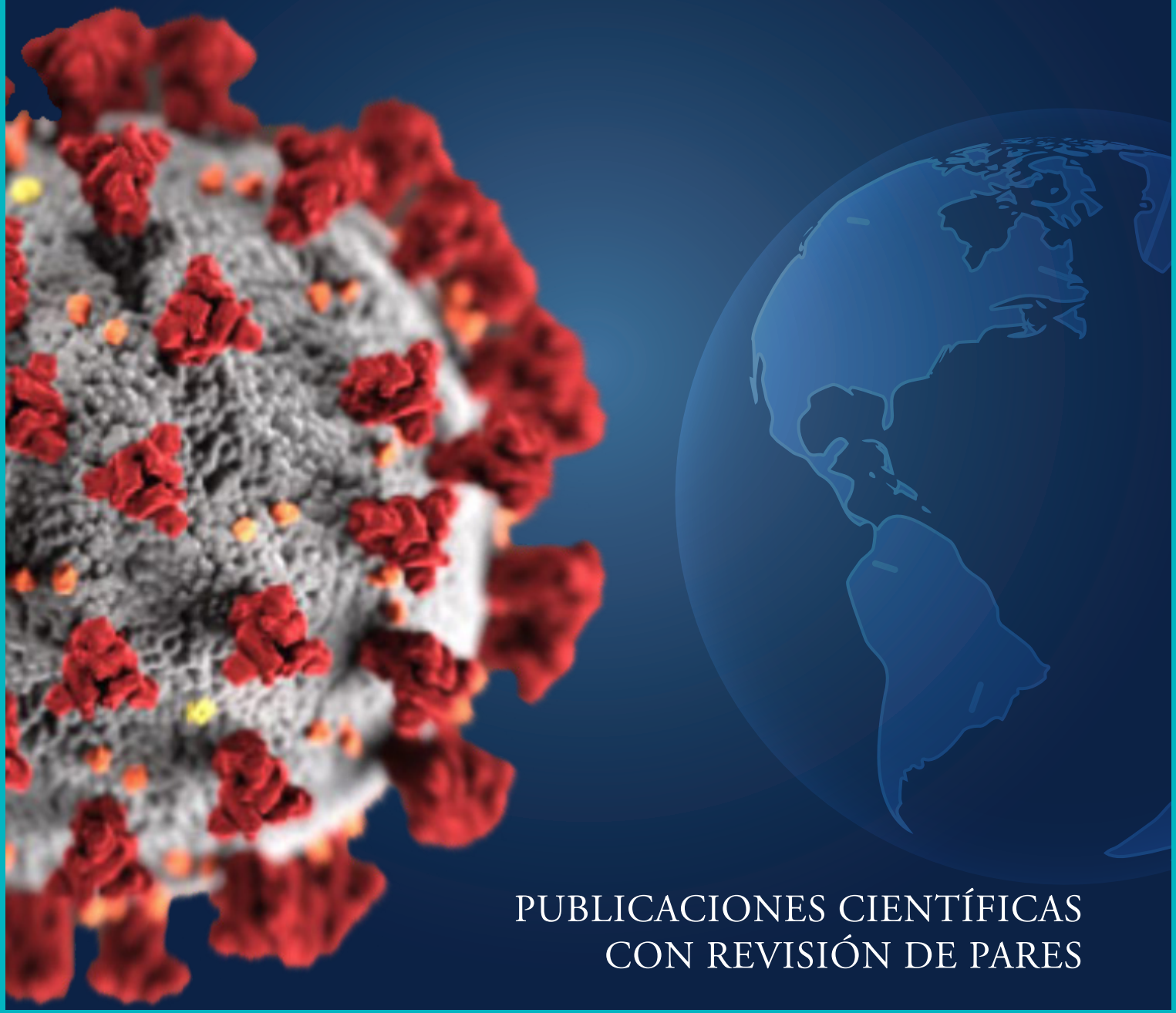
Profesor Dr. Roberto Hirsch • Profesor Dr. Héctor Carvallo

IVERMECTINA EN COVID-19

PROFILAXIS y TRATAMIENTO



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PRÓLOGO DE LOS AUTORES

Los albores de la pandemia por Sars Cov 2 despertaron en nosotros la inminente necesidad de poner al servicio de la ciencia nuestra vieja experticia.

Con juveniles bríos, iniciamos la comparación de esta nueva patología, con otras similares, superponiendo sus fisiopatogenias, cuando a la par, nos nutríamos con la nobel bibliografía que iba apareciendo.

Así, frente a un agente patógeno desconocido buscamos similitudes con otros, con los que estábamos familiarizados (adenovirus, herpesvirus, rabdovirus, paramixovirus, denguevirus, etc).

Ese fue el secreto para no correr detrás del COVID-19, sino el poder sacarle, al menos, un palmo de ventaja.

Esta pandemia –a diferencia de la anterior de 1918- no se caracterizó por la falta de información, sino por un alarmante aporte excesivo de material científico, la mayoría sesgado y basado en intereses espurios.

Como debe hacerse en estos casos, es fundamental separar la paja del trigo; invariablemente, hemos optado por el trigo…

Lo hicimos "a la vieja usanza": sin cortar ni pegar, decidimos pensar y analizar.

Es así que, como aporte a la humanidad, con el mayor respeto por los Derechos Humanos de nuestros semejantes, comenzamos con los diseños de lo que a posteriori fueron nuestros protocolos IDEA, IVERCAR e IVERPREV, destinados al Tratamiento y la prevención del COVID 19.

No es este el ánimo de describir las dificultades por las que tuvimos que pasar (y seguimos transitando) respecto a las autorizaciones para su uso, el que ha demostrado superlativa efectividad tanto en la terapéutica precoz cuanto a la profilaxis.

Con renovados ímpetus (a pesar de nuestras edades) concurrimos a aportar a la Comunidad nuestros trabajos, que ofrecemos desinteresadamente, para paliar la pandemia.

Al decir de Albert Camus, en su libro "La Peste" (1947): "… para combatir la peste no hace falta heroísmo; sólo se necesita decencia…"

Profesor Dr. Roberto Hirsch . Profesor Dr. Héctor Carvallo

Ivermectina y las dificultades que obstruyen sus resultados

Al encontrarme por los medios acerca de la ivermectina, indiqué a mi productora de radio-si , otro medio ,muy heterogéneo en sus contenidos y en plena pandemia- que dieran con sus investigadores y demostraciones . Pudo leer que , empleado desde hace tiempo como antiparasitorio, podia ser empleado como factor preventivo del virus y su tratamiento en el inicio de la enfermedad en una etapa determinada.

Así se hizo, de modo que podía – se informaba – era posible emplearse para una mayor inmunización . Llevado por la curiosidad- un buen motor de conocimiento- , frente a las dificultades en cuanto a vacunas y su distribución, ofrecía interés y una posibilidad de enfrentar el ataque planetario desde otra perspectiva que resultaba importante conocer. Y, desde luego, informar

En el programa conté aquella emisión con el doctor Héctor Carvallo, quien aceptó contar el modo en que obra la ivermectina y, con los meses, tuve al alcance de las numerosas pruebas empíricas de lo expuesto. El hecho es que, a la vez, muchas publicaciones con sus resultados era respondida con declaraciones ambiguas cuando no resueltamente no recomendable sin aclarar de manera clara la objeción correspondiente , aun con demostraciones numerosas de la disminución de la carga viral por las pruebas ofrecidas.

De modo que no me conduce a una defensa científica – no me corresponde en absoluto- ni una emoción sectaria que sería deplorable , sino a la necesidad de dar a conocer todo lo que existe en el camino de la protección humana amenazada. La historia de la investigación en ese orden abunda en intereses, competencia y mercado sin reparar en resultados que pueden ser valiosos. Es por ello que tiene que ver con la libertad de investigación, sus demostraciones y el trabajo encaminado a un camino de busca y encuentro para dejar a quienes de alcance lo informado.

Mario Mactas.

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Study of the Efficacy and Safety of Topical Ivermectin + Iota-Carrageenan in the Prophylaxis against COVID-19 in Health Personnel

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Abstract

The severe acute respiratory syndrome-coronavirus-2 pandemic has had devastating health and socio-economic implications worldwide. Epidemiologic data indicate that SARS-CoV2 is spread by respiratory droplets and contact. The lack of acquired human immunity to the virus and the absence of a vaccine, has meant that current management strategies aimed at virus containment through mask wearing, social distancing and enforced lockdowns. Although the World Health Organization recommends 1,5 meters distancing to minimize transmission, recent studies have demonstrated high stability in aerosols and transmission distances up to 10 meters from emission sources .

Health care workers are at particular risk from SARS-CoV-2. At present, no reliable prophylactic therapy exists to minimize their risk of acquiring SARS-CoV-2, and so they rely solely upon hand hygiene and the wearing of appropriate personal protective equipment (PPE), which is often in limited supply. Several studies have shown that the salivary gland and tongue express the ACE2 receptor, suggesting that the oral cavity is a perfect host for the invasion of COVID. Theoretically, agents that can inhibit viral adhesion and replication within the primary sites of viral entry (the nasal and oral cavity), may have a role in preventing SARS-CoV-2 transmission. Use of these agents prophylactically, would be especially beneficial in health care workers, particularly given the delay in results from viral RNA detection diagnostic test and the fact that many infected patients may have mild or no symptoms of the virus in the early stages. Two possible substances have been identified as candidate prophylactic agents in the fight against SARS-CoV-2. Carrageenans are naturally occurring extracts from the Rhodophyceas seaweed. Recently, the viricidal capacity of carrageenan has been reported, through inhibition of viral- host cell adhesion and early replication. Iota-carrageenan demonstrates potent antiviral activity in vitro, reducing rhinovirus, herpes simplex virus and the Japanese encephalitis virus reproduction and their cytopathic effects. Similarly, ivermectin has also been shown to posess antiviral activity against a whole host of RNA viruses (Zika, dengue, yellow fever, human immunodeficiency virus type 1). Thus, the combination of both products can provide an extra protection for those at risk of contagion.

Keywords: COVID-19, Ivermectin, SARS-CoV-2.

Introduction

The severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pandemic has had devastating health and socio-economic implications worldwide. Epidemiologic data indicate that SARS-CoV is spread by respiratory droplets and contact [1].

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Binding of the virus to ACE-2 receptors expressed in the respiratory tract and eyes, is the proposed mechanisms of entry of SARS-CoV-2 into human cells. The lack of acquired human immunity to the virus and the absence of a vaccine, has meant that current management strategies aimed at virus containment through mask wearing, social distancing and enforced lockdowns. Although the World Health Organization recommends 1-5-2 meter distancing to minimize transmission, recent studies have demonstrated high stability in aerosols and transmission distances up to 10 meters from emission sources.
Health care workers are at particular risk from SARS-CoV-2. Their close proximity to infected patients during examination and procedural tasks renders them at increased risk of exposure to higher viral loads, which may result in more prolonged and severe disease. At present, no reliable prophylactic therapy exists to minimize their risk of acquiring SARS-CoV-2, and so they rely solely upon hand hygiene and the wearing of appropriate personal protective equipment (PPE), which is often in limited supply [2-4,10].

The source of contagion is related to Pflügge drops, droplets and aerosols. All of them are different sizes of salivary compounds. Whole saliva is a biomix containing crevicular fluid, desquamated oral epithelial cells, and microorganisms. Around 99% of saliva is water and the remaining 1% contains a large group of components for the purpose of digesting, tasting, buffering, balancing remineralization and antimicrobials.Several studies have shown that the salivary gland and tongue express the ACE2 receptor, suggesting that the oral cavity is a perfect host for the invasion of COVID.

For COVID-19, the salivary gland could be an important room, generating infectious saliva on a sustained basis.It has been observed that low levels of COVID-19 RNA could still be excreted in saliva even after clinical recovery. Additionally, about half of the patients reported symptoms of dry mouth and dysgeusia.These symptoms probably stem from dysfunction of the tongue expressing ACE2 and furin, and the expression of the salivary gland ACE2, apart from SARS COV 2 direct neurotropism [19-21].

Theoretically, agents that can inhibit viral adhesion and replication within the primary sites of viral entry (the nasal and oral cavity), may have a role in preventing SARS-CoV-2 transmission. Use of these agents prophylactically, would be especially beneficial in health care workers, particularly given the delay in results from viral RNAdetection diagnostic test and the fact that many infected patients may have mild or no symptoms of the virus in the early stages. Two possible substances have been identified as candidate prophylactic agents in the fight against SARS-CoV-2 [8].

Carrageenans are naturally occurring extracts from the Rhodophyceas seaweed. They are commonly used as thickening agents in the food industry with FDA approval for this indication. Recently, the viricidal capacity of carrageenan has been reported, through inhibition of viral- host cell adhesion and early replication. Iota-carrageenan demonstrates potent antiviral activity in vitro, reducing rhinovirus, herpes simplex virus and the Japanese encephalitis virus reproduction and their cytopathic effects. This effect is supposed to be mediated by the interaction of sulfated polysaccharides with positively charged domains on the glycoprotein envelope involved in binding with proteinglycans on the surface of the host cell [6].

Similarly, ivermectin has also been shown to posess antiviral activity against a whole host of RNA viruses (Zika, dengue, yellow fever, human immunodeficiency virus type 1). Recent in vitro studies have also shown effect on Covid-19 [7].

Ivermectin mechanisms of action are both extracellular and intracellular. Outside the host cell, it provokes ionophores along the virus lipoprotein nocleocapside, thus allowing the entrance of oxhidril compounds which damage the virus structure. Despite this, if the virus does enter cytosol, ivermectin blocks its transportation to the cell nucleus, by keeping the virus from using importins alpha and beta1 to do so. In vitro sutdies, ivermectin proved to reduce viral load 5000 times in laboratory specimens [5,9,11].

Materials and Method

This pilot and muti-center clinical trial assesses whether a combination of topical nasal carageenan and oral ivermectin can reduce SARS-CoV-2 infection in Health Care Workers when administered prophylactically. The safety and efficacy of this combination therapy will be discussed and compared to the use of standard PPE alone [14].

Methods

Pilot Study (clinicaltrials.gov NCT 04425850)

Ethics board approval was attained prior to the commencement of this study and all participants provided informed consent prior to study enrollment. Asymptomatic health care workers employed at the Alberto Antranik Eurnekian Hospital, Argentina and involved in the care of and contact of Covid-19 patients were recruited.

All HCW's were healthy with no Covid-19 symptoms and negative swabs for the virus immediately prior to enrollment in the study. Exclusion criteria included: Children < 18 years old, pregnancy, active breast feeding, concurrent autoimmune or chronic disease, immunosuppression, active infectious diseases and a history of previous infection with SARSCoV-2 confirmed by PCR or rapid test. Participants received active treatment with a combination of carrageenan and ivermectin and were compared to a cohort of healthy volunteers who simply adhered to the use of appropriate personal protective equipment.

Following informed consent eligible patients underwent standardized symptom questionnaire and physical examination. Those with negative CoVid-19 (PCR or rapid test) were then recruited for preventive measures with active combination treatment (IVERCAR) arm in addition to their wearing of personal protective equipment (PPE). Acohort of healthy, age Covid-19 negative health care workers using standard PPE alone was used as a comparative arm, in a prospective, observational, not randomized trial. This group was matched for age, demographics, past medical history, work environment including hours worked and possible exposure to CoVid 19 positive patients within the hospital [16-18].

Combination therapy (IVECAR) consisted of 1 spray of topical Carrageenan (Cert. No. 57,232, ANMAT (National Administration for Drugs, Food and Medical Technology) 100 ml, 0.9 g of sodium chloride and 0.17 g of carrageenan) into each nostril and four sprays of topical Carageenan into the oral cavity, followed 5 minutes later by 1 drop of ivermectin (Cert. Nº 58.382, ANMAT 100ml Ivermectin drops (0.6 mg / ml) to the tongue 5 minutes later. This dosage schedule was repeated 5 times a day (every 4 hours) for 14 days with food and liquids avoided 1 hour before and after treatment [12-15].
Patients in the PPE group and IVECAR groups were evaluated at 7 and 14 days completing symptom questionnaires (including the reporting of any adverse effects from the treatment), physical examinations and CoVid-19 testing of nasopharyngeal secretions (PCR or rapid test) at each time point. Both groups continued to adhere to standard PPEs and were evaluated at 7, 14, 21 and 28 days from the commencement of the study. Infection rates were reported for each group, with 11 contagions among those not treated, and no contagions in the treated group [22-26].

Outcomes assessed for each of the two groups included:

- Incidence of appearance of symptoms related to CoVid-19 infection
- Incidence of detection of CoVid-19 by PCR
- Incidence of reported adverse events

Statistical Analysis

Results

Pilot Study Demographics

A total of 229 health personnel were recruited for this study; 98 within the control (PPE alone) group and 131 received IVECAR treatment in addition to their wearing of PPE.

Table 1: summarizes the demographics of each group.

Health Personnel	With IVER.CAR	Without IVER.CAR
Female Nurses <40 years	20	9
Female Nurses > 40 to 55 years	5	5
Male Nurses < 40 years	12	9
Male Nurses >40 to 55 years	6	5
E.R. Female Doctors <40 years	11	7
E.R. Female Doctors >40 to 60 years	4	6
E.R. Male Doctors <40 years	10	6
E.R. Male Doctors >40 to 60 years	3	6
ICU Female Doctors < 40 years	3	5
ICU Female Doctors > 40 to 60 years	1	1
ICU Male Doctors < 40 years	2	6
ICU Male Doctors > 40 to 60 years	2	3
Female Radiologists < 40 years	5	6
Female Radiologists > 40 to 55 years	1	-
Male Radiologists < 40 years	4	5
Male Radiologists > 40 to 55 years	3	1
Female Cleaning Staff < 40 years	8	3
Female Cleaning Staff > 40 to 60 years	2	6
Male Cleaning Staff < 40 years	6	3
Male Cleaning Staff > 40 to 60 years	4	3
Female Anesthesiologists	6	2
Male Anesthesiologists	1	-
Male Hemotherapeutic Staff	5	1
Female Lab. Personnel < 40 years	6	1
Male Lab. Personnel < 40 years	2	-
Total	**131**	**98**

As far as ethnicity is concerned, all the persons included have latin origin.

