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# **Rural treatment of COVID-19 patients with pirfenidone, nitazoxanide and colchicine.**

## **Case series**

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### **Abstract**

Combined treatments against SARS-CoV-2 are emerging and some have taken into account the post-COVID-19 fibrosis. The aim of this survey was to report the experience of treating COVID-19 patients with pirfenidone, nitazoxanide (NTZ) and colchicine. It was a case series report of COVID-19 patients treated from December 2020 to March 2021, in a rural health center located in the State of Mexico, Mexico. 23 patients were included (mean age  $44.5 \pm 17.1$  years), 12 women (mean age  $45.9 \pm 17.9$  years) and 11 men (mean age  $43 \pm 16.9$  years) with four deaths (17.39%). The evolution time was of  $17.3 \pm 6.7$  days being the main symptoms

fever (82.6%), myalgia (69.6%) and cough (65.2%). The main comorbidities were overweight/obesity 18 (78.26%), type 2 diabetes mellitus (T2DM) 4 (17.39%), Chronic obstructive pulmonary disease (COPD) 5 (21.73%) and systemic hypertension 2 (8.69%). Two patients were intubated and both died; in these cases, they refused to take NTZ until after three days the medical doctor had prescribed it for the first time. It can be concluded that implementing a mixed treatment with pirfenidone, NTZ and colchicine could improve the survival rate in ambulatory patients of low socioeconomic status.

**Key words:** colchicine, COVID-19, nitazoxanide, pirfenidone, pulmonary fibrosis.

## **Introduction**

In 1935, the social service for medical doctors was created in Mexico [1], when there were not enough medical doctors to serve the country. However, since then, the length of training of medical specialists has extended in years [2], and the medical human resources have increased considerably, as has the number of medical schools. In other words, they have become a cheap labor force for the health system and in this case, they support a large part of the first level of care, for example, in 2021 there were 34,000 medical interns performing social service [3].

The duration of social service in medicine is one year, with insignificant scholarships (from around 129.22 to 177.73 dollars per month). With this limited scholarship, social service interns have to survive in precarious conditions in the assigned community, often in totally isolated areas, with high marginalization and insecurity.

The actual health system establishes a paradox, requiring doctors who practice private and institutional medicine to present their degrees (professional title and license), and yet, a good part of the Mexican health system responsibility falls on doctors without degrees (the students in the social service) [4]. This paradox distances communities from receiving medical attention by qualified and certified personnel [5].

There are several threats that face the medical students in their social service beyond the low monetary stipend. The lack of means of communication and resources is evident in the communities where the medical students are sent for social service [6], but the most critical situation is that violence against the students during the social service is increasing [7], with many cases of sexual harassment, rapes and murders [8-12]. In this setting, the medical students have been facing the COVID-19 pandemic with a huge pressure to get optimal results.

On the other hand, pulmonary fibrosis is a fatal sequelae for some severe or critical COVID-19 cases [13]. In this regard, irrespective of patient lung function, traditional antifibrotics used in idiopathic pulmonary fibrosis should be encouraged [14]. Although several options from new drugs to traditional Chinese medicine have been tested to fight against pulmonary fibrosis [15], there is no universal consensus.

An outstanding Bayesian network meta-analysis of randomized controlled trials showed that Imatinib, intravenous immunoglobulin, and tocilizumab have a lower risk of death compared with the standard of care; baricitinib plus colchicine, dexamethasone, recombinant human granulocyte colony stimulating factor, remdesivir, and tocilizumab reduced the risk of mechanical ventilation; baricitinib, remdesivir, sarilumab, tocilizumab, and tofacitinib increased the hospital discharge rate; convalescent plasma, ivermectin, ivermectin plus

doxycycline, hydroxychloroquine, NTZ, and proxalutamide resulted in better viral clearance. Also, the use of antineoplastic agents has been associated with fewer cases of deaths [16].

It is very important to take into account that to define a treatment against SARS-CoV-2 in a rural community, the students had to choose from the national compendium [17], on which the one managed by the Health Institute of the State of Mexico (ISEM) is also based, finding in fact a previous descriptive experience with nitazoxanide (NTZ) [18], an Internal Medicine thesis in which the authors used colchicine [19] and at last, pirfenidone was added as an anti-inflammatory drug.

