ORIGINAL ARTICLE

COVID 19 AND THEN, WHAT? DIAGNOSTIC-THERAPEUTIC APPROACH TO RESPIRATORY SEQUELS

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SUMMARY:

Pulmonary involvement in COVID 19 is mediated by the cytokine cascade, endotheliitis , and thrombosis. These pictures lead to evolution to pulmonary fibrosis, or worsening of pre-existing morbid respiratory conditions . In this article, we analyze the existing alternatives to avoid these consequences.

INTRODUCTION:

At the end of December 2019, the incidence of atypical pneumonia of unknown cause was reported in the Chinese city of Wuhan.

This species was named SARS-CoV-2 due to its structural similarity to SARS-COV.

The only significantly different portion is a furin -binding domain on protein S of SARS-CoV-2, which has been speculated could expand the tropism or increase the transmission of the virus, compared to SARS - CoV of 2003.

Since its first report, different variants have followed one another, some of them of concern.

Variant classification scheme defines four classes of SARS-CoV-2 variants:

Supervised variant (VBM)

Alpha (lineages B.1.1.7 and Q)
Beta (B.1.351 and descendant lineages)
Gamma (P.1 and descendant lineages)
Delta (B.1.617.2 and AY lineages)
Epsilon (B.1.427 and B.1.429)
Eta (B.1.525)
Iota (B.1.526)
Kappa (B.1.617.1)
1,617.3
Mu (B.1.621, B.1.621.1)
Zeta

Variant of Interest (VOI)

Variant of Concern (VOC)

Omicron (lineages B.1.1.529, BA.1, BA.1.1, BA.2, BA.3, BA.4 and BA.5)

High Consequence Variant (VOHC)

To date, no high consequence variants have been identified.

Globally, the number of new cases and deaths from COVID-19 has continued to decline since the end of March 2022.

During the week of May 2-8, 2022, more than 3.5 million cases and more than 12,000 deaths were reported, decreases of 12% and 25%, respectively, compared to the previous week. However, an increase in the number of new weekly cases was reported in the Region of the Americas (+14%).

As of May 8, 2022, more than 514 million confirmed cases and more than six million deaths have been reported worldwide.

If it is considered that the confirmed cases are only a percentage of the total cases (since the asymptomatic ones will not attend the consultation, nor will they be systematically tested), it is concluded that mortality would be well below 1% (Fig. 1).).

Proportionally, the African Continent -the least affected by the current pandemic- will present an even greater decrease in the incidence of this pathology, close to 94%, during the current year, according to the latest WHO projection.

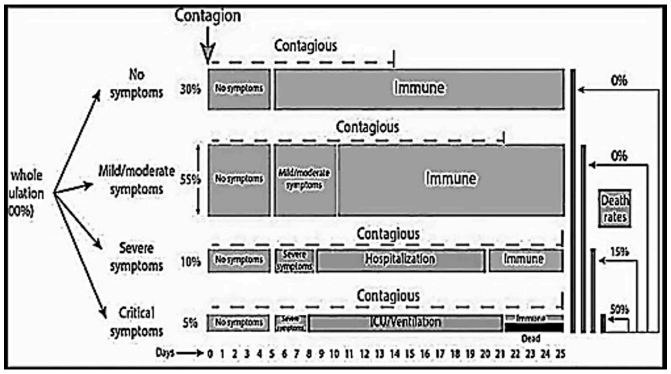


FIG. 1: CLINICAL MANIFESTATIONS AND POSSIBILITY OF CONSULTATION

CURRENT KNOWLEDGE ABOUT COVID IN THE RESPIRATORY SYSTEM

The first reported cases, as has already been said, refer to the compromise of the respiratory system.

This is the apparatus most frequently compromised by severe forms of the disease.

To quantify the extent of infection, a severity score was calculated by adapting and simplifying the Radiographic Assessment of Pulmonary Edema (RALE) score proposed by Warren et al.