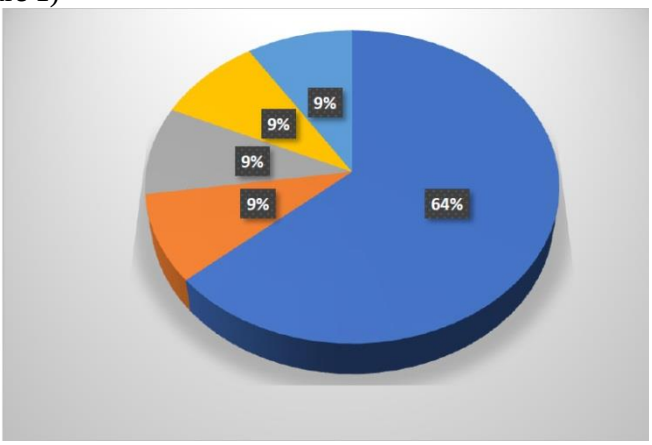
Statistical Analysis

COVID-19 transmission rates in both arms were compared by chi squared test. Transmission rate in the treated group is statistically significantly lower in the treated group ($p < 0.0001$). Relative risk reduction was calculated based on literature, and found to be 15 % for the add-on nasal and buccal iota carrageenan + ivermectin nasal + buccal preventive treatment.

Infection rates

None of the health personnel treated with IVERCAR tested positive for CoVid19 during the 14 day treatment period. Furthermore none returned positive swabs in the 3 weeks´post completion of their initial treatment. Eleven health personnel (11.1%) in the comparator PPE group yielded positive swabs.

7 of the 11 patients with positive swabs were nurses. 1 Intensivist, 1 anesthesiologist, 1 hemotherapeutic technician and 1 laboratory technician also returned positive swabs. (see Figure 1)



Blue: Nurses; Orange: Anesthetiologist; gray: Lab. Personnel; ocre: ICU Personnel; Light Blue: Hemotherapeutic Pnel.

Further Multicenter Study

Following the promising results of the initial study (see above), a larger multi-center study was performed with health care personnel recruited from Alberto Antranik Eurnekian Hospital, and 3 other hospitals; Hospital Municipal Angel Marzetti (Canuelas), Cuenca Alta Hospital (Buenos Aires Province) and Centro Medico Caseros (C.A.B.A). The study period was from June 1 2020 – August 1 2020. A modification of the initial protocol was performed for ease of medication delivery. Carageenan application was reduced to 4 x a day at the same total dose, and Ivermectin was administered as once per week dose of 12mg. Each of the 4 centers used the same dosing protocol. Again, two arms were built: those who received the prophilaxis and standard PPEs, and a cohort who only used PPEs.

Both standardized symptom questionnaire and physical examination were repeated. Those with negative CoVid-19 (PCR or rapid test) were then recruited for preventive measures with active combination treatment (IVERCAR) arm in addition to their wearing of personal protective equipment (PPE). A cohort of healthy, age Covid-19 negative health care workers using standard PPE alone was used as a comparative arm, once again in a prospective, observational, not randomized trial. No further demographic details were collected, except for successive swabs during the 60 days´ follow-up.

A total of 1,195 health care workers were recruited from 4 major hospitals in Argentina with 730 from Alberto Antranik Eurnekian Hospital, 150 from Hospital Municipal Angel Marzetti, 150 from Cuenca Alta Hospital and 15 from Centro Medico Caseros.

788 participants received IVERCAR and PPEs, while the remaining 407 simply adhered to standard PPEs.

Infection Rates - Pooled Results

The overall infection rate in health care workers recruited for this study was 20% with 237 testing positive for CoVid 19 during the 3 month study recruitment. Of those infected, all patients were from the comparator group of using PPE alone. This represented an overall infection rate of 58.2% (237 of 407) in the PPE group.

No patients of the 788 treated with IVERCAR tested positive for CoVid 19 during the study.

Infections Rates – Per Hospital

Alberto Antranik Eurnekian Hospital – EZEIZA City:

Total participating personnel 730; 600 received IVERCAR and 130 used PPE alone. 120 of 130 92.3% personnel in the PPE alone group returned positive CoVid 19 swabs, while 0 of the 600 individuals receiving IVERCAR treatment in addition to PPE tested positive for CoVid-19 in the study period.

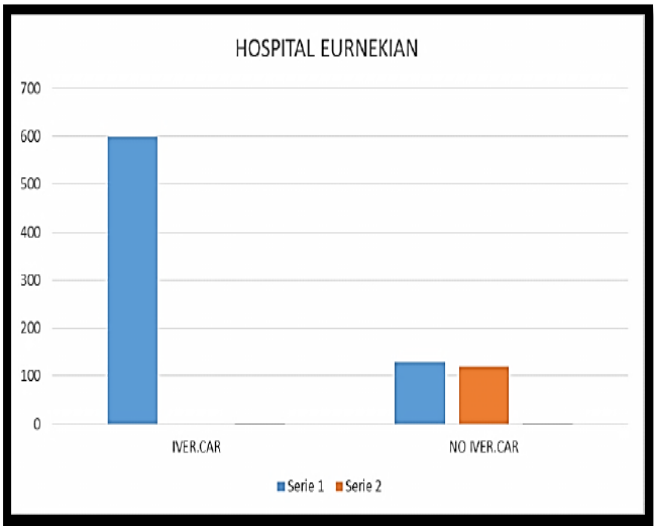


Figure 1: Light Blue: Participant Personnel; Orange: Personnel Infected

Hospital Municipal Ángel Marzetti – CAÑUELAS City:

Total participating personnel 150; 90 received IVERCAR and 60 used PPE alone.47 health care personnel (78.3%) in the PPE alone group returned positive CoVid 19 swabs, while 0 of the 90 individuals receiving IVERCAR treatment in addition to PPE tested positive for CoVid-19 in the study period.

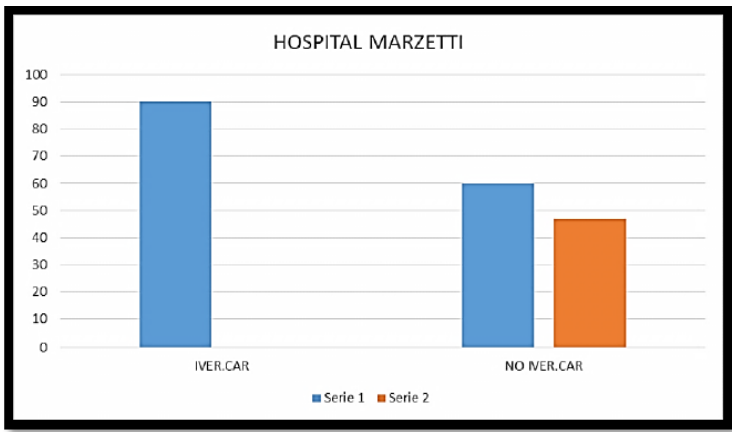


Figure 2: Light Blue: Participant Personnel; Orange: Personnel Infected

Cuenca Alta Hospital – BUENOS AIRES Province:
Total participating personnel 300; 90 received IVERCAR and 210 used PPE alone. 65 health care personnel (30.9%) in the PPE alone group returned positive CoVid 19 swabs, while 0 of the 90 individuals receiving IVERCAR treatment in addition to PPE tested positive for CoVid-19 in the study period.

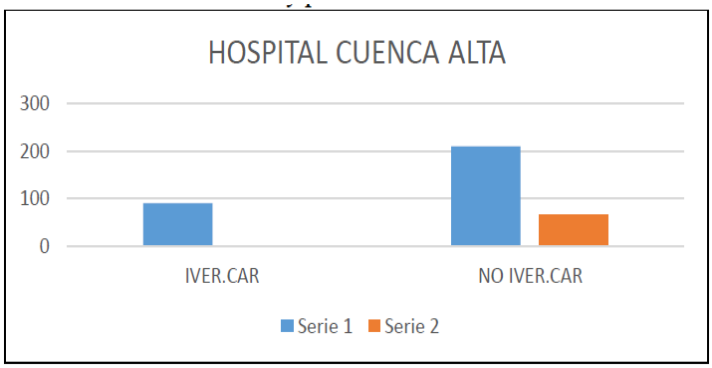


Figure 3: Light Blue: Participant Personnel; Orange: Personnel Infected

Centro Medico Caseros – Buenos Aires City:
Total participating personnel 15; 8 received IVERCAR and 7 used PPE alone.5 health care personnel (71%) in the PPE alone group returned positive CoVid 19 swabs, while 0 of the 8 individuals receiving IVERCAR treatment in addition to PPE tested positive for CoVid-19 in the study period.

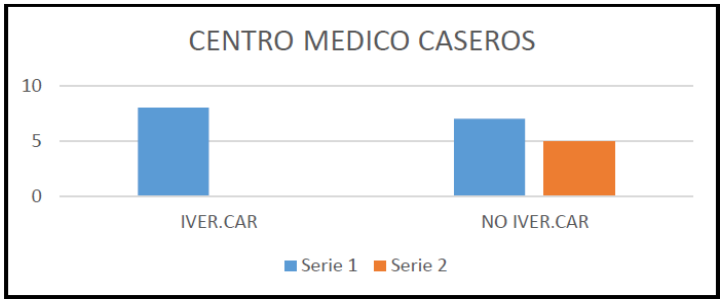


Figure 4: Light Blue: Participant Personnel; Orange: Personnel Infected

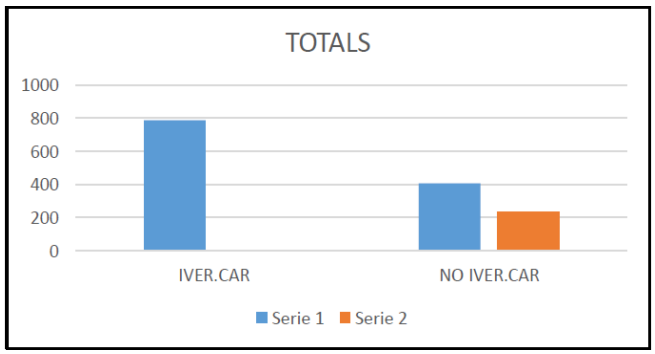


Figure 5: Light Blue: Participant Personnel; Orange: Personnel Infected

Discussion

In the present two clinical trias, the ethnic and age characteristics, previous health, personal protection measures, performance areas, work hours, and type of patients assisted were the same in each arm.
If we consider the following facts:

1) Drops and sprays are a major source of human-to-human transmission.
2) The sources mentioned above depend on different sizes of saliva droplets.
3) The contagion comes from symptomatic and asymptomatic patients.
4) The proportion of asymptomatic patients exceeds 30% of all cases.
5) The concentration of ivermectin and carrageenan is adequate in the nasal mucus and salivary glands.
6) The combined oral solution can offer double protection: on the one hand, it reduces the spread and, on the other hand, it reduces the viral load.
7) Both (ivermectin and carrageenan) are present in the international pharmacopoeia, and their use is widely accepted.
8) Their respective "off label" applications do not involve any risk.
9) Health Personnel are constantly at risk of contagion, thus locking down all their co-workers, and preventing the community from the access to appropriate health care.

We conclude that by using ivermectin in oral solution and carrageenan in nasal spray form, we are providing an inexpensive, safe and effective means to protect people from contagion and serious forms of the disease.

Consent for Publication: Written informed consent was obtained from the patient for the publication.

Conflicts of Interest: The authors declare no conflict of interest.

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Ivermectin as Prophylaxis Against COVID-19: Retrospective Cases Evaluation.

Roberto R Hirsch, Carvallo and Héctor E.

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Ivermectin as Prophylaxis Against COVID-19 Retrospective Cases Evaluation

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ABSTRACT

The current SARS COV2 (COVID 19) pandemic has generated a high number of infections among Health Agents. Around 25% of them have had to leave - temporarily or permanently - their jobs, due to having contracted the disease.

Likewise, numerous deaths have been lamented within this group, which acts as the first defense against this and other pathologies that threaten the individual.

All this has happened despite Personal Protective Equipments (PPEs), which makes it essential to optimize -from the pharmacological point of view- these elements, in order to reduce the risk of contagion as much as possible.

In this sense, Ivermectin has shown its usefulness against SARS COV2, both in treatment and in prophylaxis.

Therefore, this work compiles the characteristics of the group of Health Agents (and their close contacts) from a Buenos Aires Hospital specialized in Infectious Diseases, who resorted to it, as well as the results that were obtained.

Keywords
COVID-19, Virus, Ivermectin.

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

This species, initially named nCOV19 and later renamed SARS-CoV-2 due to its structural similarity to the homonymous species, quickly spread. The early association identified between SARS-CoV and SARS-CoV-2 was supported by subsequent analyzes of protein S (spike) [1].

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

On the other hand, one of the most conserved portions of the protein is the receptor-binding domain (RBD), which has a similar (or reportedly higher) affinity to angiotensin converting enzyme type 2 (ACE2) in comparison with SARSCoV [2].

A second receptor, TMPRSS2, would also be involved in the entry of the virus into the host cell.

To the proteiform manifestations of presentation, must be added those of the comorbidities that accompany the patient, which will negatively affect their prognosis.

The vast majority of patients will present mild forms and / or will be asymptomatic, but the high contagiousness of this viral entity makes a rapid and accurate diagnosis imperative to prevent them from becoming silent disseminators of the pathology in the community (Figure 3).

It has been confirmed that the most severe cases present with an overlap of hyperinflammation and hypercoagulability (Figure 4) [3,4].

The percentage of cases that evolve into critical and / or fatal forms is highly variable and there is no initial form - however slight - that can predict them. Thrombotic risk is significantly affected by age and comorbidities, along with accumulating evidence of the importance of coagulopathy in the pathogenesis of COVID-19, these are findings that increase the intriguing possibility that pulmonary vasculopathy could contribute evolutionary differences in the malignancy of the condition, which highlights the age susceptibility to mortality from COVID -19 (Figures 5 and 6).

If to all these comorbidities and greater age susceptibility we add work performance in the area of greatest risk of contagion (Figures 7 and 8), it can easily be deduced that the most enormous efforts should be applied to avoid the spread of the virus within Health personnel.

Updated Knowledge About Ivermectin (IVM)

Ivermectin (IVM) is an antiparasitic (endodecticide), with nematicidal and ectoparasiticidal properties [5]. It is a macrocyclic lactone derived from avermectins, a group of highly active endodecticidal antiparasitic agents isolated by fermentation of the soil microorganism Streptomyces avermitilis. It was discovered in 1960 in Japan by Satoshi Omura. In 1981, William C. Cambell began the studies that allowed its veterinary use. Both received the Nobel Prize in Physiology and Medicine in 2015.

In 1985, the French proved its usefulness in onchocerciasis in Africa. It was approved in 1997 by the FDA for treatments of: strongylidiasis and crusted scabies, in patients with AIDS.

In Human Medicine, it has been used in children from 5 years of age onwards, for the management of ecto and enteroparasitosis [6].

Orally, in humans, it does not cross the blood-brain barrier. It is contraindicated in pregnancy.

Recently, its viricidal effects on flaviviruses, dengue, Zica, Chikungunya, among others, have been compiled [7,8].

Ivermectin is an inhibitor of the causative virus (SARS-CoV-2). This activity is due to the dependence of many RNA viruses on IMPα / β1 during infection. Recently, another mechanism of action has been proposed, assuming its role as an ionophore agent. Ionophores have many oxygen atoms internally, and are essential for binding cations and transporting them through phospholipid bilayers (cell membranes; phospholipid capsid of the virus). As a consequence, it determines an ionic imbalance between the external and internal environment, with the consequent osmotic lysis.

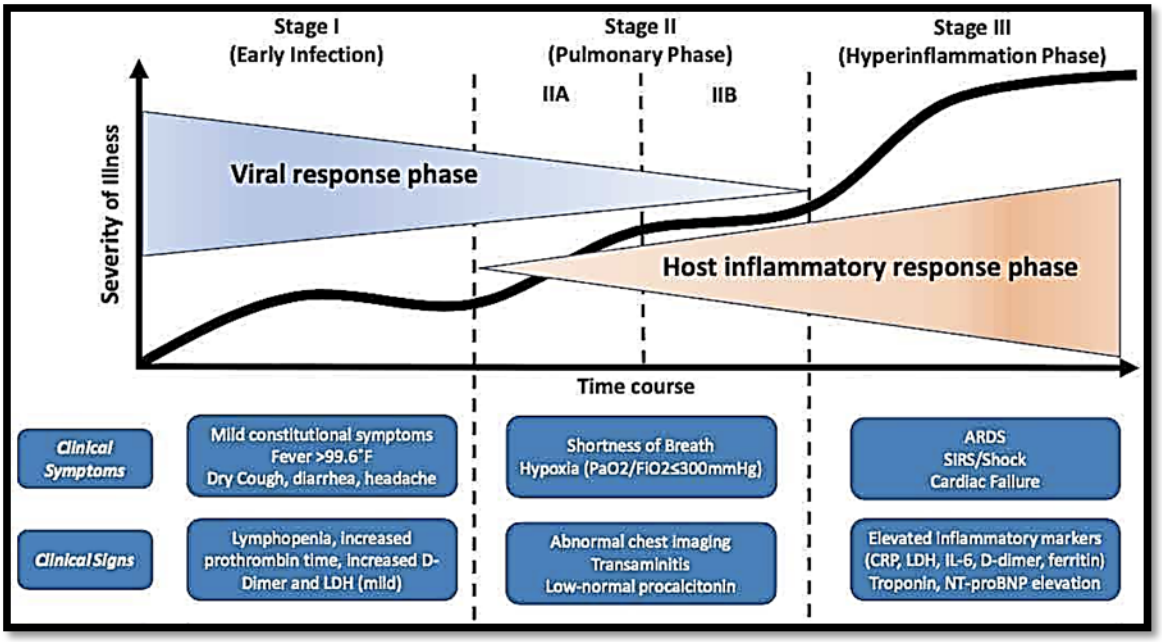

Figure 1: Covid Infection Cycle.

