6) 100% negative PCR HCQ Group (N = 14) 57% negative PCR Control Group (N = 16) 12.2% negative PCR 6 (p <0.01)

			refused to participate) daily PCR and HCQ serum level	8 with low respiratory symptoms (CT pneumonia) 6 asymptomatic		
Hydroxychloro-quine (HCQ))	Molina et al. MMI 2020	France	Adult patients with PCR + HCQ (600mg/day for 10 days) + Azithromycin (500mg/ 1 day and 200mg from 2 to 5 days) Serum HCQ measurement	11 patients	Virus clearing from nasopharynx by PCR 5th and 6th day	1 death- 5 days 1 patient - QT enlargement (treatment suspended) Positive PCR on day 5: 8/10 pts (80% CI 49-94) HCQ serum level: 678 ng/ mL (varied 381-891 ng/ mL)
Hydroxychloro-quine (HCQ)	Guatret et al. MI 2020	France	Descriptive HCQ (200mg 3x daily dose of 600mg/day for 10 days) + Azithromycin (500mg / 1 day and 200mg from 2 to 5 days) Serum HCQ measurement Patient News Score > 5, same schedule + ceftriaxone ECG before treatment and two after beginning	80 patients	D7 PCR virus clearing D8 virus culture Use of oxygen therapy and/or transfer to the ICU after 3 days of treatment	Discharge 65/80 (81%) patients 93% with low NEWs score 15% received oxygen therapy 3 patients transferred to ICU 1 death 86 years old patient D7 80% PCR (-) D8 9D8 93% viral culture (-)
Hydroxychloro-quine (HCQ)	Chen et al. J ZU 2020	China	1: 1 randomization Inclusion Criteria: Pts PCR + HCQ Group (400mg / d for 5 days) x control group	30 patients	Virus clearing from nasopharynx by PCR 7th day Hospitalization time Symptoms: fever	HCQ group N = 13 (PCR (-) 86.7%) Control group N = 14 (PCR -) 93%) P> 0.05 No difference in symptoms
Hydroxychloro-quine (HCQ)	Chen et al. medRxiv 2020	China	Randomization 1: 1 Inclusion Criteria: Pts PCR + CT pneumonia patients R SaO2 / SPO2> 93% R PaO2 / FIO2> 300 Check the exclusion criterion in the Trial: retinopathy, arrhythmia, block, liver disorder, etc. HCQ group (400mg/d for 5 days) vs. Control group	62 patients	D5 Symptoms Recovery time Radiological findings	No difference in age and gender in the two groups HCQ Group; shorter duration of fever (p = 0.008) and cough (p = 0.0016) Improvement in pneumonia Chest CT image 25/31 (80%), p = 0.048 Adverse effects 2 (6.4%) Control group: Improvement of pneumonia Chest CT image 17/31 (54.8%) Adverse effects: 0
				Anticoagulants		
Heparin	Tang N et al. JTH 2020	China	Retrospective study. "Sepsis-induced coagulopathy" (SIC) score validation and other coagulation parameters to identify patients who would benefit from anticoagulant therapy	449 patients with severe COVID-19 admitted between 1st Jan-13 Feb/2020. Retrospective analysis of the use of unfractionated or low molecular weight heparin for ≥7 days		99/449 (22%) patients received heparin (94 enoxaparin-40-60 mg/day and 05 heparin 10,000-15,000U/day) for ≥7 days; 97/449 (21.6%) had SIC ≥4 at the time of classification as severe Around the 28th day of evolution, 315 (70.2%) survivors X 134 (29.8%) deaths.

						There was no difference in 28-day mortality between users and non-users of heparin (30.3% X 29.7%; P = 0.910). In stratification of the SIC score and D-dimer result, mortality at 28 days for patients who used heparin and with SIC score ≥4 was lower (40% X 64.2% (P = 0.029) when compared with SIC <4. In D-dimer stratification, mortality among heparin users did not change. However, in the group without heparin, mortality increased with an increase in D-dimer. D-dimer value> 3.0 ug/mL showed a 20% reduction in mortality with heparin (32.8% X 52.4%; (P = 0.017). Anticoagulant therapy (mainly with low molecular weight heparin) can benefit selected populations of COVID-19 patients, such as those who meet criterion of SIC ≥4 or with significantly elevated D-dimer
Antithrombin and / or heparin	Camprubí-Rimblas M et al. JTH 2020	Spain	Experimental study with the objective of studying the effects of nebulization with antithrombin III (TA) associated or not with heparin in an animal model of acute lung injury.	Acute lung injury induced in rats by the administration of hydrochloric acid and lipopolysaccharide. Antithrombin III only (500 IU/Kg) or associated with heparin (1,000 IU/Kg) in nebulization (intervention group) X control group with nebulization + saline	Evaluation of coagulation factors and pulmonary inflammatory response	Nebulization with anticoagulants reduced the concentration of proteins in the lungs and lung injury mediated by coagulation factors (tissue factor, plasminogen activation inhibitor, fibrinogen degradation product plasminogen) and inflammation (tumor necrosis factor, interleukin) in the alveolar space without affecting the coagulation system or bleeding. The combination of AT IIIe and heparin did not produce a synergistic effect.