A score of 0-4 was assigned to each lung depending on the degree of involvement by consolidation or GGO (0 = no compromise; 1 = <25%; 2 = 25-50%; 3 = 50-75%; 4 => 75% of participation).

The data for each lung was added to produce the final severity score.

Examples are given in Figure 2, divided into A, B, C and D.

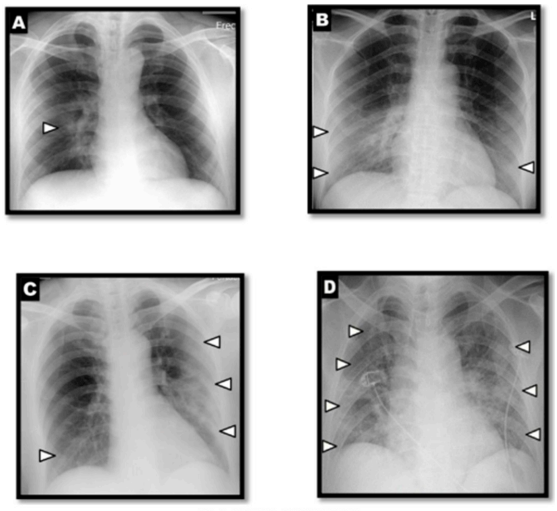


FIG. 2: RADIOGRAPHIC FINDINGS

RESPIRATORY COMPROMISE AND COMPUTED TOMOGRAPHY

Most patients with COVID-19 pneumonia have typical imaging features such as ground-glass opacities (GGO) (87 [86.1%]) or mixed GGO and consolidation (65 [64.4%]), vascular enlargement in injury (72 [71.3%]) and traction bronchiectasis (53 [52.5%]).

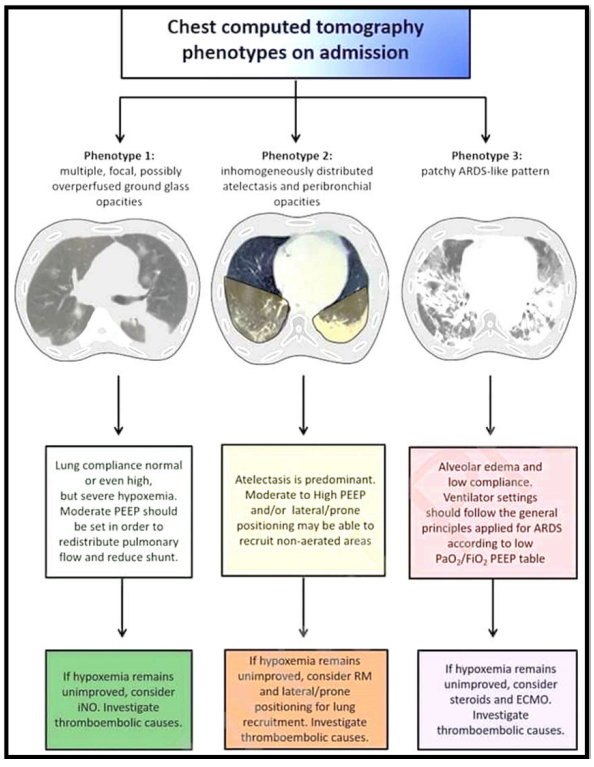
Lesions present on CT images might be more likely to have a peripheral distribution (88 [87.1%]) and bilateral involvement (83 [82.2%]) predominantly lower lung (55 [54.5%]) and multifocal (55 [54.5%]) .

Patients in the emergency group were older than those in the non-emergency group.

Architectural distortion, traction bronchiectasis, and CT involvement score will aid in the assessment of the severity and extent of the disease.