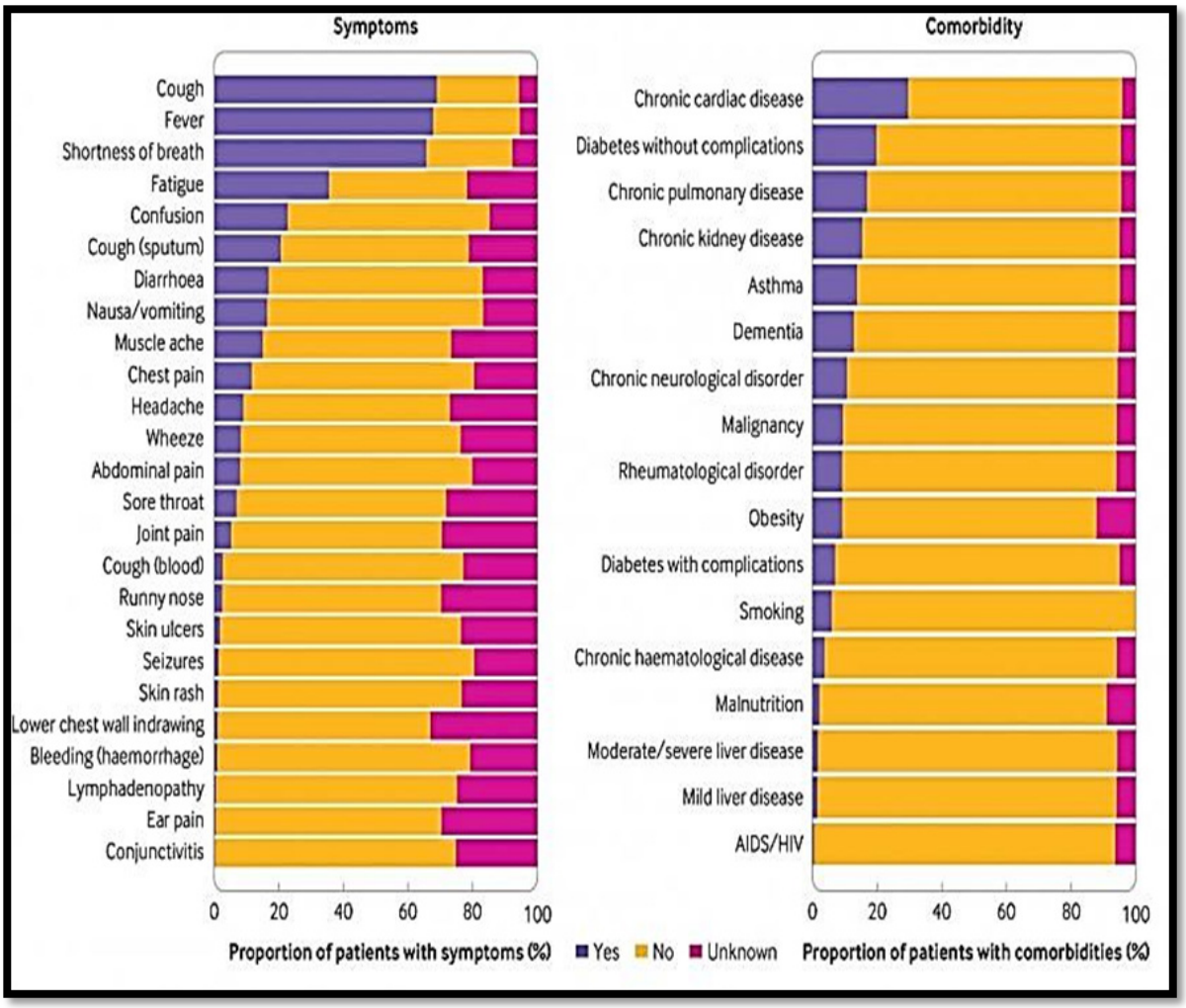

Figure 2: Comorbidities and Symptoms.

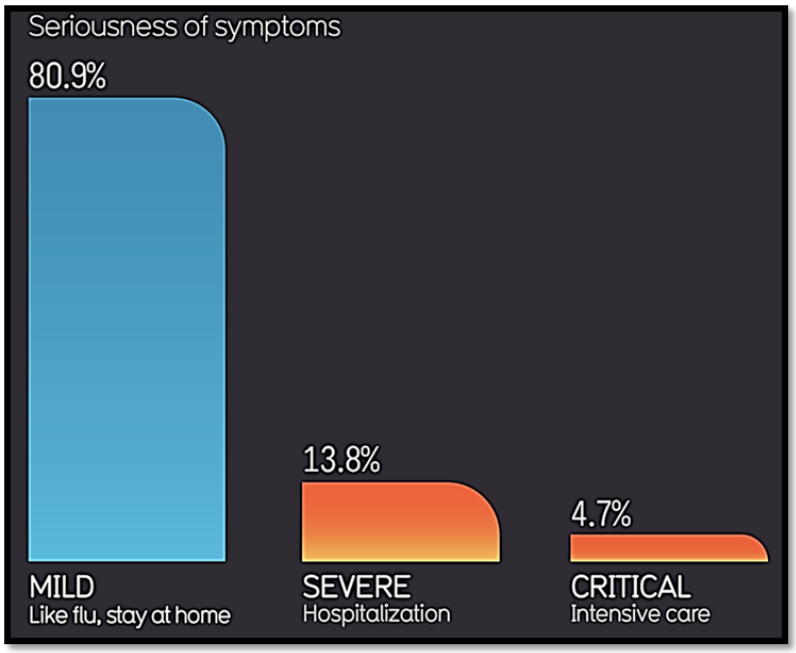

Figure 3: Covid Distribution According To Severity.

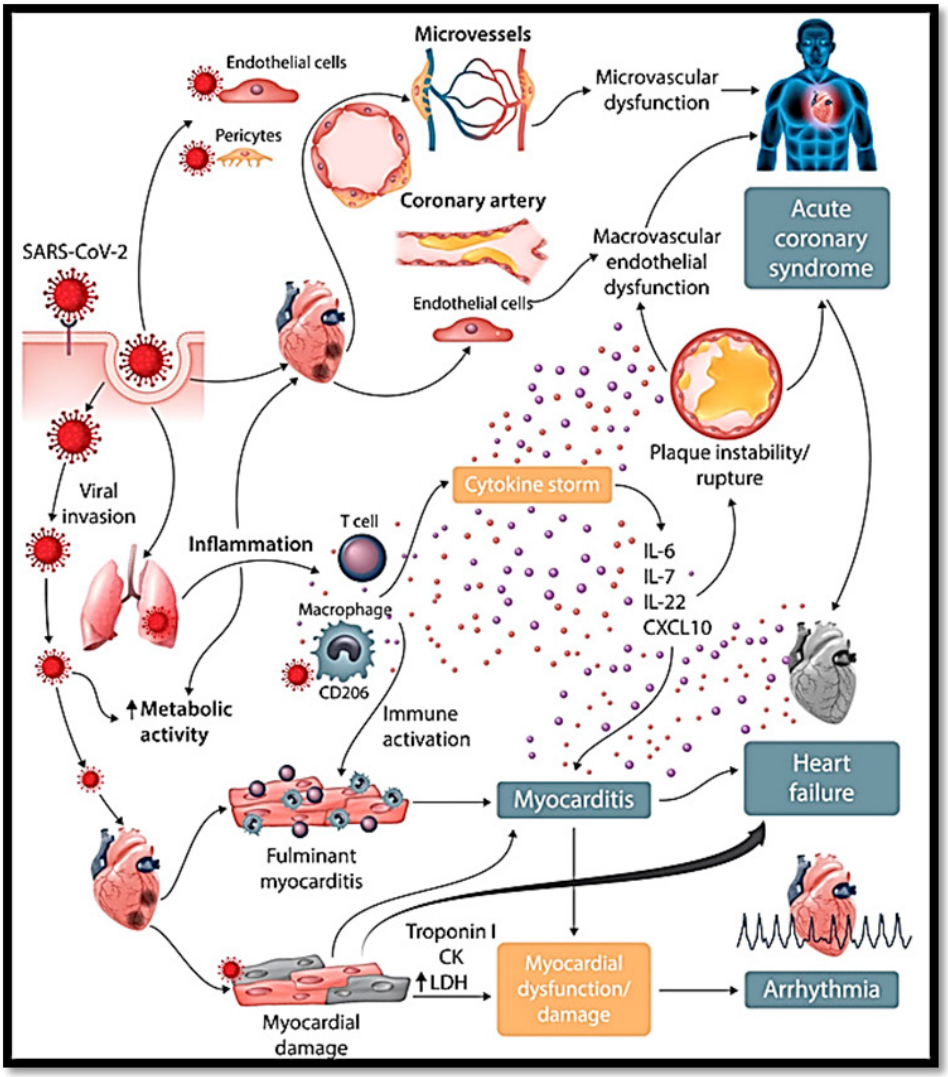

Figure 4: Hypercoagulability and Hyperinflamation Related To Covid.

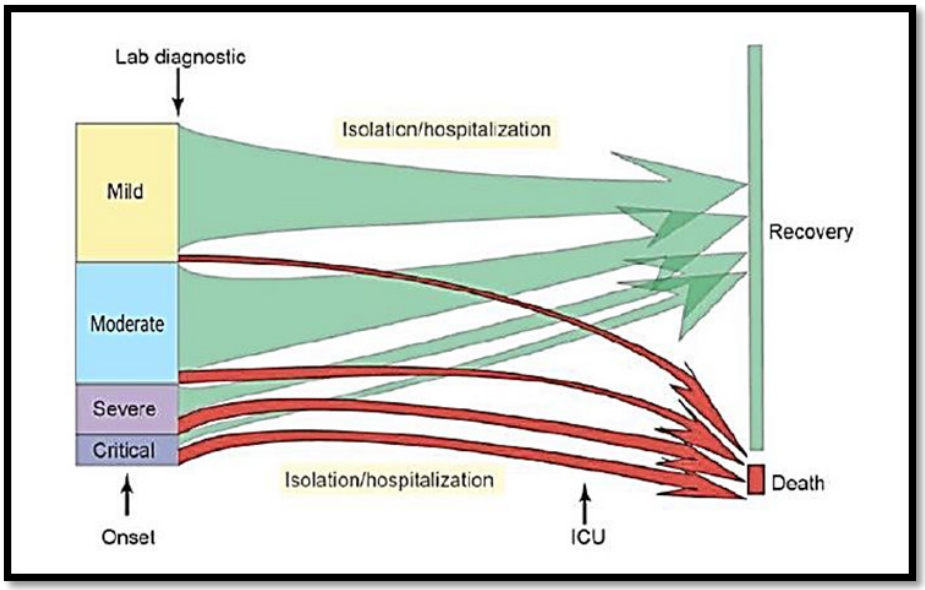

Figure 5: Average Evolution of All Symptomatic Cases.

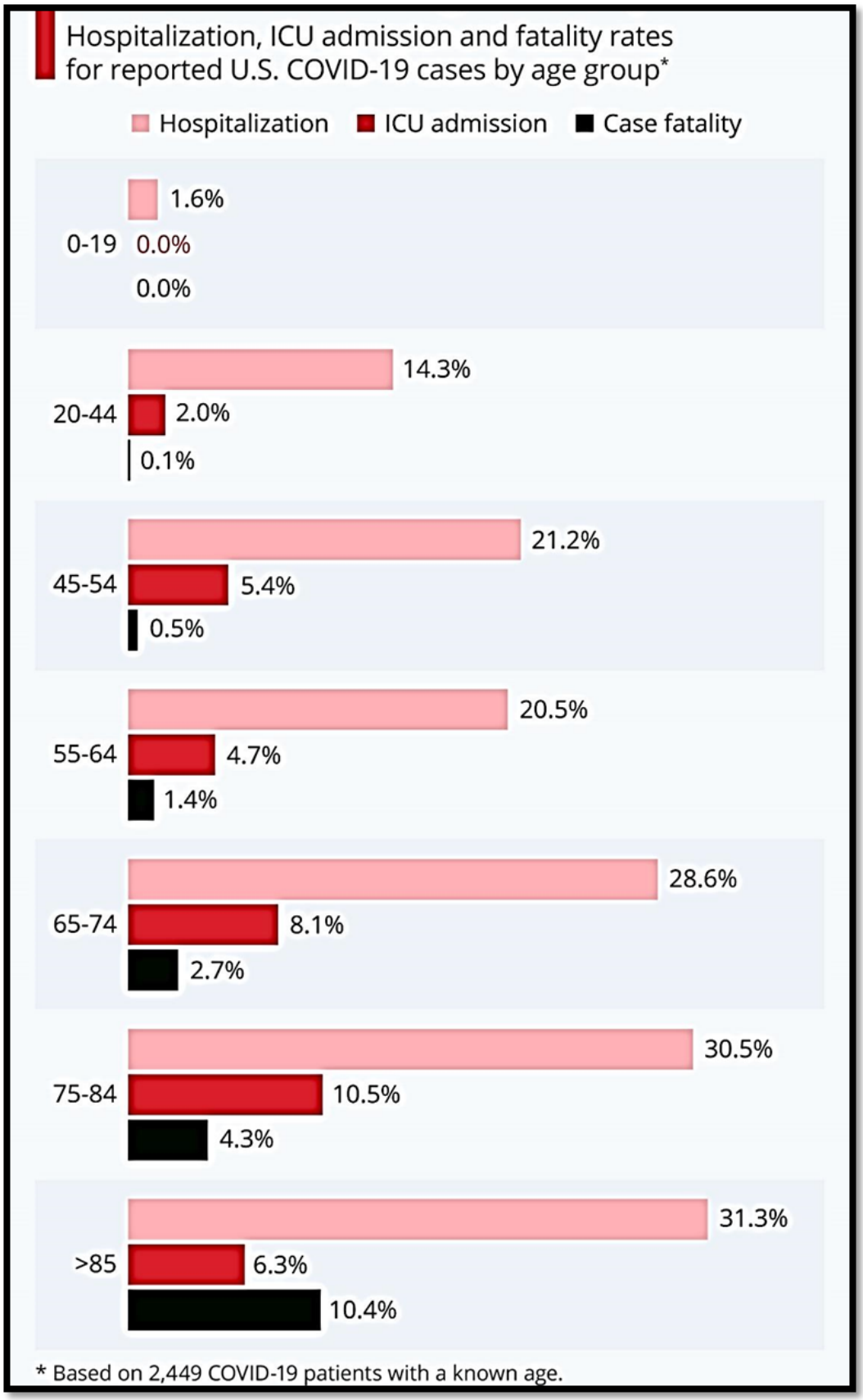

Figure 6: Evolution According To Patients Age.

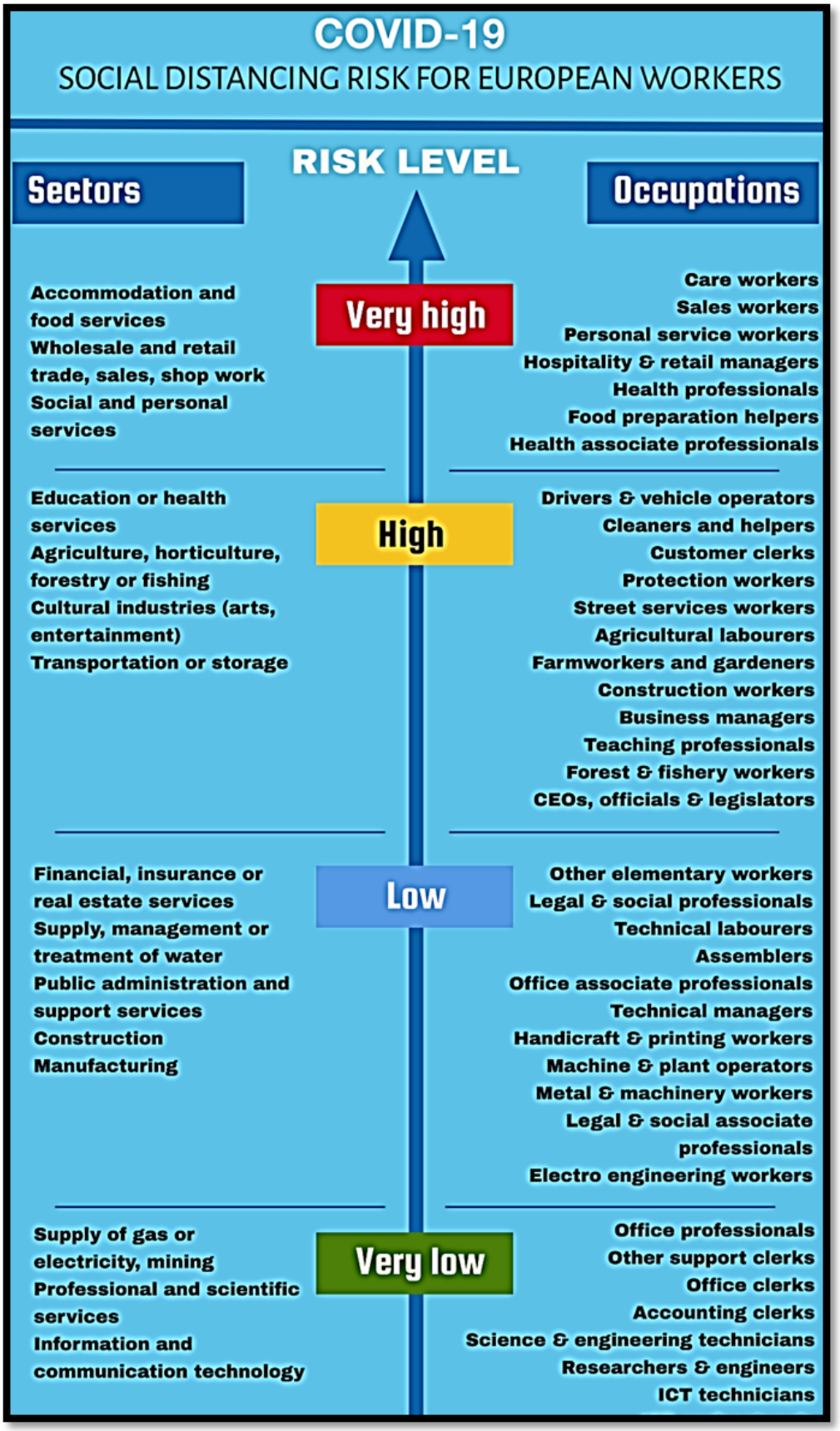

Figure 7: Activity-Related Risk.