It is well known that pirfenidone has anti-fibrotic activity through the overexpression reduction of connective tissue growth factor, platelet-derived growth factors. Transforming Growth Factor-beta (TGF- $\beta$ ) and Tumor necrosis factor (TNF)- $\alpha$  [20]. Some studies reveal that pirfenidone delays the decline of forced expiratory vital capacity, thereby partly reducing the mortality in patients with idiopathic pulmonary fibrosis [21,22]. NTZ, its metabolite (tizoxanide) [23,24], and colchicine [25] also have anti-inflammatory properties. The aim of this survey was to report the experience of medical students working in a social service treating COVID-19 patients using a mix of drugs including pirfenidone, NTZ, and colchicine, prescribed simultaneously, in a rural community to reduce the lung fibrosis.

## **Materials and Methods**

This is a narrative description of a retrospective number of COVID-19 patients attended by medical students working in the social service, from December 2020 to March 2021, in a rural health center located at San Felipe del Progreso, State of Mexico, Mexico, 59 km from Toluca City, the capital of the State of Mexico, Mexico.

In San Felipe del Progreso, 51.4% of the population is in moderate poverty and 24.5% in extreme poverty, 39% has no access to sewage systems, 26.4% lack a water supply network, 5.12% have no bathroom, and 2.91% lack electricity [26]. One fourth of the municipality's inhabitants speak the native language, mainly Mazahua, although they can be considered bilingual because to carry out any public or private service the language of communication is Spanish.

The established treatment regimen was pirfenidone 600 mg bid for two weeks, NTZ 500 mg orally q6H for seven days, and colchicine 0.5 mg bid one day and then 1 mg bid for two weeks. NTZ and colchicine were added due to recent findings showing their effectiveness against the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [27-29] and the same

criteria was for colchicine [30]. Besides, more drugs were prescribed depending on the symptomatology.

The anthropometric and laboratory data were placed in an Excel sheet and the mean and percentages of the variables were calculated. Informed consent was waived as the data was extracted from archived medical files.

## Results

We included 23 patients in this report (mean age  $44.5 \pm 17.1$  years), 12 women (mean age  $45.9 \pm 17.9$  years) and 11 men (mean age  $43 \pm 16.9$  years). Eighteen (78.26%) patients had been in contact with a first relative with COVID-19 and five (21.74%) did not. Table 1 shows the main data of the patients. Four patients (2 women and 2 men) died (17.39%).

The time from the onset of symptoms until the patient was discharged or death was  $17.3 \pm 6.7$  days in the total population,  $16.9 \pm 7.6$  days in women and  $17.7 \pm 5.9$  days in men. The patients received treatment for  $13.3 \pm 7$  days for the total sample,  $14.1 \pm 7.6$  days for women and  $12.4 \pm 6.5$  for men. Three (13.04%) patients were hospitalized.

The main symptoms are listed in Table 2. Based on a previous publication managing a severity scale [22], our patients had a mean of  $23.1 \pm 14.2$  (range 1-41, from a maximum possible number of 43). Overweight/obesity (18, 78.26%), type 2 diabetes mellitus (T2DM) (4, 17.39%), chronic obstructive pulmonary disease (COPD) (5, 21.73%), and systemic hypertension (2, 8.69%) were the main comorbidities found.

Other drugs prescribed besides NTZ, pirfenidone, and colchicine include paracetamol (91.3%), ambroxol (91.3%), levofloxacin (69.6%), budesonide (60.9%), dexamethasone (56.5%), vitamin D (56.5%), enoxaparin (47.8%), rivaroxaban (43.5%), clarithromycin (26.1%), acetylcysteine (21.7%), loperamide (21.7%), furosemide (8.7%), insulin (8.7%), metoclopramide (8.7%), oseltamivir (8.7%), candesartan (4.3%), losartan (4.3%), metamizole (4.3%), metformin/pioglitazone (4.3%), metformin/sitagliptin (4.3%), paroxetine (4.3%), and tocilizumab (4.3%).

Eleven (47.82%) patients had oxygen at home (four with mask and oxygen concentrator, one with nasal cannula and oxygen concentrator, one with mask and five with nasal cannula) and 14 (60.9%) patients received palmopercussion. Two patients were intubated and both died, in these cases they refused to take NTZ until three days after the time prescribed.