Score Summary

- Up to approximately 50% of patients with COVID-19 infection may have CT scans 0 to 2 days after onset of symptoms similar to COVID-19 complaint
- RT-PCR sensitivity of COVID-19 can be as low as 60-70%; therefore, the Patients with pneumonia due to COVID-19 may have lung abnormalities on CT scans chest but an initially negative RT-PCR.
- Lung abnormalities during the early course of COVID-19 infection generally peripheral focal or multifocal ground-glass opacities that arise to both lungs in approximately 50% to 75% of patients.
- As the disease progresses, the “crazy pavement” pattern and consolidation predetermined in CT dominants, reaching a maximum of 9 to 13 days, followed of a slow cleaning of about 1 month and more. basic tomographic findings are summarized in Figure 3.



In a Mexican study of 59 patients admitted for COVID and submitted to tomographic studies, the percentage findings were as follows:

tomographic pattern
Ground Glass Opacities (29)
Consolidation (2)
Stoned (30)
Mixed (39)
Location
One-sided (12)
Two-sided (88)
Lobe involvement
Top (36)
Middle or lingula (5)
Bottom (55)
All (4)
Distribution
Subpleural (48)
Peribronchovascular (central) (16)
Subpleural-peribronchovascular (16)
Patches (20)
Other findings
Lymphadenopathy (25)
Atelectasis (23)
Nodules (9)

CLINICAL MANIFESTATIONS

However, there has been no parallel between the extent of lung lesions and the degree of dyspnea.
Thus, patients have been seen whose blood oxygen saturation levels are extremely low, but who hardly present dyspnea.
In these patients, the disease does not present as respiratory distress syndrome acute (ARDS).
The concern with this presentation, called “silent hypoxia,” is that patients presenting to the hospital in worse health than they think.
Many coronavirus patients present to hospital with oxygen saturations close to 80, but not all feel dyspneic.
There are three main reasons why people experience breathlessness.
One is something that obstructs the airways, which is not a problem in COVID-19.
Another is when carbon dioxide builds up in the blood.
A good example of that phenomenon is during exercise: increased metabolism means more carbon dioxide production, which leads to intense breathing to exhale all that CO2.
A third phenomenon, particularly important in respiratory disease, is decreased lung compliance (pulmonary compliance). This also happens in COVID-19.
But in some patients, the fluid buildup isn’t enough to make the lungs particularly stiff.
Your oxygen levels may be low for an unknown reason that doesn’t involve fluid buildup, and one that doesn’t trigger the need to go into tachypnea.

PATHOLOGICAL ANATOMY

In China and other countries, biopsy samples were taken from the lung, liver, and heart tissue of patients who died in the course of COVID 19 infection.
Histological examination showed bilateral diffuse alveolar damage with fibromyxoid exudates. Cell phones . The right lung showed obvious desquamation of pneumocytes and membrane formation. Hyaline, indicating acute respiratory distress syndrome (ARDS).
Left lung tissue showed pulmonary edema with hyaline membrane formation, suggestive of early ARDS.
Interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes, were observed in both lungs.
Multinucleated synsytial cells with atypical enlarged pneumocytes were identified characterized by large nuclei, amphiphilic granular cytoplasm, and prominent nuclei in the intraalveolar spaces , showing viral cytopathic changes.
Obvious intranuclear or intracytoplasmic viral inclusions were identified.
The pathological features of COVID-19 closely resemble those seen in SARS and the Middle East respiratory syndrome (MERS) coronavirus infection .
In addition, liver biopsy samples from the COVID-19 patient showed steatosis microvesicular and mild lobular and portal activity, indicating that the lesion could have been caused by SARS-CoV-2 infection or drug-induced liver injury.
There were some interstitial mononuclear inflammatory infiltrates, but no other damage.Ssubstantial in cardiac tissue. Peripheral blood was prepared for flow cytometry analysis.
We found that peripheral CD4 and CD8 T-cell counts were substantially reduced, while their status was hyperactivated , as evidenced by high proportions of HLADR (CD4 3; 47%) and CD38 (CD8 39; 4%) double-positive fractions.
In addition, there was a higher concentration of highly proinflammatory CCR6 + Th17 in TCD4 cells.
In addition, CD8 T cells were found to harbor high concentrations of granules cytotoxic , in which 31 6% of the cells were positive for perforation, 64; 2% cells were positive for granulisin and 30; 5% of cells for granulisin and double positive for performance .
These results imply that the hyperactivation of T cells, manifested by the increase in Th17 and the high cytotoxicity of CD8 T cells, explains, in part, the severe immune injury in this patient.
Huang et al. suggested a cytokine storm (ie, higher concentrations of granulocyte colony-stimulating factor, gamma interferon-induced protein 10, monocyte chemoattractant protein 1, inflammatory protein 1α, and tumor necrosis factor α) might be associated with severity of the illness. FIG. 4