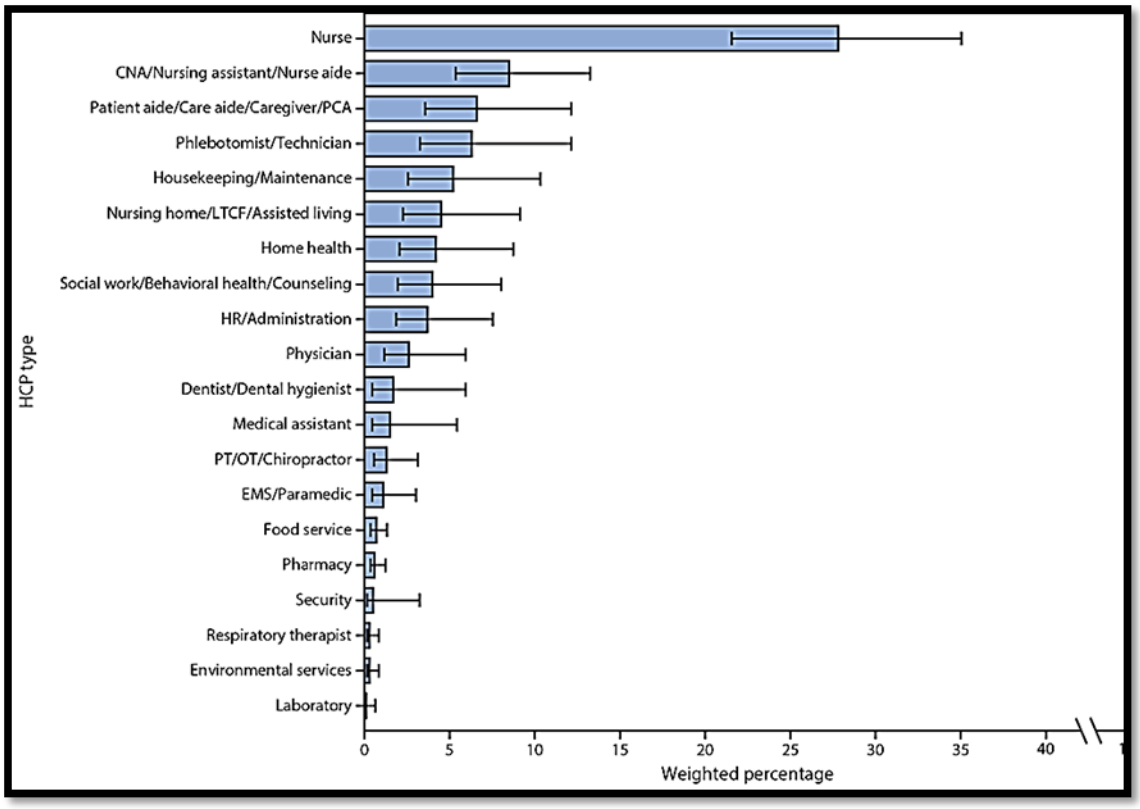

Figure 8: Risk According To Health-Care Occupation.

These results, as a whole, demonstrated that ivermectin possesses antiviral action against SARS-CoV-2 in vitro, with a single dose capable of controlling viral replication in 24-48 hours, and the possibility of repeating it periodically.

Research has been added on other forms of action of IVM in the face of COVID disease, not directly on the causative agent, but on the pathophysiological mechanisms through which its deleterious activity develops (hyperinflammation and hypercoagulability).

All of the above is summarized in Figure 9 [9-12].

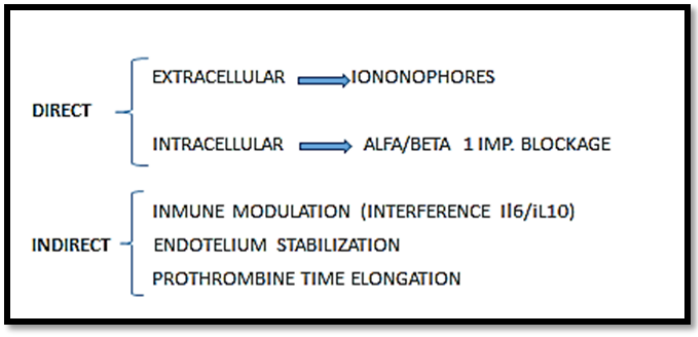

Figure 9: Ivm Mechanisms of Action Against Covid.

Material and Method

In the period between June 1 and December 15, 2020, and in the absence of prophylactic pharmacological measures against SARS COV2, a high number of Health Agents from a Metropolitan Infectious Hospital used -of their own free will- Ivermectin (IVM) to alleviate this deficiency.

In all cases, this drug was used at a rate of 0.2 mg per kilogram of weight, in a weekly dose, for eight weeks, followed by an interval of 4 (four) months of rest.

This prophylaxis was extended to the close contacts of the Health Agents, taking into account that the eventual contagion can occur in the workplace or anywhere else, with the home being a conflictive and vulnerable point at the same time.

In the above period, 163 (one hundred sixty-three) people received prophylaxis.

One of them (Health Agent) resigned from her position so it was impossible to follow up on her evolution.
With that desertion, 162 people remained in self-evaluation.

The distribution by sex was: 75 men (46.01%), and 87 women (53.98%) (Figure 10).

The average age was 51.6 years, plus / minus 11 years (2 standard deviations), with a dispersion between 10 and 85 years (Figure 11).

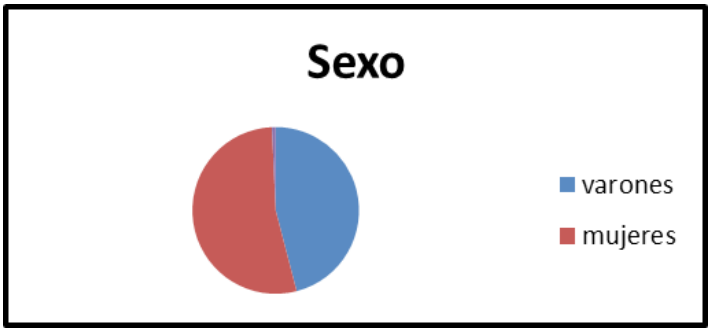

Figure 10: Sex Distribution.

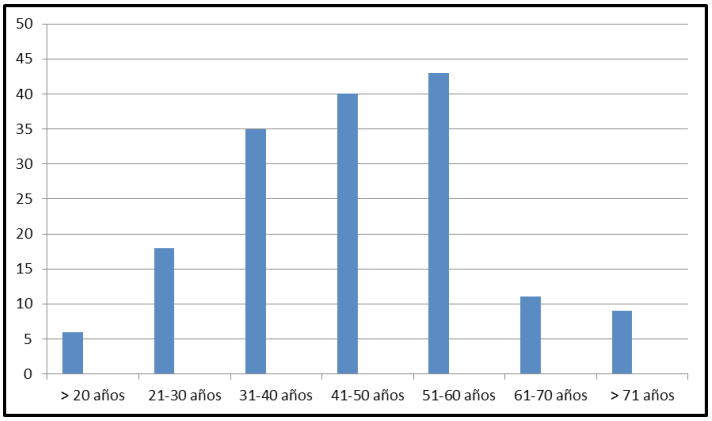

Figure 11: Age Distribution.

To date, 105 (one hundred five) people have completed the first series (8 weeks of prophylaxis and 16 of rest), while 57 (fifty-seven) people have already entered the second series (of them, 17 have completed the 8 weeks of IVM).

No infections were recorded among the 162 subjects during the period mentioned at the beginning.

Conclusion

The world literature, registered during this pandemic, refers not less than 25% of infections among Health Agents dedicated to the care of Infectious Areas in general, and of COVID in particular [13]. This implies that –throughout the six-monthly follow-up of the subjects included in this collection, no less than 35-45 infections should have been registered, an event that did not occur.

From the data included in this compilation, it appears that Ivermectin has been an excellent adjuvant method for Personal Protective Equipment, for the prophylaxis of SARS Cov 2 in health personnel and their contacts [14].

As such, it is not only recommended to extend it to all Health Agents, but also to all vulnerable population groups (geriatric and psychiatric institutes, orphanages, prisons, etc.).

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COVID 19: Children should be Treated Even in Absence of Symptoms.

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Review Article

COVID 19: Children should be Treated Even in Absence of Symptoms

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ABSTRACT

The current pandemic by COVID 19 leaves new teachings at every moment. One of them is that children (especially those from early childhood) have a viral load of COVID 19 up to 10 times higher than adults, even though they are, in their vast majority, asymptomatic. This is of enormous sanitary importance, since they are "healthy" carriers, who can transmit the disease. For this reason, the authors emphasize the need to treat this age group with nasal and oral carrageenan, in order to cut the chain of contagion.

Keywords: Children; Covid-19; Symptoms

INTRODUCTION

The early association identified between SARS-CoV with SARS-CoV-2 was supported by the analyzes made to the protein S (spike) that characterizes these two viruses, where an important similarity in these transmembrane structures was made clear, making them practically superimposable each. The only significantly different portion is a furin-binding domain in the SARS-CoV-2 protein S, which could expand tropism or increase virus transmission, compared to SARS-CoV of 2003. On the other hand, one of the most conserved portions of the protein is the receptor-binding domain (RBD), which has a similar (or reportedly higher) affinity to angiotensin-converting enzyme type 2 (ACE2) in comparison with SARSCoV [1]. This functional receptor is found in tissues, including lung alveolar epithelium, arterial and venous endothelium, smooth muscle, renal tubular epithelium, and small intestine epithelium, largely explaining the clinical presentation of COVID-19 patients. Furthermore, it has been shown that the activation of the virus ACE2 binding also requires the participation of the TMPRSS2 receptors, the hyperexpression of which would justify the greater severity in men, especially those with androchronogenetic allopecia. Diagnostic confirmation is made through laboratory studies, which can be performed on a wide variety of biological samples.

In pediatric patients, fever and cough are the common symptoms of COVID-19 (Figure 1).

Also odynophagia, excessive fatigue or diarrhea. In general, they will be mild, even asymptomatic (which does not prevent them from being contagious but, on the contrary, increases the risk of community spread).

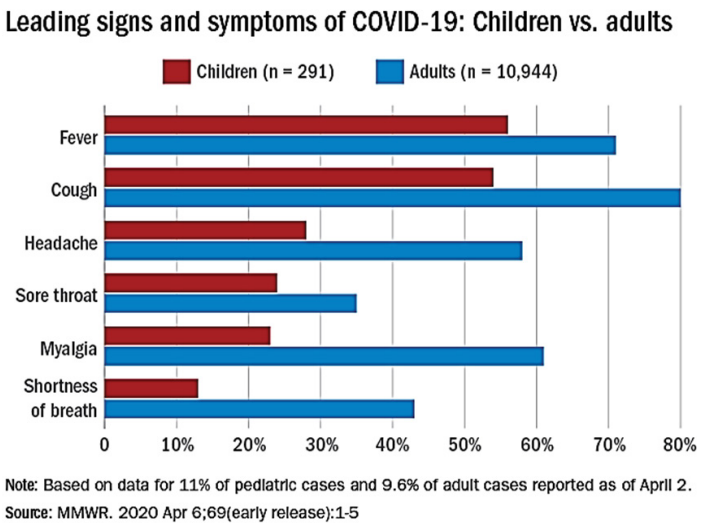

Figure 1: Signs of COVID-19, Adult Vs. Children.

Rates of serious illness were lower in older children, but there were rare cases of children in each age group requiring hospitalization. A small number of children between the ages of 2 and 15 have been observed to have experienced pediatric multisystemic inflammatory syndrome, or PIMS, for its acronym in English [2]. PIMS can cause vasculitis. PIMS have characteristics in common with toxic shock syndrome and Kawasaki disease. Children are susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection but generally have mild symptoms compared to adults. Children cause the spread of respiratory and gastrointestinal diseases in the

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population, but data on children as sources of spread of SARS-CoV-2 is scarce. Early reports found no strong evidence that children were the main contributors to the spread of SARS-CoV-2, but school closings early in responses to pandemic thwarted large-scale investigations of schools as a source of community transmission (Figure 2).

As public health systems seek to reopen schools and day care centers, understanding the potential for transmission in children will be important to guide public health measures. Replication of SARS-CoV-2 in older children leads to similar levels of viral nucleic acid in adults, but significantly higher amounts of viral nucleic acid are detected in children younger than 5 years. The behavioral habits of young children and locked rooms at school and daycare are of concern for the amplification of SARS-CoV-2 in this population as public health restrictions are eased. In addition to the public health implications, this population will be important in directing immunization efforts as SARS-CoV-2 vaccines become available [3].

An example of the risks that reopening (especially the school one) can cause if the appropriate measures are not taken, was Israel. At first, handling the pandemic in Israel was considered successful. It had closed schools in March and quickly implemented remote learning for its two million students. But after the face-to-face reopening, Jerusalem's Gymnasia Ha'ivrit High School soon became the largest single-school outbreak in the country and worldwide.

There were 154 students and 26 staff members infected. Despite the fact that the Ministry of Education had issued safety instructions such as the use of masks, the opening of windows, the frequent washing of hands and the safety distance, a key aspect failed: the social distancing [4]. It was thus that, inevitably, the coronavirus passed from schools to homes. And then to neighbors, who in turn transmitted it to other students, and it reached more educational institutes and teachers.

The Ministry of Education closed more than 240 centers and quarantined more than 22,520 teachers and students. The balance at the end of the school year was 977 infected students and teachers.

Many pointed to the anticipated reopening of schools as the trigger for a second wave of Covid-19 infections.

Siegal Sadetzki, who resigned as Israel's Director of Public Health Services, acknowledged that insufficient precautions in schools had to do with the new outbreak. Eli Waxman, a professor at the Weizmann Institute of Science and chairman of the team advising Israel's National Security Council on the pandemic, called the hasty reopening back to face-to-face classes a major failure. He also warned other countries not to follow their example [5].

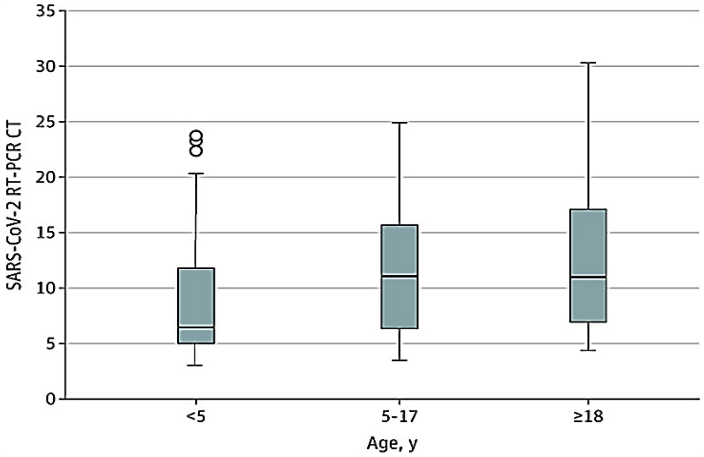

Figure 2: Graph showing SARS-CoV-2 RT-PCR CT with respect to age in children.

COVID-19 AND SALIVA

Saliva contains crevicular fluid, desquamated oral epithelial cells, and microorganisms.

90% of saliva is secreted with a pH of 6 to 7. 99% of saliva is water and the remaining 1% contains a large group of components. Saliva is known to play a role in early diagnosis and close contact transmission in COVID 19.

Chen et al. [6] found COVID-19 nucleic acid, suggesting that the salivary glands are infected by the new virus. Several studies have shown that the salivary gland and tongue express the ACE2 receptor, suggesting that the oral cavity is a perfect host for the invasion of COVID. In a previous study on severe acute respiratory syndrome-coronavirus (SARS-CoV), epithelial cells of the salivary glands were infected with high expression of ACE2. COVID-19 would generate infectious saliva in a sustained manner. ACE2 expression in the minor salivary glands was higher than in the lungs, suggesting that the salivary glands are a potential target for COVID-19. The positive rate of COVID-19 in the saliva of patients can reach 91.7%, and saliva samples can also cultivate the live virus. Some virus strains have been detected in saliva up to 29 days after infection with coronavirus [7].

FORMS OF CONTAGION

Estimating the prevalence and contagion of new undocumented coronavirus infections is critical to understanding the overall prevalence and pandemic potential of this disease. Observations of reported infections in China, along with mobility data, a dynamic network metapopulation model, and Bayesian inference, have been attempted to infer critical epidemiological characteristics associated with SARS-CoV-2, including the fraction of undocumented infections and their contagion. An estimated 86% of all infections were undocumented (95% confidence interval (CI) 82%-90%) prior to the January 23, 2020 travel restrictions. The transmission rate of undocumented infections per person was 55% of the transmission rate of documented infections (95% CI: 46%-62%), however, due to their higher number, undocumented infections were the source of 79% of documented cases. These findings explain the rapid geographic spread of SARS-CoV-2 and indicate that containment of this virus will be particularly difficult. According to studies carried out on a larger scale, of 100% of infected people, 30% will not present any symptoms. This implies that it will not consult at any time, but it will be as infectious as manifest cases [8]. Del restante 70%, más de la mitad (cerca del 38%) se presentará oligosintomático, por lo que es dable que tampoco consulte (aunque la infectividad y contagiosidad estén presentes).