Due to the low socioeconomical level of the patients, only five patients could pay for blood samples, and in those with a lung computed tomography scan, we found a clear remission of the lung damage (Figure 1 A,B). Unfortunately, Mexico still does not have a universal health

system, which makes it difficult for the most impoverished population to receive medical attention for any disease.

## **Discussion**

It is important to keep in mind that the efforts of social service students are praiseworthy as they do not have the same management options against COVID-19 as in the United States, for example, resources regarding ventilators, and medications [31-32]. Moreover, despite the geographical proximity to the United States, generally speaking, there will always be an authorization first by the Food and Drug Administration (FDA) of that country for any medicine, then by its Mexican counterpart Federal Commission for the Protection against Sanitary Risk (COFEPRIS), and although the North American Free Trade (NAFTA) exists, this does not facilitate the circulation of medicines in Mexico that have been already marketed in the United States or Canada.

It is important to note that in Mexico, rural municipalities reported a higher number of COVID-19 cases and mortality related to COVID-19 per million than urban municipalities [33]. To explain a little the real situation of San Felipe del Progreso, this community has a COVID-19 lethality rate of 16.98% [34]. Patients in this location have a mean month income of 3700 Mexican pesos ( $\approx$ 176 US dollar). Mazahua campesino systems in San Felipe del Progreso is dependent of draught animals with a significant correlation between ownership of them and incomes [35].

In relation to health, inhabitant from San Felipe del Progreso depend almost entirely on what can be given to them for free through the ISEM. Specifically, in this community there is only one general hospital for the general population, which has a general medicine office and 60 hospital beds [36]. In this circumstance, when a patient from San Felipe del Progreso requires hospitalization, the nearest hospital is located in Atlacomulco, half an hour away but when their services are saturated, they must refer patients to Toluca City, 90 min far away, meaning a risk of clinical compromise to the patients.

To date, different and varied drug options have been proposed, with actions at different points in the SARS-CoV-2 viral invasion and replication process [37]. As a matter of fact, fibrosis may become one of the major COVID long-term complications, even in asymptomatic individuals. Currently, despite the best efforts of the global medical community, there are no treatments for COVID-induced pulmonary fibrosis [38].

Many patients with post COVID-19 fibrosis do not improve with standard care, thus other drugs to limit the cytokine storm, severe inflammation, and oxidative stress are being researched.

Following this line of research, pirfenidone may have anti-inflammatory and antioxidant properties apart from being anti-fibrotic. In fact, it decreases lipo-polysaccharide (LPS)-induced lung injury and subsequent fibrosis by suppressing NLRP3 inflammatory reaction [39]. A previous article reported two cases of men with COVID-19 treated with pirfenidone 400 mg BID, which was later increased to 600 mg TID along with dexamethasone, empirical antibiotics, supplemental oxygen, and non-invasive ventilator support. Both patients improved and were discharged [40]. Also Momen described a good experience with prifenidone in five patients [41].

Concerning combinations, administering nintedanib with add-on pirfenidone is supposed to enhance its therapeutic benefit by simultaneously acting on two different pathogenic pathways. However, little information is available about their drug-drug interactions, which is important mainly in polymedicated patients [42].

Finally, immunostimulants could improve the prognosis of critical-type patients with COVID-19 [43]. Additional studies are needed to define the role of more drugs combinations in the treatment of COVID-19.

On the other hand, the possible benefit of NTZ has been argued in several studies [44,45] and more recently, the combined use of NTZ, ivermectin, ribavirin, and zinc supplement effectively cleared the SARS-COV2 from the nasopharynx in a shorter time than symptomatic therapy [46]. There are studies with contradictory information on colchicine, some encouraging its use [47,48] and others leaving a doubt on its effectiveness [49,50].

In a mixed strategy, a 60-year-old female was managed at home with corticosteroids, NTZ, a single dose of subcutaneous enoxaparin, and colchicine added at the third day of treatment. This addition led to clinical improvement, discontinuation of the medications, and the oxygen therapy two weeks after the initial consultation [51]. Although in Mexico research was done with a mixture of ivermectin, azithromycin, montelukast, and acetylsalicylic acid [52], ours is the first report of a wide drug mixture with pirfenidone + NTZ and colchicine. Even more, different schemes have been used in Mexico City to treat COVID-19, but besides the fact that these options are very expensive, they are not associated with decreased hospital mortality [53,54].