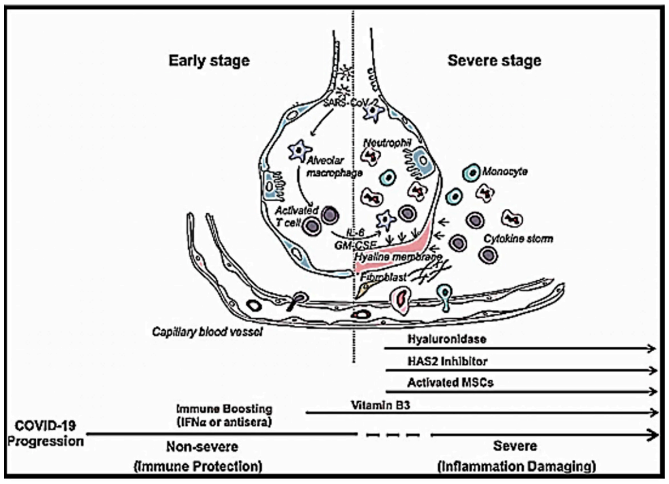


FIG. 4: CYTOKINE STORM

Another study from China reported that increased expression of interleukin (IL)-2R and IL-6
appears to predict the severity and prognosis of COVID-19 patients.
In addition, pathological examination of patients who died from COVID-19 revealed infiltrates Interstitial mononuclear inflammatory cells in both lungs, dominated by lymphocytes.
Therefore, cytokine storms should not be neglected in the treatment of COVID-19.
In a study conducted on 28 patients in South Korea , except for 2 patients who did not show symptoms, six of the 26 patients were hospitalized and required supplemental oxygen therapy.
The others showed little limitation in daily activity during hospitalization.
Although neutrophilia or neutropenia were not common, regardless of severity Clinically , lymphopenia (defined as ≤ 1.0 × 109/L) was more common in severe cases (33.3%, 2/6) than in mild cases (18.2%, 4/22) during the clinical course.
High levels of protein C are reactivated in the blood and are seen more frequently in severe cases as the clinical course worsens during the period 5-7 days after the onset of symptoms.
Endothelial dysfunction is a major determinant of microvascular dysfunction by shifting the vascular balance toward increased vasoconstriction with subsequent organ ischemia, inflammation with associated tissue edema, and a procoagulant state.
Therefore, pulmonary thrombosis (micro and mesothrombosis) largely explains the respiratory failure observed in these patients.
These demonstrations show the presence of viral elements within the endothelial cells and an accumulation of inflammatory cells , with evidence of inflammatory and endothelial cell death.
These conclusions suggest that SARS-CoV-2 infection facilitates the induction of endotheliitis in various organs as a direct consequence of viral involvement (as seen with the presence of viral bodies) and the inflammatory response of the host, due to disruption of Virchow's Triad. FIG. 5 and 6
Furthermore, the induction of apoptosis and pyroptosis could play an important role in endothelial cell injury in COVID-19 patients.
COVID -19 endotheliitis could explain the systemic microcirculatory function in different Vascular beds and their clinical sequelae in patients with COVID-19.