Of the remaining 70%, more than half (about 38%) will present oligosymptomatic, so it is possible that they also do not consult (although infectivity and contagiousness are present). As long as the tests are not really massive (not limited to multi-symptomatic patients), the true impact of COVID 19 on our society will be unknown.

In addition to restrictions on people's mobility, the World Health Organization and governments have prescribed maintaining an interpersonal distance of 1.5 or 2 m from one to another, to minimize the risk of contagion through the drops that we generally spread to around us by nose and mouth. However, recently

published studies support the hypothesis of virus transmission at a distance of more than 2 m from an infected person (Figure 3).

Researchers have shown the greater aerosol and surface stability of SARS-COV-2 compared to SARS-COV-1 (with the virus being viable and infectious in aerosol for hours) and that the transmission of SARS-CoV in air can occur at more than the anticipated distance between contacts. In fact, there is reasonable evidence about the possibility of airborne transmission of SARS-COV-2 due to its persistence in aerosol droplets in a viable and infectious form. Based on available knowledge and epidemiological observations, it is plausible that small virus-containing particles can spread in indoor environments that cover distances of up to 10 m from emission sources, representing a type of transmission by aerosolization [9].

Field studies conducted within Wuhan Hospitals showed the presence of SARS-COV-2 RNA in air samples collected in hospitals and also in the surrounding area, leading to the conclusion that the air route should be considered a important pathway for viral spread. The interpersonal distance of 2 m can be considered reasonable as an effective protection only if everyone wears face masks in activities of daily living, but it is not sufficient in the case of aerosolization of secretions, and even less if external conditions (wind, etc.) convey these secretions at a greater distance.

THERAPEUTIC PROPOSAL FOR THE CHILD POPULATION, IN ORDER TO CUT THE CHAIN OF CONTAGION

Current knowledge about carrageenans

Carrageenans are extracts from the Rhodophyceas seaweed.

There are 3 basic types of carrageenan: Kappa, Iota, and Lambda (Figure 4).

Carrageenans are used in the food industry either as a stabilizer, thickener or gelling agent. The foods most commonly treated with carrageenan are dairy products, meat products, pastry and confectionery.

Recently, the viricidal capacity of carrageenan has been reported, resulting from the interference with the early steps of viral replication, by inhibitory action on the viral coupling to the host cell. This effect is supposed to be mediated by the interaction of sulfated polysaccharides with positively charged domains on the glycoprotein envelope involved in binding with proteinglycans on the surface of the host cell. Thus, iota-carrageenan demonstrates a potent antiviral activity *in vitro*, reducing rhinovirus reproduction and its cytopathic effects. The same results were obtained with the herpes simplex virus and the Japanese encephalitis virus (Figure 5).

The binding and entry of coronaviruses, including SARS-CoV-2, is mediated by the Spike Glycoprotein (SGP).

Recently, a SARS-CoV-2 Spike Pseudotyped Lentivirus (SSPL) was developed that enables the study of spike-mediated cell entry through luciferase reporter activity in a BSL2 environment. Iota-carrageenan can inhibit cellular entry of SSPL in a dose-dependent manner. SSPL particles were effectively neutralized with an IC50 value of 2.6 µg/ml iota-carrageenan. *In vitro* data on iota-carrageenan against various rhino and coronaviruses showed similar IC50 values and was easily translated into clinical efficacy when a nasal spray containing iota-carrageenan demonstrated a reduction in the severity and duration of symptoms of the common cold, caused by various respiratory viruses. Consequently, our *in vitro* data on SSPL suggest that the administration of iota-carrageenan may be an effective and safe prophylaxis or treatment for SARS-CoV-2 infections. The antiviral action of carrageenan is due to the fact that this polymeric compound would function as an electrical

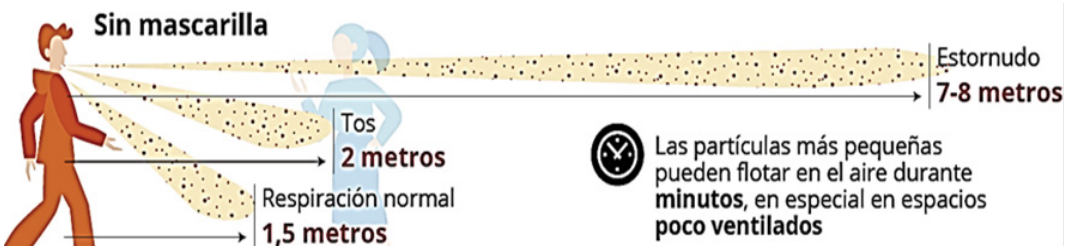

Figure 3: The hypothesis of virus transmission at a distance of more than 2 m from an infected person.

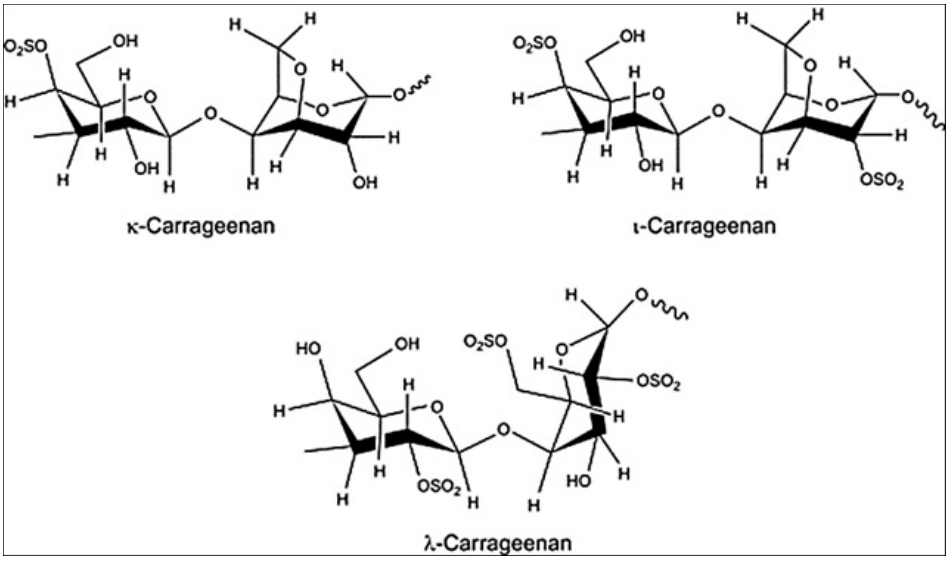

Figure 4: The 3 basic types of carrageenan; Kappa, Iota, and Lambda.

barrier that, thanks to its negative charge, would bind to the viral particles, whose envelope contains positively charged proteins, thus preventing the virus from joining the virus. cell surface and blocking their entry into them. Carrageenan can also capture viral particles released by cells that have already been infected. Topical carrageenan has two different effects in relation to SARS-CoV-2. On one hand, it slows down infection through the nose in healthy individuals, by shielding the cells that form the epithelium of the nasopharyngeal mucosa. On the other hand, in the case of infected patients who were recently diagnosed, it prevents the viral particles released by the dying cells from colonizing new cells, for example from the olfactory epithelium, and that allows the pathogen to spread to new routes, to end up arriving to the central nervous system; or infect more cells of the respiratory epithelium, on the way to the lower respiratory tract (Figure 6).

By preventing the virus from reaching the bronchi and lungs, the respiratory system would not be compromised, reducing the number of patients with COVID-19 in severe or even moderate condition [10].

HOW TO USE CARRAGEENAN IN SPRAY

Topical carrageenan is easy to apply; It has no side effects and gives a special resistance to entry, further proliferation and dissemination of the virus. It has been in the Argentine pharmacopoeia for almost 10 years, and in other countries (United Kingdom, Austria, Australia, etc.) for almost two decades. Carrageenan has come under fire, as some reports claim that it can cause potential damage

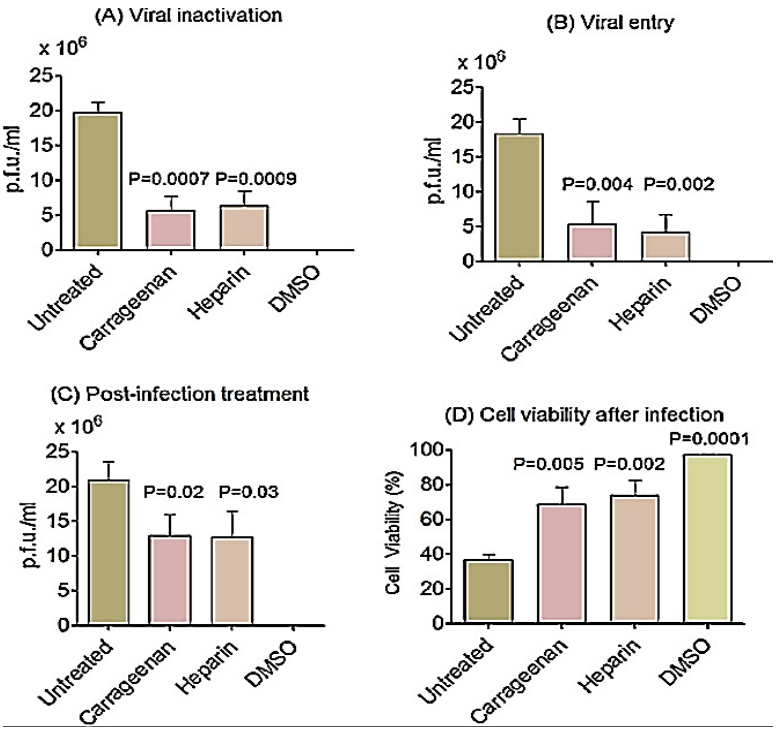

Figure 5: The results obtained with the herpes simplex virus and the Japanese encephalitis virus.

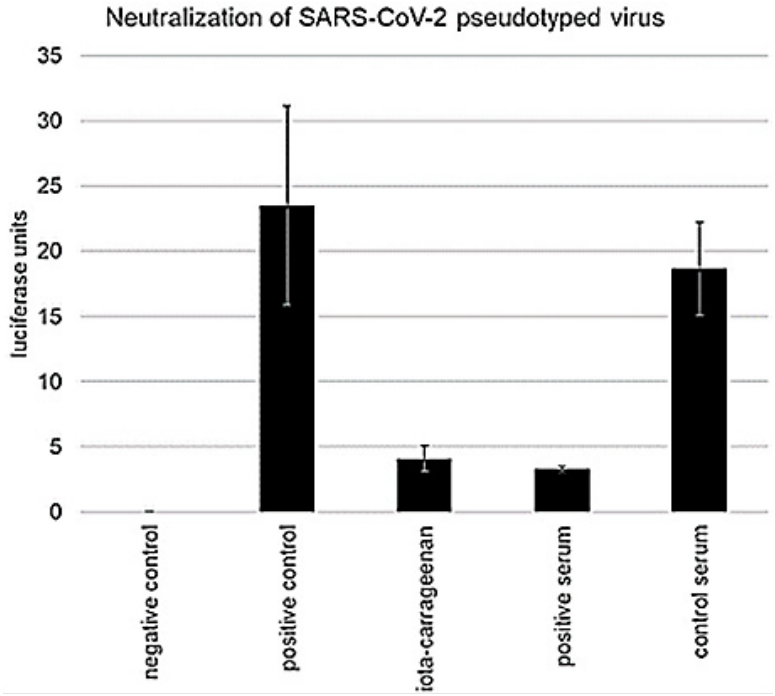

Figure 5: The results obtained with the herpes simplex virus and the Japanese encephalitis virus.

to the digestive system. Meanwhile, the FDA along with the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) recognize carrageenan as a safe ingredient for consumption and a recent study further supports this idea. The debate over carrageenan is not new; It has been under careful investigation since the 1960s. Carrageenan is a key ingredient in foods and beverages, offering the desired stability, texture, and mouthfeel. Some even consider it to be the "perfect stabilizer." It is also offered as a vegetarian and vegan alternative to gelatin in confectionery products. The criticism surrounding the ingredient involves the fact that it is an "unhealthy" additive and that it is found in organic and natural products. Some health experts say it causes inflammation, and in severe cases it can lead to ulcers, bleeding, and even cancer. However, James McKim conducted a two-year study looking at the possible health outcomes of carrageenan. McKim's research confirms that carrageenan does not have an impact on the human body when consumed in food in the long term. Even less, when it is used as a medication, in the short and or medium term. In addition to antiviral active ingredients, typically, the present composition comprises at least one pharmaceutically acceptable carrier and, optionally, other additives or active ingredients. A suitable vehicle can be a diluent, for example water or saline, an excipient or other suitable and useful vehicle for the administration of the active ingredients. Carrageenan can be used in the form of any pharmaceutically acceptable salt, for example sodium salts of carrageenan can be used. Carrageenans of the iota type are available in the Argentine Pharmacopoeia (Nasitral). Carrageenan has been found to be non-toxic in oronasal administration, even at extremely high doses, and has therefore been classified as "Generally Recognized as Safe" (GRAS) by the Food and Drug Administration (FDA) from the US.

The antiviral pharmaceutical preparation is for the treatment or prophylaxis in an individual who is especially susceptible or at increased risk of a rhinovirus infection, such as a high-risk patient selected from the group consisting of an asthmatic patient, a person with allergies and a person suffering from an inflammatory disease (Figure 7).

Typically, the composition will be provided as a sterile, non-pyrogenic preparation. However, the pharmaceutical composition could also come to be used to coat solid surfaces of hygiene or sanitary articles, for example, articles for hygiene or facial care that are typically used in the oral or nasal regions, such as handkerchiefs. or paper nose pads and pocket tissues [11].

More specifically, the pharmaceutical composition can be applied, for example, sprayed, in much the same way as disinfectants, onto toilet paper gloves, tissues or wipes, including nose tissues, to exert a vricidal effect, at least to some extent, thus helping to reduce repeated self-infection of an individual by contamination of the fingertips and also to reduce viral spread between different individuals who are in close contact with each other, for example, hand-to-hand.

Depending on the nature of the sanitary or hygiene article, said article may be covered, moistened or otherwise impregnated with the pharmaceutical composition [12].

Such carrageenan treated articles may also include, but are not limited to, cotton swabs, dust masks, or face masks. Even lipsticks can be formulated to contain an antiviral effective amount of iota-carrageenan. These hygiene or health care items can be used prophylactically or in conjunction with therapeutic treatment against a viral infection and can be helpful in preventing or reducing the risk of infection. Accordingly, the antiviral composition is applied by coating or impregnation on the solid surface of a hygiene or sanitary care article, in particular of a glove, washcloth or tissue of hygiene or sanitary paper, especially a tissue or paper towel for the nose.

CONCLUSION: THE BENEFIT OF CARRAGEENANS

If we consider the following facts:

- Drops and aerosols are a major source of human-to-human transmission.
- The sources mentioned above depend on different sizes of saliva droplets.
- The contagion comes from symptomatic and asymptomatic patients.
- The proportion of asymptomatic patients exceeds 90% of all pediatric cases.
- Carrageenan concentration is adequate in the nasal mucosa and salivary glands.
- Oral solution can offer a double protection: On the one hand, it reduces the spread and, on the other hand, it reduces the viral load.
- Carrageenan is in the pharmacopoeia, and its use is accepted almost worlwide.
- Its application does not imply any risk.
- We conclude that by using carrageenan in the form of a nasal and oral spray, we may be providing an inexpensive, safe and

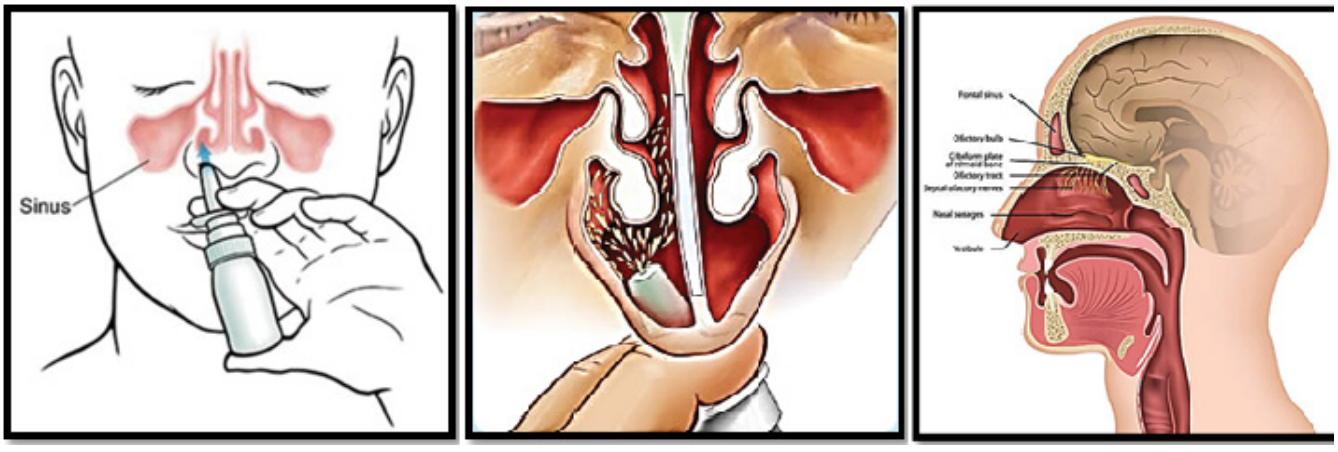

Figure 7: The antiviral pharmaceutical preparation in the treatment or prophylaxis.

effective means of protecting people from contagion and serious forms of the disease.

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Safety and Efficacy of the Combined Use of Ivermectin, Dexamethasone, Enoxaparin and Aspirina against Covid-19: the I.D.E.A. Protocol.

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Research Article

Safety and Efficacy of the Combined Use of Ivermectin, Dexamethasone, Enoxaparin and Aspirina against Covid-19 the I.D.E.A. Protocol

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ABSTRACT

From the first outbreak in Wuhan (China) in December 2019, until today (05/28/2020), the number of deaths worldwide due to the coronavirus pandemic exceeded 2.5 millions.