Bestetti *et al.* supports the experience that we shared, and proposed that a combination of colchicine, inhaled budesonide, and NTZ, along with nonpharmacological measures, would be useful against COVID-19 based on efficacy and costs. This is critical for middle-income countries [55].



We acknowledge the limitations of these case reports (for example, children were not included) and recognize that additional studies are needed to determine the actual benefit from pirfenidone + NTZ + colchicine to reduce lung fibrosis after COVID-19, but for rural conditions with a huge responsibility of medical students being pressured to get results in communities where they can suffer violence, the drug combination shared in this manuscript could be a good alternative. Finally, only a well-designed double-blind randomized controlled test could effectively analyze this hypothesis.

### **Conclusion**

Pirfenidone added to NTZ and colchicine was used in a rural Mexican community to treat COVID-19 patients at an early stage in populations without access to a third level hospital reaching a survival rate of 82.6%.

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**Table 1. General characteristics of the patients**

	<b>Full population (n=23)</b>	<b>Women (n=12)</b>	<b>Men (n=11)</b>
<b>Variable</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>
Age (years)	44.5 ± 17.1	45.9 ± 17.9	43 ± 16.9
MAP (mmHg)	89.6 ± 6.3	91.3 ± 7.2	87.7 ± 4.7
Heart rate (bpm)	98.9 ± 14.9	95.2 ± 12.8	102.9 ± 16.5
Breathe rate (rate per min)	17.2 ± 3.7	16.5 ± 3.4	18.0 ± 3.9
BMI (kg/m <sup>2</sup> )	29.2 ± 4.2	28.6 ± 5.0	30.0 ± 3.3
Temperature (°C)	37.2 ± 0.7	37.1 ± 0.4	37.3 ± 0.9
SO <sub>2</sub> (%)	81.7 ± 9.4	83.8 ± 6.6	79.2 ± 11.7

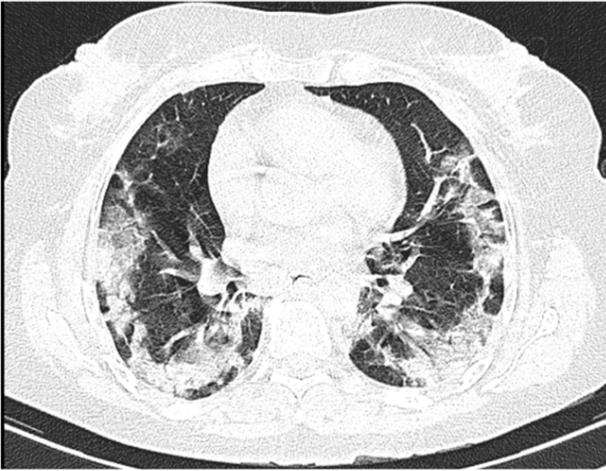
BMI, body mass index, MAP, mean arterial pressure, SO<sub>2</sub>, oxygen saturation.

**Table 2. Main symptoms in percentage.**

<b>Variable</b>	<b>Full population (n=23)</b>	<b>Women (n=12)</b>	<b>Men (n=11)</b>
Fever	82.6	75	90.9
Myalgia	69.6	34.8	72.7
Cough	65.2	66.7	63.6
Odynophagia	60.9	58.3	63.6
Dyspnea	52.2	33.3	72.7
Conjunctivitis	47.8	50.0	45.5
Arthralgia	43.5	33.3	54.5
Chest pain	56.5	58.3	54.5
Diarrhea	56.5	50.0	63.6
Nausea	43.5	41.7	45.5
Anosmia	39.1	50.0	27.3
Rhinorrea	34.8	50.0	27.3
Headache	30.4	25.0	36.4
Dysgeusia	21.7	25.0	18.2
Threw up	13.0	16.7	9.1
Diaphoresis	8.7	8.3	9.1
Anorexia	4.3	8.3	0.0

Figure 1. Chest computed tomography (CT) of one COVID-19 patient treated with pirfenidone, nitazoxanide and colchicine. A) Acute stage, B) control CT after 30 days.

**A**



**B**