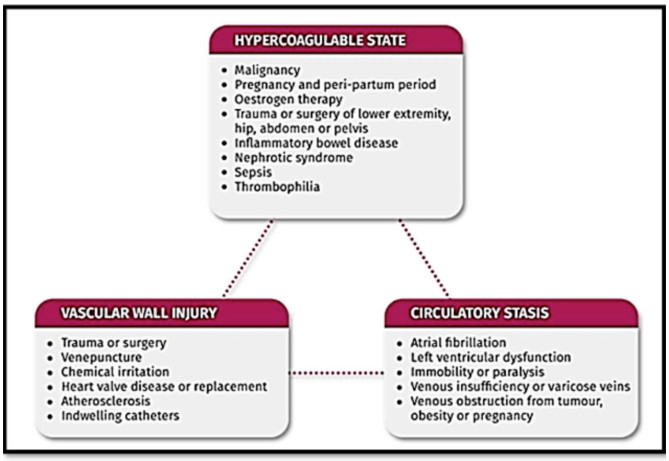


FIG. 5: VIRCHOW'S TRIAD DISRUPTION

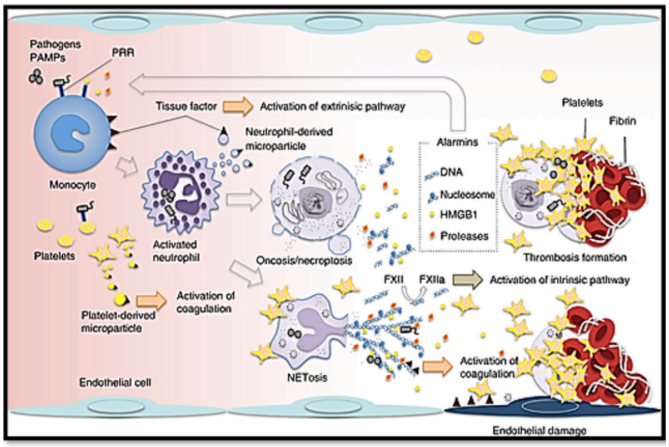


FIG. 6: THROMBUS FORMATION FROM ENDOTHELITIS

SEQUELS OF COVID 19 INFECTION

They have been compiled in an extensive work carried out in the Middle East, and can summarizes as follows:

A. Cardiorespiratory

1. Cardiology

Increased incidence of coronary heart disease

2. Respiratory

Thickening of the intralobular and interlobular septum
FEV 25-75 impaired
Reduced diffusion capacity
Cor pulmonale secondary to mesothrombosis and fibrosis

B. Glycometabolic

1. Increased risk of dyslipidemia
2. Increased risk of hyperglycemia

3. Endocrinological complications
hypocortisolism
primary and central hypothyroidism
C. Neuropsychiatric
1. Neuromusculoskeletal
Persistent musculoskeletal aches and pains
femoral head necrosis
Residual lesions to stroke
2. Psychiatric complications
depression
Post-traumatic stress disorder and panic disorder
somatoform pain disorder
Chronic Fatigue Syndrome

THICKENING OF THE INTERALVEOLAR SEPTA

pathological finding is the substrate of Pulmonary Fibrosis (FP) and Interstitial Lung Diseases (ILD). FIG. 6