Only in Argentina, 50,000 deaths have been confirmed so far. There haven't been so far any clear diagnostic pattern for this exceptional entity except unilateral skin involvement, early onset of symptoms, positive ANA and negative tests for Borrelia burgdorferi. Hence, we report a new case of a young Moroccan man.

No treatment tested worldwide has shown unquestionable efficacy in the fight against COVID 19, according to W.H.O, NIH and NICE reports and accumulated data.

Our proposal consists of the combination of drugs, based on the pathophysiology of the virus. We have designed a treatment called I.D.E.A., based on four affordable drugs already available on the pharmacopoeia in Argentina, on the following rationale:

- Ivermectin (IVM) solution to lower the viral load in all stages of COVID 19
- Dexamethasone 4-mg injection, as anti-inflammatory drug to treat hyperinflammatory reaction to COVID-infection
- Enoxaparin injection as anticoagulant to treat hypercoagulation in severe cases.
- Aspirin 250-mg tablets to prevent hypercoagulation in mild and moderate cases

Except for Ivermection oral solution, which was used in a higher dose than approved for parasitosis, all other drugs were used in the already approved dose and indication. Regarding Ivermectin safety, several oral studies have shown it to be safe even when used at daily doses much higher than those approved already. A clinical study has been conducted on COVID-19 patients at Eurnekian Hospital in the Province of Buenos Aires, Argentina. The study protocol and its final outcomes are described in this article. Results were compared with published data and data from patients admitted to the hospital receiving other treatments.

None of the patient presenting mild symptoms needed to be hospitalized. Only one patient died (0.59 % of all included patients vs. 2.1 % overall mortality for the disease in Argentina today; 3.1 % of hospitalized patients vs. 26.8 % mortality in published data). I.D.E.A. protocol has proved to be a very effective alternative to prevent disease progression of COVID-19 when applied to mild cases, and to decrease mortality in patients at all stages of the disease with a favorable risk-benefit ratio.

Keywords: Ivermectin; Aspirin; Dexamethasone; Enoxaparin; Covid-19; I.D.E.A.

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INTRODUCTION

In late December 2019, the incidence of atypical pneumonia cases of unknown cause was reported in the Chinese city of Wuhan.

PCR (Polymerase Chain Reaction) studies found a coronavirus, which was >85% similar to a bat SARS-type CoV (bat-SL-CoVZC45).

SARS-type CoV (bat-SL-CoVZC45)

The early association identified between SARS-CoV with SARS-CoV-2 was supported by subsequent analyzes, where an important similarity in these transmembrane structures was made clear.

The only significantly different portion is a furin-binding domain in the SARS-CoV-2 protein S, which may expand tropism or increase virus transmission.

Studies on SARS-CoV proteins have revealed a potential role for IMPα/β1 during infection in the signal-dependent nucleocytoplasmic closure of the SARS-CoV nucleocapsid protein, which may affect host cell division. The predilection and competitiveness of the virus over ACE2 cell receptors has already been demonstrated, and its subsequent need for the importin described above is also confirmed. This functional receptor is found in multiple tissues, including alveolar epithelium of the lung, arterial and venous endothelium, smooth muscle, renal tubular epithelium, oropharyngeal mucosa and epithelium of the small intestine, largely explaining the clinical presentation of patients with COVID-19. So has its interaction with TMPRSS2 receptors (Figure1).

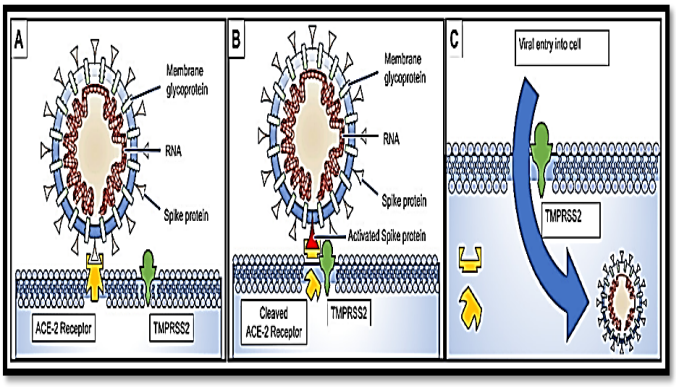

Figure 1: COVID 19 and ACE2 receptors

DEVELOPMENT OF CLINICAL EVENTS

Before proceeding to list them, we must emphasize two premises:

Between 30 and 50% of patients who contract COVID 19 will be asymptomatic or oligosymptomatic. This fact will not give rise to the consultation, and will directly affect a notorious under-registration of the cases.

The second, even more disturbing, premise is that these patients are as contagious as the moderate and severe cases.

The virus incubation period has been calculated at 5.1 days (95% CI, 4.5 to 5.8 days), and 97.5% of patients are said to have symptoms at 11 days (95% CI 8.2 to 15.6 days).

A mortality of 3.1 % has been calculated.

The average COVID patient presents with fever (78%), cough (60-79%) and myalgias or fatigue (35.8 to 44%).

55% develop dyspnea, which appears on average 8 days after the onset of symptoms.

To the manifestations expressed above, the presence of bilateral conjunctival injection should be added, without associated secretions, hypogeusia, skin rash and hyposmia.

Diagnostic confirmation is made through laboratory studies, which can be performed on a wide variety of biological samples.

Bronchoalveolar lavage samples showed the highest sensitivity (93%), followed by sputum samples (72%), nasal swabs (63%), fiberoptic brush biopsy (46%), pharyngeal swabs (32%), feces (29%) and, finally, blood (1%). A sensitivity of 91% is reported in saliva samples.

Computed Axial Tomography (CAT) is very useful as a complementary study in the diagnostic approach of COVID-19, but this does not discredit follow-up by conventional Radiology, if more sophisticated means are not available.

Evidence suggests that a subgroup of patients with severe forms of COVID 19 may have cytokine storm syndrome.

Therefore, we recommend the identification and treatment of hyperinflammation using existing approved therapies with proven safety profiles to address the immediate need to reduce increasing mortality (see Therapeutic Proposal).

Secondary Hemophagocytic Lymphohistiocytosis (SHLH) is a poorly recognized hyperinflammatory syndrome characterized by fatal and fulminant hypercytokinemia with multiple organ failure.

In adults, SHLH is most often triggered by viral infections, and occurs in 3.7–4.3% of sepsis cases.

The cardinal features of sHLH include constant fever, cytopenias, and hyperferritinemia; Pulmonary involvement (including ARDS) occurs in approximately 50% of patients.

A cytokine profile that resembles sHLH is associated with the severity of COVID-19 disease, characterized by an increase in interleukin (IL) -2, IL-7, granulocyte colony stimulating factor, protein 10 inducible by interferon-γ, monocyte chemoattractant protein, macrophage inflammatory protein 1-α and tumor necrosis factor-α.

Mortality predictors from a recent multicenter retrospective study of 150 confirmed cases of COVID-19 in Wuhan, China included elevated ferritin (mean 1297.6 ng / ml in non-survivors versus 614.0 ng / ml in survivors; $p<0.001$) and IL-6 ($p<0.0001$), suggesting that mortality could be due to viral hyperinflammation (Figure. 2).

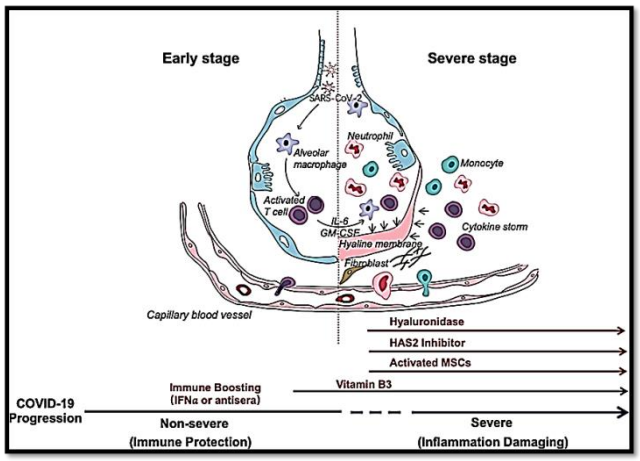

Figure 2: Aggressive forms of infection.

However, cases have been reported where tissue and organ involvement has been found whose concentration of ACE receptors is very dissimilar (myocardium, brain). In all of them, the common denominator was small vessel thrombosis, as seen in entities such as Catastrophic Antiphospholidic Syndrome.

More than a century ago, Virchow proposed that the formation and spread of thrombi was caused by abnormalities in three key areas:

Blood flow

The vascular wall

The components of blood

These three factors are known as the Virchow triad (Figure.3).

Currently the Virchow triad factors have been narrowed down in more detail:

Circulatory stasis: abnormalities of hemorrheology and turbulence in vascular bifurcations and stenotic regions.

Injury to the vascular wall: abnormalities in the endothelium, such as atherosclerosis and associated vascular inflammation.

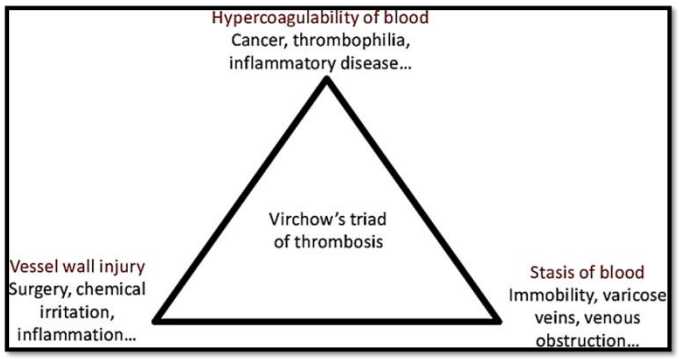

Figure 3: Updated virchow triad.

Hypercoagulable state: Abnormalities in the coagulation and fibrinolytic pathways and in platelet function associated with an increased risk of VTE and other cardiovascular diseases (such as Coronary Artery Disease [CPA], heart failure and stroke in patients with AF). All lead to a state of hypercoagulability, which could explain the formation of microthrombosis in different locations, As has been repeatedly reported in patients with COVID 19.

BASES OF THE PROPOSED THERAPEUTICS

They rest on four pillars: Ivermectin, Aspirin, Dexamethasone and Enoxaparin.

IVERMECTIN

Ivermectin is a broad-spectrum antiparasitic, with vermicidal and ectoparasiticidal properties. It was discovered and marketed for animal use in the early 1980s.

Approved in 1997 by the FDA for single-dose strongyllidiasis of 200 mcg /kg and crusted scabies (Scabies Norway) in patients with AIDS at a dose of 200 mcg/kg, every week for 2 weeks.

In Argentina, it has been available for human use for almost 20 years.

But, much more recently, its viricidal effects have been compiled on different varieties of flavivirus, dengue, Zica, Chikunguña, etc.

Ivermectin has been reported to be a SARS-CoV-2 inhibitor. This activity is believed to be due to the dependence of many different RNA viruses on IMPα/β1 during infection. These reports suggested that the inhibitory activity of ivermectin nuclear transport may be effective against SARS-CoV-2, since they demonstrate that ivermectin has antiviral action against the clinical isolate of SARS-CoV-2 in vitro, with a single dose capable to control viral replication in 24-48 hours in vitro.

Apart from the intracell effect of IVM, more mechanisms of action have been described (Figure 4).

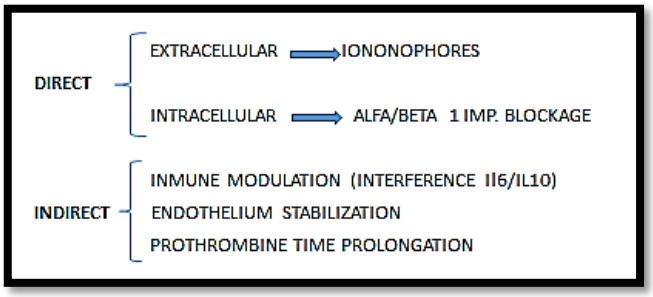

Figure 4: Invermectin mechanisms of action against covid infection.

Although in vitro studies have used doses that –extrapolated to those recommended in the treatment of ectoparasitosis in humans– might seem high, the truth is that studies carried out in healthy volunteers, more than two decades ago, proved that the usual doses they can be increased tenfold, without significant side and / or adverse effects.

ASPIRIN

Aspirin is the common name for acetylsalicylic acid. The chemical production is based on the salicylic acid obtained by synthesis. Its most common uses and for what it was first used was as an analgesic (for pain), antipyretic (to lower fever) and anti-inflammatory. It is classified as a non-steroidal anti-inflammatory drug (NSAID). In 1989 the first large study was published that proved that Aspirin reduces cardiovascular risk, acting as an antiplatelet agent.

These were low-dose Aspirin, and the risk of myocardial infarction was found to decrease by 44% when the previously named dose of Aspirin was administered.

HEPARIN AND ENOXAPARIN

Heparins are injectable anticoagulant substances. A distinction should be made between standard heparin or unfractionated heparin (HNF) and low molecular weight heparins (LMWH).

HNF is made up of a heterogeneous mixture of polysaccharide

chains of variable length.

LMWHs are the result of fragmentation of HNF by different methods to achieve products with lower and more homogeneous molecular weights. They are also made up of a mixture of polysaccharide chains and their average molecular weight is much lower. The antithrombotic and anticoagulant activity of HNF is related to the ability to inhibit factor Xa and factor IIa respectively. LMWHs have less inhibitory activity to thrombin or factor IIa but maintain the same potency with respect to factor Xa, so it is expected that they present a lower risk of bleeding but the same antithrombotic activity.

CORTICOSTEROIDS

Systemic corticosteroids are powerful anti-inflammatory and immunosuppressive agents. They can be administered intravenously, intramuscularly, orally, intralesionally, and topically. Its side effects increase with high, long and frequent doses.

Corticosteroids are drugs frequently used in various clinical situations, because they are powerful anti-inflammatories and immunomodulators.

Glucocorticoids passively diffuse through the cell membrane, then join soluble receptor proteins in the cytoplasm. They are used, among others, for the treatment of some rheumatic diseases. A separate case, well known but not studied in the current contingency, is acute adrenal insufficiency. The RECOVERY Trial proved DM is useful to reduce mortality.

MINOR CRITERIA	MAJOR CRITERIA
Fever less than 38.5 ° Isolated diarrheal episodes Hyposmia or Hypogeusia Mild desaturation (between 96 and 93%) Dyspnea without matter Polymyoarthralgias Persistent headache Abdominal pain	Fever higher than 38.5 ° Diarrhea (more than 3 diarrheic stools / day) Flictenular conjunctivitis Strong desaturation (less than 92%) Tachypnea (FR> 25 / minute) Livedo reticularis Giant urticharia

Table 1: Criterias.

I.D.E.A. TRIAL

Based on the precedent data, we performed a Clinical Trial based on the above-mentioned four drugs, on a gradual scale, and according the severity of each case That Trial, and its outcomes, were duly submitted to the National Library of Medicine (USA) in July 2020. It consisted in a prospective, two-arms (not randomized but based on consentments), study. The control group received all the other options available (hydroxicloroquine, lopinavir-ritonavir, convalescent plasma, etc.).

In order to determine the dose and combination, we developed our own severity score.

INTERPRETATION

Mild cases	Moderate cases	Severe cases
Only minor criteria findings	3 major crit. findings, or 2 major + 2 minor	4 major crit. Findings or 3 major + 2 minor

Table 2: Interpretation.

Disease severity	Ivermectin	Corticoid		Ventilation
Firm Suspicious Case or Confirmed case	24 mg orally at a dose of 200 ug / kg in a single dose, to be repeated a week later	No	Aspirin 250 mg orally	No
Moderate clinical stage	36 mg orally at a dose of 400 ug / kg in a single dose, to be repeated a week later	Dexamethasone 4 mg (parenteral)	idem	Low Flow Washed Oxygen or Oxygen Concentrator
Severe case with bilateral pneumonia	48 mg via gastric cannulae, at a dose of 600 ug/kg in a single dose, to be repeated a week later	idem	Enoxaparin100 UI/kg (1 mg/kg)	Mechanical Ventilation

Table 3: Disease severity.

EQUIVALENCES

Dose of 300 micrograms/kg orally, 0.6% drops=1.5 drops/kg of weight

Dose of 400 micrograms/kg orally, 0.6% drops=2.25 drops/kg of weight

Dose of 600 micrograms/kg orally, 0.6% drops=3 drops/kg of weight

When possible, we preferred to use IVM solution instead of tablets, because of its easier absorption and the velocity to reach Tmax and tissue concentration. Solution is also a better alternative if gastric cannulae shall be used.

OUTCOMES

According to our clinical criteria, patients were divided into two major groups: outpatients and admitted patients. Among the admitted patients (Figure 5), death rate was 7 times less with the I.D.E.A. protocol, if compared to all other applied treatments.

In this case, it is important to mention that corticosteroids and or enoxaparin were used on both arms.

It is important to emphasize that death was taken as final "adverse reaction", thus avoiding any subjective bias.

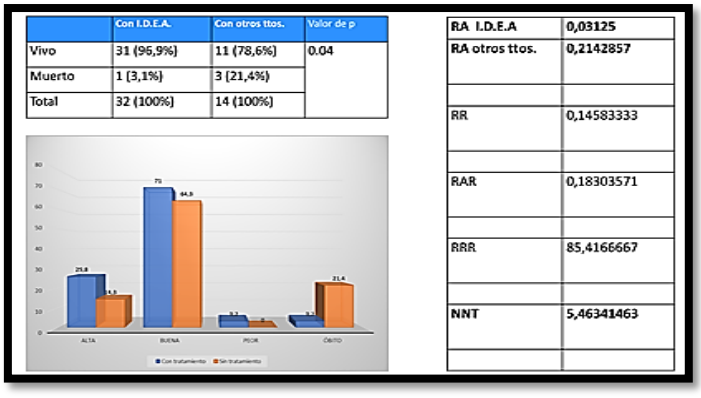

Figure 5: Outcomes in admitted patients.