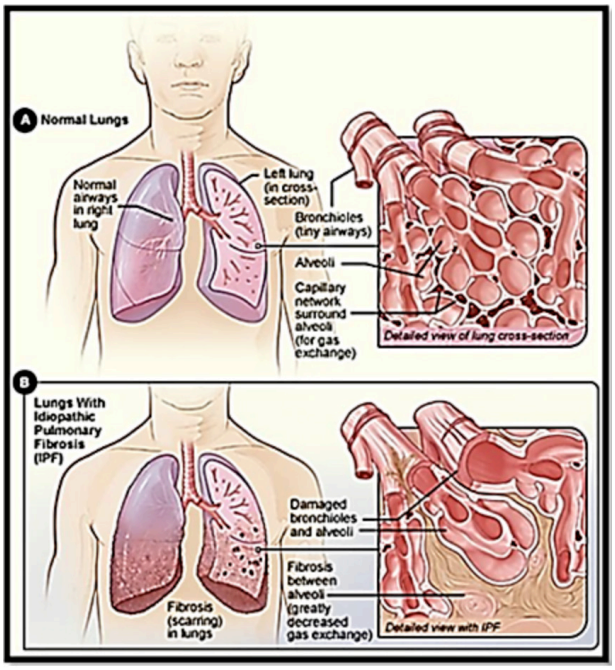


FIG. 6: FINDINGS IN PULMONARY FIBROSIS

Interstitial lung diseases include a heterogeneous group of disorders characteristics by thickening of the alveolar septa, appearance of fibroblasts, deposition and, if the process continues unchecked, pulmonary fibrosis.
These diseases can be classified using different criteria (eg, acute and chronic, granulomatous and non-granulomatous, with known and unknown causes, primary lung disease and disease secondary to systemic disorders).
Pulmonary fibrosis is characterized histologically by inflammation and fibrosis, which affects predominantly to the alveolar walls and perialveolar structures with remodeling of the lung tissue.
Inflammation is the result of damage to the alveolar-capillary unit, which can recover completely or partially, or progress to fibrosis.
This can vary in extent and speed of progression.
In children, it may have known causes or be idiopathic.
Among the many possible causes, the most important are connective tissue disorders and occupational pulmonary exposures and many drugs.
Several interstitial lung diseases of unknown etiology that have typical histologic, clinical, or presentation features and are therefore considered unique diseases, such as:
Eosinophilic lung diseases
histiocytosis (granulocytosis)
Lymphangioleiomyomatosis
Pulmonary alveolar proteinosis
Sarcoidosis
In up to 30% of patients with unexplained interstitial lung diseases, the disorders are distinguished primarily by histopathologic features; these disorders are called idiopathic interstitial pneumonias.
As the knowledge of these entities advances, the number of “idiopathic”, but it still implies a high percentage.
The list is extensive; and COVID 19 must be added to it. It is also clear that those patients who previously suffered from PF will see their condition worsen if they contract COVID.

CHANGES IN FEV 25/75: ITS DETERMINATION USING FORCED SPIROMETRY

It is the most useful and most commonly used technique.
The mechanics of forced expiration are active, and dependent on the force produced by the chest wall. The expiratory abdominal and intercostal muscles comprise the thorax, and the latter to the alveoli, giving rise to an alveolar pressure + that pushes air out.
That amount of air exhaled, and the speed at which it moves, determines multiple values spirometric :
Forced Vital Capacity (FVC, or Forced Vital Capacity, FVC)
Peak expiratory volume in the first second (FEV, or Forced Expiratory Volume1, FEV1)
FEV1 / FVC ratio (Represented in some spirometers as FEV1 / FVC % or FEV1%)
Maximum expiratory flow (PEF, or Peak expiratory Flow, PEF)
Peak expiratory flow at 50% (FEF50%)
Peak expiratory flow at 25% (FEF25%) and at 75% (FEF75%)
Forced vital capacity in 6 seconds (FVC6 or Forced Vital Capacity6, FVC6)
FEV1 / FVC6 ratio
Peak expiratory volume in 0.5 seconds (FEV0.5, or Forced Expiratory Volume0.5, FEV0.5)
Lower Limit of Normal (LLN, or Lower Limit of Normal, LLN)
Extrapolated volume (VE, or Extrapolated Volume , EV)
Forced expiration time (TEF, or Forced expiratory time , FET)
Peak expiratory time (TPE, or Peak expiratory time , PET)
Let’s see the value that is the reason for our study:
Peak expiratory flow between 25% and 75% of FVC or

mid- expiratory flow (Forced
Expiratory flow25–75%, FEF25–75%)
It provides information on how much of the total air exhaled makes it between 25 and 75% of the expiration time. It is a flow, and can be expressed as ml/s or as a percentage against its theoretical figures. Its normal value is greater than 60%.
Since for its calculation it eliminates the initial and final part of the flow-volume curve (which are more effort-dependent, and therefore less objective), is considered an early marker of damage to the small airways, so that it can be altered much earlier than the other spirometric data.