In the outpatients´group, the adverse effect considered was the need of ulterior admittance, as it has been observed worldwide that this happens in up to 10 % of the mild cases, during the two weeks posterior to diagnosis.

None of those 135 patients (0,0 %) needed to be admitted (Fig. 6)

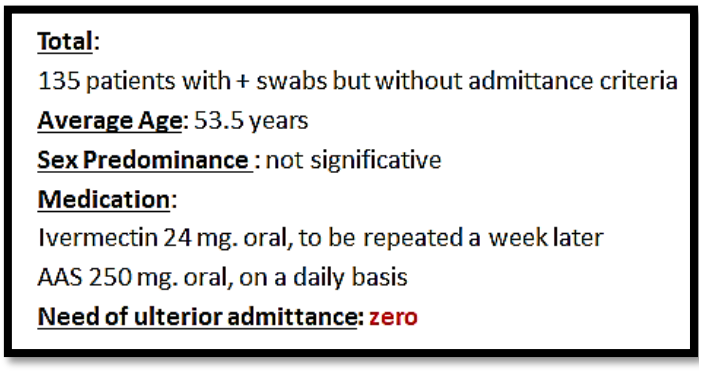

Figure 6: Mild cases outcomes.

CONCLUSION

Given the rapid advance of the pandemic, the sequel of death that it leaves behind, the lack of sustainable evidence in the experimental treatments proposed up till now, the presence of all the drugs proposed by us in the national pharmacopoeia, their low cost in relation to the other trials, the scarce incidence of side effects, and the possibility of massive use without the limitations of dose, we conclude that the combination ivermectin + aspirin + dexamethasone + enoxaparin is a very desirablealternative.

Since we finished our Trials, 54 more ones have been submitted to the NLM (USA), 35 of which already contain results. A meta-analysis of those 37 Trials concluded all of them had positive results, and the possibility of bias was almost inexistent (Figure 7).

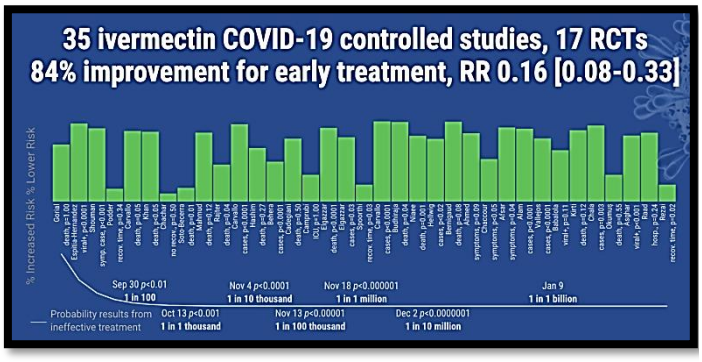

Figure 7: Meta-Analysis of trials using Ivm.

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Conflict of Interest

The Authors manifest no conflict of interests.

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Covid 19 and Ivermectin Prevention and Treatment Update

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Abstract

The number of new COVID 19 contagions and related deaths is increasing worldwide. Our early protocols (NCT04425850 and NCT04425863) duly submitted and released through the National Library of Medicine (USA) have given unmatched profs of efficacy and safety, but still await their time to become widespread. In the meantime, we have simplified their use, and added some extra tools to combat this permanent peril. The results of our further investigations are summarized below.

Keywords: COVID19; Prophylaxis; Treatment; Update

Conceptual Field

From the first imported case of COVID 19 (from Milan, Italy, on March 3, 2020), until today (October 16), 966,000 infections and 25,723 deaths, have been registered in Argentina [1]. If we consider the under-registration that emerges from those not tested - and we are based on the fact that the level of testing in Argentina is one of the lowest in the world - we conclude that the REAL number of cases should be exceeding 4 million by far of people. Likewise, if we take into account the excess of deaths, deaths from COVID should be counted at about 50,000 [2]. Surely, we will never know exactly one or the other data. The truth is that - in recent times - the WHO has definitively ruled out some drugs that initially seemed promising, but that successive clinical studies ended up stoning. This is the case with remdesivir, the ritonavir/lopinavir combination, hydroxychloroquine, and interferon [3]. Likewise, the trials carried out with convalescent plasma at the Hospital de Clínicas José de San Martín and the Hospital Italiano (both in CABA), as well as the multicenter one carried out by the Ministry of Health of the Province of Buenos Aires, yielded disappointing results [4-6]. There are still treatments with equine serum, monoclonal antibodies and ivermectin, which we have dedicated ourselves to, and which we will update below.

Ivermectin in Prevention

Ivermectin has been used both alone and associated with carrageenan- for the prophylaxis of the population groups most exposed to contagion, such as Health Agents [7,8]. Its administration alone or in combination, has demonstrated unobjectionable efficacy, greatly optimizing biosecurity measures and personal protection elements (which it does not replace). In this sense, there are certain updates: 1) the use of ivermectin as a preventive of COVID 19 should not be limited only to Health Agents, but should be extended to the Security Forces, to all Essential Personnel who must be transferred in mass media, to population groups in confinement and / or overcrowded conditions (geriatric, psychiatric, prison, orphanage, slums, etc.), their cohabitating contacts and people with comorbidities.

2) Ivermectin should be used at a rate of 200 micrograms per kilogram of weight, in a weekly dose, which will be repeated

in the same period, up to 8 weeks. After these two months, the adipose tissue will have accumulated enough ivermectin for its protective effect to last for another four months [9]. Those four "extra" months can be covered with carrageenan, which may have been used since the beginning of prevention or just added in the ninth week, since its use can be prolonged indefinitely [10].

Ivermectin in Treatment

The I.D.E.A. Protocol has been replicated in several Provinces (Corrientes, Jujuy, Salta, Tucumán) and is being incorporated in many others (Misiones, Santa Fe, Chubut, etc.). Several amendments have been added, due to the results obtained and new concepts that have emerged since the completion and elevation of the protocols in June 2020 [11]. They are detailed below:

1) The doses are repeated weekly, as many weeks as necessary in each individual case, until the patient is free of disease and / or risk.

2) The weekly schedule can be shortened to every 5 days, if the patient's condition so requires.

3) Bromhexine has been associated with success, outside of the original protocol, since it adds a blocking factor on TMPRSS2 receptors that is not achieved with other medications [12].

4) Carrageenan can be added –also outside the original protocol- in order to reduce the dissemination by aerosols of patients, minimize endogenous reinfection, and the risk of the Health Personnel in charge of their care [13].

5) Once the patient is released, the immune response achieved through "natural active immunization" should be measured, which means having contracted the disease. This immunity is inconsistent at the humoral level, and there is still no infrastructure to massify the search for cellular immunity [14,15]. For this reason, we consider that if the patient has not elevated the specific IgG in a qualitatively/ quantitatively satisfactory way, he should continue with the prophylaxis scheme, once externalized. Below, we include a list of the international Trials dealing with Ivermectin that have been currently submitted to the National Library of Medicine (USA). In capital letters, we marked our Trials, which have already been completed and have results (NCT 04425850 and NCT 04425863).

Title
Ivermectin vs. Placebo for the Treatment of Patients With Mild to Moderate COVID-19
Safety and Efficacy of Ivermectin and Doxycycline in Treatment of Covid-19
Efficacy of Ivermectin in Adult Patients With Early Stages of COVID-19
Hydroxychloroquine and Ivermectin for the Treatment of COVID-19 Infection
Effectiveness and Safety of Ivermectin for the Prevention of Covid-19 Infection in Colombian Health Personnel
Efficacy and Safety of Ivermectin and Doxycycline in Combination or IVE Alone in Patients With COVID-19 Infection.
Ivermectin in Adults With Severe COVID-19.
Ivermectin Effect on SARS-CoV-2 Replication in Patients With COVID-19
Ivermectin and Nitazoxanide Combination Therapy for COVID-19
Ivermectin Nasal Spray for COVID19 Patients
Ivermectin vs. Placebo for the Treatment of Patients With Mild to Moderate COVID-19
Clinical Trial of Ivermectin Plus Doxycycline for the Treatment of Confirmed Covid-19 Infection
Outpatient Use of Ivermectin in COVID-19
Usefulness of Topic Ivermectin and Carrageenan to Prevent Contagion of Covid 19
Efficacy of Ivermectin in COVID-19
The Efficacy of Ivermectin and Nitazoxanide in COVID-19 Treatment
Sars-CoV-2/COVID-19 Ivermectin Navarra-ISGlobal Trial
Ivermectin and Doxycycine in COVID-19 Treatment
Prophylactic Ivermectin in COVID-19 Contacts
Max Ivermectin- COVID 19 Study Versus Standard of Care Treatment for COVID 19 Cases. A Pilot Study
Ivermectin vs Combined Hydroxychloroquine and Antiretroviral Drugs (ART) Among Asymptomatic COVID-19 Infection
Ivermectin-Azithromycin-Cholecalciferol (IvAzCol) Combination Therapy for COVID-19

A Comparative Study on Ivermectin and Hydroxychloroquine on the COVID19 Patients in Bangladesh
Efficacy of Subcutaneous Ivermectin With or Without Zinc and Nigella Sativa in COVID-19 Patients
Early Treatment With Ivermectin and LosarTAN for Cancer Patients With COVID-19 Infection
Ivermectin, Aspirin, Dexamethasone And Enoxaparin as Treatment of Covid 19
A Preventive Treatment for Migrant Workers at High-risk of COVID-19
Novel Regimens in COVID-19 Treatment
Novel Agents for Treatment of High-risk COVID-19 Positive Patients
Comparative Study of Hydroxychloroquine and Ivermectin in COVID-19 Prophylaxis
A Study to Compare the Efficacy and Safety of Different Doses of Ivermectin for COVID-19
Trial of Combination Therapy to Treat COVID-19 Infection
Anti-Androgen Treatment for COVID-19
Comparative Study of Hydroxychloroquine and Ivermectin in COVID-19 Prophylaxis
Early Treatment With Ivermectin for Patients with COVID-19 Infection
Comparative study on new drugs against SARS COV 2

Ivermectin (IVM) Mechanisms of Action

There are two mechanisms of action already described that explain IVM ways of preventing COVID 19 activity. The first one is outside host cells, by provoking ionophores along the viral nucleocapside, thus allowing OH compounds in. This deconstructs the virus structure.

The other mechanism is inside the host cell, preventing the virus to use the alpha and beta1 importing as carriers to reach the cell nucleus.

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Bromhexina. un paso más en la estrategia terapéutica contra covid-19.

Héctor Carvallo, Roberto Hirsch.

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BROMHEXINA. UN PASO MÁS EN LA ESTRATEGIA TERAPÉUTICA CONTRA COVID-19

Bromhexine. One more step in the therapeutic strategy against COVID-19

Héctor Carvallo[1], Roberto Hirsch[2]

RESUMEN

La repentina aparición de la pandemia de COVID-19 puso en jaque a la comunidad médica internacional y a la humanidad toda.
Nuestro protocolo I.D.E.A. (ivermectina, dexametasona, enoxaparina y aspirina) ha mostrado una tendencia muy efectiva, avalada por los datos estadísticos. No obstante, el descubrimiento de nuevas formas de atacar al virus abren formas impensadas de interacción medicamentosa, algunas inaccesibles desde el punto de vista de los costos sanitarios masivos. Proponemos el agregado de bromhexina, que no incide en el bajo costo inicial del protocolo I.D.E.A., pero suma recursos ante la pandemia.

Palabras claves: COVID-19, bromhexina, TMPRSS2.

ABSTRACT

The sudden appearance of the COVID-19 pandemic sent the international medical community and humanity off balance.
Our I.D.E.A. protocol (ivermectin, dexamethasone, enoxaparin and aspirin) has shown a very effective trend, supported by statistical data.
However, the discovery of new ways to attack the virus opens unthinkable forms of drug interaction; some of them are inaccessible from the point of view of massive healthcare costs.
We propose the addition of bromhexine, which does not affect the low initial cost of the I.D.E.A. protocol, but adds resources to the fight against the pandemic.

Key words: COVID-19, bromhexin, TMPRSS2.

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MARCO CONCEPTUAL

A finales de diciembre de 2019, se reportó en la ciudad china de Wuhan la incidencia de cuadros de neumonía atípica de causa desconocida[1].
Dicha especie fue denominada SARS-CoV-2 por su similitud estructural con el SARS-CoV, haciéndolas prácticamente superponibles entre sí.
La única porción significativamente distinta es un dominio de unión a furina en la proteína S de SARS-CoV-2, el cual se ha especulado podría expandir el tropismo o incrementar la transmisión del virus, en comparación del SARS-CoV de 2003.
Una de las porciones más conservadas de la proteína es el dominio de unión a receptor (RBD), el cual presenta una afinidad mayor a la enzima convertidora de angiotensina tipo 2 (ECA2) en comparación con SARS-CoV[2,3].

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Este receptor funcional se encuentra en diversos tejidos, incluyendo epitelio alveolar del pulmón, mucosa rinoorofaríngea, endotelio arterial y venoso, músculo liso, epitelio tubular renal y epitelio del intestino delgado, y explica en gran medida la presentación clínica de los pacientes con COVID-19.
Además, se ha comprobado también la afinidad del COVID-19 con un segundo receptor, el TMPRSS2.
Su expresión parece explicar la mayor incidencia de casos severos en varones, principalmente aquellos con alopecía androcronogenética (**Figura 1**).
El compromiso de órganos con mucha menor concentración de estos receptores (p. ej.: SNC) demuestra, mínimamente, que hay otra(s) forma(s) de acción deletérea.
El período de incubación del virus se ha calculado en 5,1 días (intervalo de confianza del 95% [IC95%]: 4,5-5,8 días), y se sabe que el 97,5% de los pacientes tendrán síntomas a los 11 días (IC95%: 8,2-15,6 días).
Las manifestaciones clínicas se detallan en la **Figura 2** [4-9].
La confirmación diagnóstica se realiza mediante estudios de laboratorio, los que se pueden realizar en una gran variedad de muestras biológicas.
Las muestras de lavado broncoalveolar mostraron la mayor sensibilidad (93%).
Se reporta una sensibilidad del 91% en muestras de saliva, seguidas por las del esputo (72%), hisopados nasales (63%), biopsia por cepillado con fibrobroncoscopio (46%), hisopados faríngeos (32%), heces (29%) y, por último, sangre (1%).

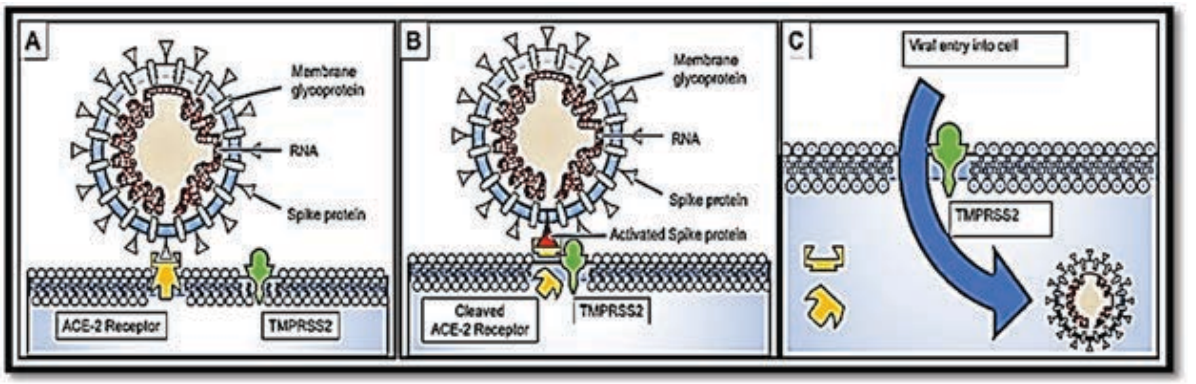


Figura 1. Mecanismo de ingreso del COVID a la célula huésped y posteriormente al núcleo de la misma.

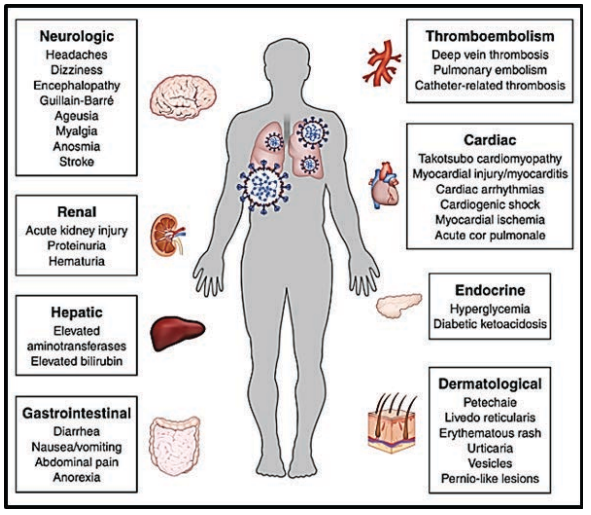


Figura 2. Manifestaciones por COVID-19; considerar la conjuntivitis flictenular como signo de mal pronóstico.

DILEMA ACTUAL ENTRE LA METODOLOGÍA TRADICIONAL Y EL "FRENTE DE BATALLA":

Las crisis importantes a menudo revelan las normas ocultas del sistema científico, haciendo públicas las prácticas bien conocidas dentro de la ciencia. El brote de COVID-19 expone una verdad incómoda sobre la ciencia: el actual sistema de comunicación académica no satisface las necesidades de la ciencia y la sociedad.

Más específicamente, la crisis pone de manifiesto dos ineficiencias en el sistema de investigación: el valor predeterminado de la ciencia cerrada y el énfasis excesivo en las publicaciones de elite, independientemente del contexto y las consecuencias de la investigación.