THE THERAPEUTIC APPROACH FOR IPF NON-PHARMACOLOGICAL AND PHARMACOLOGICAL STRATEGIES

The goals of treatment in IPF are probably to stop disease progression, reduce symptoms , prevent acute exacerbations, a major fatal complication that occurs in approximately 5% to 15% of patients, and ultimately prolong survival.
Preventive care, rehabilitation, and symptom-based treatment must begin early in each patient to combat diminished quality of life.
Inactivity due to shortness of breath leads to loss of muscle mass (sarcopenia) and disabling chronic fatigue in patients with IPF.
Pulmonary rehabilitation not only relieves symptoms by lowering the dyspnea threshold, but also improves functional status by stabilizing and/or reversing the extrapulmonary features of the disease.
Patients should be referred to rehabilitation as standard care as soon as possible after diagnosis, before the impact of symptoms on health-related quality of life becomes irreversible.
Long-term oxygen therapy is essential for patients with hypoxemia at rest or at night.
Although there are no randomized clinical trial data on the usefulness of oxygen therapy in IPF, it has been shown that oxygen therapy can improve quality of life by affecting physical and social performance.
Chest physiotherapy is a treatment program that attempts to compensate for mucociliary impairment.
By removing mucopurulent secretions , it reduces airway obstruction and its consequences, such as atelectasis and hyperinflation.
In addition, physical therapy can decrease the rate of proteolytic tissue damage by removing the infected secretions.
Conventional physical therapy (clapping, vibration, and compression, along with postural drainage and assisted coughing) is the most efficient physical therapy for sick infants and young children.
Later, mechanical chest percussion may reduce the patient's dependence on others.
The forced expiration technique is another method of self -treatment , which employs techniques expiratory breaths to expel secretions from the bronchi.
Autogenic drainage, a special breathing technique, aims to prevent compression of the airways by reducing pressure Positive expiratory transthoracic .
PEP mask physiotherapy achieves the same goal by exhaling against an obstruction external airflow.
Last but not least, physical exercise can cleanse the lungs of some CF patients and therefore offers an attractive adjunct to physical therapy.
Although they are diseases whose diagnosis and management is carried out in the specialized field of pulmonology, the treatment is followed, above all, on an outpatient basis, and since this can and usually is affected by various complications, it is important that the Primary care doctor knows the current guidelines with which the treatment of these diseases is focused, since on many occasions he will be consulted by patients with this type of problem, whether due to respiratory complications or of another type.

PHARMACOLOGICAL OPTIONS IN FP AND EPI

The lung scarring that occurs in interstitial lung disease cannot be reversed, and treatment is not always effective in stopping the final course of the disease. Treatments may temporarily improve symptoms or slow the progression of the disease.
Others can improve quality of life.

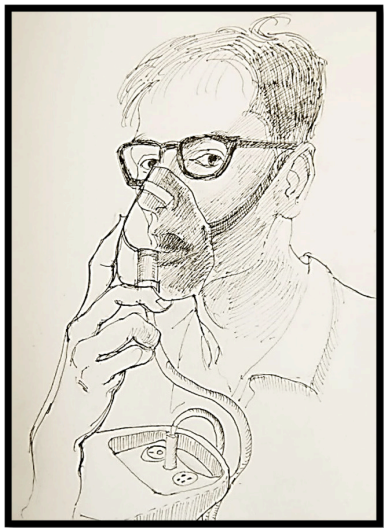
MEDICINES

Intensive research is underway to identify treatment options for types of interstitial lung disease.
However, based on currently available scientific evidence, the physician may recommend:

Ibuprofenate by inhalation.
Its use can also be extended to other forms of COLD . It is recommended to start with the administration of hypertonic ibuprofen to all patients who qualify as a suspected case of COVID-19 immediately and empirically, until the positivity of the patient's RT-PCR is confirmed. One ampoule should be nebulized every 8 hours using a nebulizer. The nebulizations will extend until the confirmation of RT-PCR negativity, if not confirmed, the administration of hypertonic ibuprofen is cancelled.
The use of hypertonic ibuprofen is contraindicated in patients with hypersensitivity to ibuprofen, ketoprofen , flurbiprofen, and naproxen. Hypertonic ibuprofen, comes in an ampoule presentation containing 50 mg/mL. The patient must use an ampoule in each session to be

performed every 8 hours for a period of not less than 20 minutes or until the 5 ml of the medication are consumed of study. The content of each ampoule should be placed in the nebulizer.

The assigned personnel must evaluate the patient throughout the session, not in person, and in case of intensification of bronchial hyperreactivity, act accordingly. For nebulize the patient, an OMRON NE-C801 nebulizer, Melipal , model 1002, will be used C series, or similar models.



The duration of the treatment must be carried out until the RT-PCR is negative. Thetreatment could vary depending on the conditions in which it is encounters the patient at the beginning and the concomitant diseases that he/she presents, should not exceed 28 days, but if it is kept longer it should not cause any damage.

It should be noted that there are patients who are receiving this medication for a period more than a year on a daily basis.

In any case, it is recommended to stop the medication when the patient has criteria for discharge, or cure of, COVID-19, based on the criteria of the treating physician.

Patient with pneumonia, includes clinical/radiological diagnosis of pneumonia, but without criteria for intubation, start with 1 ampoule of 50 mg/ml every 8 hours. In this condition to prevent aerosolization , the patient must be in an isolated room possible . If possible, use a nebulizer that guarantees the arrival of the drug to the alveolus. The antiviral filter must be replaced every 30 days.

The duration of treatment should not be less than 14 days or until confirming the negative nasopharyngeal swab (according to the protocol of the province of Córdoba).

Safety measures, hypertonic ibuprofen has been shown to be a very safe drug in the patients used, but could the patient experience cough at the beginning of the nebulizations and progressively begin to yield with successive sessions.

Corticosteroids. Many people who are diagnosed with lung disease interstitial , they are initially treated with corticosteroids (prednisone), sometimes combined with other drugs that suppress the immune system.

Depending on the cause of interstitial lung disease, this combination may slow or even stabilize disease progression. In order to achieve greater bioavailability in the lung, and -at the same time- reduce the secondary impact on the body, this modality can be used by inhalation, through:

Budesonide aerosol, alone or in combination (budesonide + formoterol)

Fluticasone aerosol, alone or in combination (Fluticasone + salmeterol)

Beclometasone aerosol, alone or combined (Beclometasone + salbutamol)

Immunomodulators . Medications that slow the progression of idiopathic pulmonary fibrosis.

The medicines pirfenidone and nintedanib can slow down how fast the disease progresses .

disease .

Treatment-related side effects can be significant, limiting its use.

Anti-GER medications.

Gastroesophageal reflux disease affects the majority of people with idiopathic pulmonary fibrosis and is associated with increased lung damage.

These include H2 receptor antagonists or proton pump inhibitors, such as omeprazole and pantoprazole , and drugs that act locally, reacting with hydrochloric acid in the stomach to form a “buffer” effect, such as sucralfate.

Mucus fluidizers at the ciliary level.

They are: n-acetyl cysteine and 3% hypertonic sodium chloride solution for nebulizing.

In the last 2 decades, both have been used as mucolytic agents , with very good results.

Their low cost, lack of undesirable side effects, and the possibility of combining them with corticosteroids and/or aerosolized bronchodilators , constitute a very remarkable option.

Oxygen therapy.

Oxygen cannot stop lung damage, but it can:

Facilitate breathing and physical activity.

Prevent or lessen the complications of low blood oxygen levels.

Reduce blood pressure on the right side of the heart.

Improve sleep and sense of well-being.

You are more likely to be given oxygen while you sleep or exercise, although some people may need it all the time.

Surgery.

Lung transplantation may be an option of last resort for some people with severe interstitial lung disease who have not benefited from other treatment options.

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