Wellcome Trust calificó al coronavirus como una "amenaza importante y urgente para la salud global" y pidió a "investigadores, revistas y patrocinadores que se aseguren de que los resultados de la investigación y los datos relevantes sobre este brote se compartan rápida y abiertamente para informar la respuesta a la salud pública y así ayudar a salvar vidas". Los firmantes de esta declaración se comprometieron a hacer que todos los datos e investigaciones sobre el brote se abrieran de inmediato: en repositorios de *preprints* para aquellos artículos que no hubieran sido revisados por pares y en plataformas de revistas para aquellos ya revisados. Este paso positivo no llega a cubrir las necesidades del público científico y, peor aún, no reduce la permanente pérdida de vidas que la pandemia produce.

La pandemia de COVID-19 representa la mayor crisis de salud pública mundial de esta generación y, potencialmente, desde el brote de influenza pandémica de 1918.

La velocidad y el volumen de ensayos clínicos lanzados para investigar posibles terapias para COVID-19 destacan la necesidad y capacidad de producir evidencia de alta calidad, incluso en medio de una pandemia.

No se ha demostrado,hasta la fecha, la efectividad de las terapias.

EVIDENCIAS (O FALTA DE ELLAS) EN LAS OPCIONES TERAPÉUTICAS ENSAYADAS HASTA AHORA

No existe, al momento de redactar estas líneas, un tratamiento que se haya erigido como eficaz contra el COVID-19.

HIDROXICLOROQUINA

La hidroxicloroquina se considera un fármaco antirreumático. Su síntesis se obtiene a partir de la quinidina y esta de la quinina; las dos últimas son fármacos antipalúdicos, cuyos primeros usos se remontan al imperio incaico. Puede disminuir el dolor y la hinchazón de la artritis, prevenir el daño articular y reducir el riesgo de discapacidad a largo plazo. No está claro por qué la hidroxicloroquina es eficaz en el tratamiento de enfermedades autoinmunes; se cree que interfiere en la modulación del sistema inmunológico.

Un metaanálisis de los 142 ensayos llevados a cabo desde su propuesta de uso en la pandemia hasta el 14/4/2020 demostró que la hidroxicloroquina no evidenció efectos beneficiosos[10,11].
Por el contrario, su característica arritmógena, sumada a que la mayoría de los primeros pacientes eran de edad avanzada (propensos a las arritmias cardíacas) y a que en los casos de neumonía se la asociaba a un macrólido (azitromicina). también arritmógeno, concluyeron por descartarla del escaso arsenal terapéutico existente.

KALETRA

Kaletra contiene dos medicamentos usados contra el HIV: iopinavir y ritonavir. Está aprobado por la FDA para el tratamiento de la infección por el HIV en adultos y niños mayores de 14 días de vida. Se utiliza siempre asociado a otros antirretrovirales en tomas diarias, y se cree que también reduce el riesgo de transmisión del HIV al descender la carga viral.
Kaletra puede causar efectos secundarios graves, potencialmente mortales, entre ellos, trastornos del hígado, pancreatitis, arritmias cardíacas, reacciones alérgicas graves e interacciones medicamentosas[12,13].
Entre sus efectos secundarios considerados "menores" se hallan el dolor abdominal intenso y la alteración del ritmo evacuatorio, diarrea. Ambos son parte de la signosintomatología observada en el período de estado de la infección por COVID-19, y su exacerbación inducida por la medicación puede llegar a impedir su uso.
Además, no existe, a la fecha, ningún estudio que con rigor científico (universo de estudio extenso, comparación con otros fármacos y no con placebo) demuestre su eficacia en esta pandemia.

REMDESIVIR

Es un análogo de nucleótido experimental, del cual se cree que interfiere con la polimerización del ARN del virus. Se desarrolló inicialmente como tratamiento para la enfermedad por el virus del Ébola[14]. Se han publicado estudios abiertos sobre su uso compasivo, cuyos resultados deben interpretarse con cautela, dado que la recopilación de datos en un programa de uso compasivo es limitada, el tamaño de la cohorte analizada es pequeño, no existe un grupo de control aleatorizado y el tiempo del seguimiento de los pacientes es corto.
Recientemente se han publicado los resultados de un estudio aleatorizado, doble ciego y controlado con placebo. Este estudio incluye 237 pacientes (158 tratados con remdesivir y 79 tratados con placebo) con infección grave. La variable principal usada fue "tiempo hasta mejoría clínica". En este estudio, remdesivir no mostró diferencia frente a placebo en el tiempo hasta la mejoría clínica (*hazard ratio* [HR]=1,23; IC95%: 0,87-1,75).
Entre sus efectos secundarios, destacan:

- Reacción inmediata a la infusión, con síntomas tales como hipotensión, náuseas, vómitos, sudoración, escalofríos y temblores.
- Reacción alérgica grave, cuyos síntomas incluyen erupción cutánea, picazón/inflamación (especialmente en la cara/lengua/garganta), mareos intensos y disnea.

TOCILIZUMAB Y OTROS AGENTES BIOLÓGICOS

El tocilizumab (TCZ) es un medicamento biológico aprobado para tratar la artritis reumatoide (AR) en adultos, la artritis reumatoide juvenil (ARJ) poliarticular y la forma sistémica de la artritis idiopática juvenil (AIJ) en niños. TCZ es un agente inmunosupresor, inhibidor de la IL-6.
Los medicamentos biológicos son artificiales y se fabrican por medio de técnicas de ingeniería genética[15]. Se los utiliza para suprimir el sistema inmunitario en las enfermedades autoinmunes.
Aunque están en marcha numerosos ensayos clínicos, en los que se está evaluando la eficacia y seguridad de TCZ y otros fármacos similares para el tratamiento de SARS-CoV-2, no existe por el momento evidencia procedente de ensayos clínicos controlados.
No se recomienda el uso de TCZ (o similares) en caso de:

- Valores de AST/ALT superiores a 10 veces el límite superior de la normalidad.
- Neutrófilos <500 células/mmc.
- Plaquetas <50.000 células/mmc.
- Sepsis documentada por otros patógenos, no por SARS-CoV-2.
- Presencia de comorbilidades que puedan predecir mal pronóstico.
- Diverticulitis complicada o perforación intestinal.
- Infección cutánea en curso (p. ej.: piodermitis no controlada con tratamiento antibiótico).

Las reacciones adversas más graves identificadas en los tratados con TCZ fueron infecciones graves, complicaciones de la diverticulitis, reacciones de hipersensibilidad, neutropenia y/o trombocitopenia, riesgo de sangrado y daño hepático.

INTERFERÓN BETA-1B E INTERFERÓN ALFA-2B

Aunque se están realizando ensayos clínicos donde se está evaluando la eficacia y seguridad de los interferones de tipo I para el tratamiento de SARS-CoV-2, no existe por el momento evidencia procedente de ensayos clínicos controlados. Es más, existen evidencias recientes que muestran cómo el interferón es capaz de aumentar la expresión de ECA2 en células epiteliales humanas, lo cual puede favorecer la mala evolución de la infección[16].

SUERO Y/O PLASMA DE CONVALECIENTES

El uso de suero y plasma fresco datan desde los albores del siglo XX. Es indudable el beneficio del suero antiofídico

dado que, a pesar de su corta vida media, ésta excede la de la toxina inoculada por las víboras.
Del mismo modo, el plasma fresco ha sido un excelente aporte de factores de coagulación K dependientes, en los pacientes con insuficiencia hepática. En ellos, a diferencia del caso anterior, la persistencia del daño funcional hepático hace inviable su uso prolongado.
La administración de sueros heterólogos (p. ej.: equinos) fue útil para el tratamiento precoz de clostridios (*Clostridium tetani*), pero su uso se abandonó cuando se obtuvieron inmunoglobulinas sintéticas, lo cual reducía los efectos adversos de aquellos.
En el mejor de los casos, el suero y/o plasma tiene una duración muy limitada[17].
Si es una premisa fundamental para el éxito terapéutico la aplicación precoz del tratamiento, esto aleja la posibilidad de usar suero y/o plasma en todos los casos leves.

PROTOCOLO I.D.E.A.

Nosotros proponemos el uso de ivermectina vía oral, asociada a corticoides, aspirina y/o enoxaparina, ajustados según la severidad del cuadro clínico a tratar.
Sería redundante explicar las indicaciones y los mecanismos de acción de la aspirina, la enoxaparina y la dexametasona, los cuales son harto conocidos y documentados. Valga, sí, enfatizar que los dos primeros están orientados a prevenir (la aspirina) o a corregir (la enoxaparina), el estado de hipercoagulabilidad. Y que la dexametasona está indicada como inmunomodulador, a fin de frenar la hiperinflamación. Y que estos dos procesos (hipercoagulabilidad e hiperinflamación) son los responsables de la severidad y la letalidad de la infección por COVID-19.
En lo referente a la ivermectina, debemos extendernos más.
La ivermectina es un antiparasitario (endodecticida) es decir con propiedades nematicida y ectoparasiticidas.
Es una lactona macrocíclica que se deriva de las avermectinas, grupo de agentes antiparasitarios endodecticidas y sumamente activas, aisladas por fermentación del microorganismo del suelo *Streptomyces avermitilis*.
Fue descubierta en 1960 en Japón por el microbiólogo Satoshi Omura, del instituto Kitasato, y luego (1981) enviado a Merck & Co., NJ. USA, donde el Dr. William C. Campbell inicia los estudios que permiten ser comercializada para uso animal a comienzos de los años ochenta. Ambos recibieron el Premio Nobel en Fisiología y Medicina en 2015.
En 1985 los franceses demostraron su utilidad en oncocercosis, en África. Fue aprobada en 1997 por la FDA para estrongiloidosis en dosis única de 200 g/kg y en escabiosis costrosa (sarna noruega) en pacientes afectados de SIDA en dosis de 200 g/kg, cada semana por 2 semanas. Está siendo usada en 90 países.
Una vez que la ivermectina ha sido absorbida después de la administración oral o sistémica, es generalmente transportada rápidamente al hígado.
El hígado y el tejido adiposo pueden almacenar la droga, liberándola lentamente para producir un efecto sostenido. Tiene un tiempo máximo de concentración de 2,7 a 4,3 horas y una vida media de 28 horas. La ivermectina es ampliamente metabolizada por los microsomas del hígado humano en por lo menos 10 metabolitos, y muchos de ellos son hidroxilados y desmetilados.
Fue demostrado que el citocromo P4503A4 es la enzima responsable del metabolismo de la ivermectina.
La dosis recomendada tiene un amplio margen de seguridad.
El principal neurotransmisor periférico en el hombre, la acetilcolina, no se altera por la ivermectina. La ivermectina no penetra fácilmente en el sistema nervioso central de los mamíferos, donde el GABA funciona como neurotransmisor; de allí su relativa seguridad para uso humano.
El efecto de la ivermectina en oncocercosis se produce a los pocos días y persiste entre 6 y 12 meses; es cuando debe repetirse la dosis.
Mientras la parálisis de los parásitos es el efecto más importante de la ivermectina, la supresión del proceso de reproducción es también muy significativo.
En múltiples estudios se ha demostrado la efectividad de la ivermectina oral como endodecticida. (para el tratamiento de endoparásitos y ectoparásitos.) Hay reportes de su manejo en escabiosis, miasis, oncocercosis, larva migrans cutánea e incluso en pediculosis, a tal punto que hoy en día es el fármaco de elección para el tratamiento y el control de la oncocercosis humana.
La ivermectina se considera el tratamiento de elección para la estrongiloidosis no complicada, con dos dosis únicas de 200 μg/kg orales de ivermectina administrada en 2 días consecutivos o 2 semanas de diferencia.
Algunos de sus efectos adversos, como diarrea, el prurito, la anorexia y el aumento de los niveles de transaminasas, son infrecuentes y generalmente leves.
Otros efectos colaterales reportados son fiebre, cefalea, prurito, edema, mialgia y artralgias en 64% de los pacientes con la primera dosis, y de 50% con la segunda, pero de leve a moderada intensidad que cedieron fácilmente con aspirina y/o antihistamínicos, con lo que se concluye que la droga es bien tolerada en niños mayores de 5 años.
Administrada oralmente, no atraviesa la barrera hematoencefálica.
Está contraindicada en el embarazo, aunque han sido reportados estudios donde en forma inadvertida fue dada a mujeres en el primer trimestre del embarazo sin encontrarse efectos teratogénicos.
Se debe evitar su uso concomitante con drogas que actúan sobre los receptores GABA, barbitúricos y benzodiazepinas.

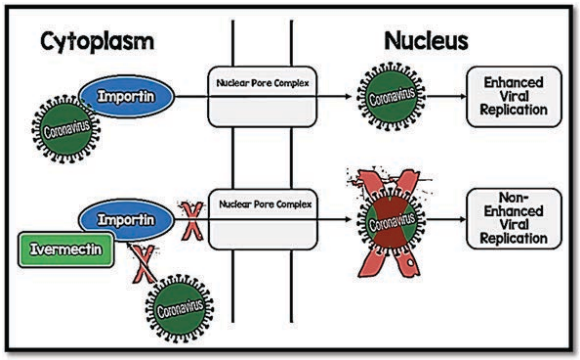


Figura 3. Mecanismo más conocido de acción de la ivermectina sobre COVID-19.

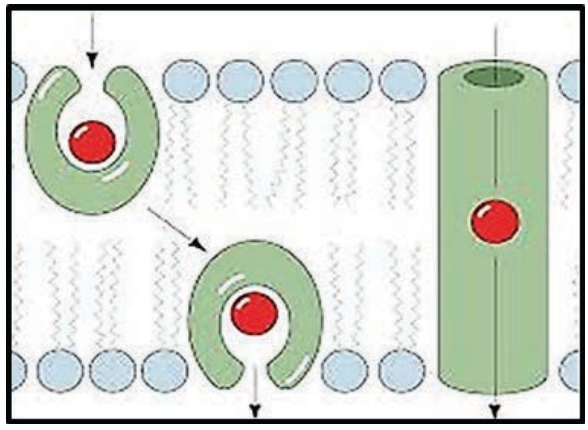


Figura 4. Formación de ionóforos a nivel de la cápside lipídica del COVID-19.

Pero, mucho más recientemente, se han hallado nuevos usos para la ivermectina.

Así, se han ido recopilando sus efectos viricidas sobre distintas variedades de flavivirus, el dengue, zica, chikungunya e infección del *West Nile*[18].

Simultáneamente, se han ido optimizando las dosis adecuadas a cada caso.

Es, además, un inhibidor del virus causante (SARS-CoV-2). Con una sola adición a células vero-hSLAM 2 horas después de la infección con SARS-CoV-2 es capaz de efectuar una reducción de ~5000 veces en el ARN viral a las 48 hs. Por lo tanto, justifica una mayor indicación para posibles beneficios en humanos. Se cree que esta actividad de amplio espectro se debe a la dependencia de muchos virus de ARN diferentes en IMPα / β1 durante la infección.

Los estudios sobre las proteínas del SARS-CoV han revelado un papel potencial para IMPα / β1 durante la infección en el cierre nucleocitoplasmático dependiente de la señal de la proteína de la nucleocápside del SARS-CoV, que puede afectar la división celular del huésped.

Además, se ha demostrado que la proteína accesoria del SARS-CoV ORF6 antagoniza la actividad antiviral del factor de transcripción STAT1 al secuestrar IMPα/β1 en la membrana rugosa de ER/Golgi.

Para evaluar la actividad antiviral de la ivermectina hacia el SARS-CoV-2, se infectaron las células vero/hSLAM con el aislado SARS-CoV-2 Australia/VIC01/2020 a un MOI de 0,1 durante 2 hs, seguido de la adición de 5 μM de ivermectina.

El sobrenadante y los sedimentos celulares se recogieron en los días 0-3 y se analizaron por RT-PCR para la replicación del ARN del SARS-CoV-2. A las 24 hs, hubo una reducción del 93% en el ARN viral presente en el sobrenadante (indicativo de viriones liberados) de muestras tratadas con ivermectina en comparación con el vehículo DMSO.

Del mismo modo, se observó una reducción del 99,8% en el ARN viral asociado a células (indicativo de viriones no liberados y no empaquetados) con el tratamiento con ivermectina.

A las 48 hs, este efecto aumentó a una reducción de ~5000 veces del ARN viral en las muestras tratadas con ivermectina en comparación con las muestras de control, lo que indica que el tratamiento con ivermectina resultó en la pérdida efectiva de esencialmente todo el material viral en 48 hs.

No se observó toxicidad de la ivermectina en ninguno de los puntos de tiempo analizados, ni en los pocillos de la muestra ni en muestras de fármaco analizadas en paralelo[19,20].

Estos resultados demuestran que la ivermectina tiene acción antiviral contra el aislado clínico de SARS-CoV-2 *in vitro*, con una dosis única capaz de controlar la replicación viral en 24-48 hs.

Se insiste en que, supuestamente, esto es probable mediante la inhibición de la importación nuclear de proteínas virales mediada por IMPα/β1, como se muestra para otros virus de ARN (**Figura 3**).

Posee un efecto antiviral eficaz para el SARS-CoV-2 si se administra a los pacientes en una etapa temprana de la infección, y ayuda a limitar la carga viral, prevenir la progresión grave de la enfermedad y reducir la transmisión de persona a persona[21-23].

Recientemente, se ha propuesto otro mecanismo de acción, como agente ionóforo.

Los ionóforos presentan internamente muchos átomos de oxígeno, y son indispensables para unir cationes y transportarlos a través de bicapas fosfolipídicas (membranas celulares; cápside fosfolipídica del virus).

Como consecuencia, determinarían un desequilibrio iónico entre el entorno externo e interno, con la consiguiente lisis osmótica (**Figura 4**).

CRITERIOS DE INCLUSIÓN EN EL PROTOCOLO I.D.E.A.

Pacientes con COVID-19, en todos sus estadios y grados de compromiso (considerándose como tales los observa-

TABLA 1. Terapéutica.

Ivermectina	Corticoides	AAS /enoxaparina	Ventilación
24 mg oral en una sola dosis (o su equivalente a 300 µg/kg), a repetir en una semana	No	Aspirina 250 mg oral (1 vez por día)	No
Ídem	Dexametasona		
4 mg (parenteral) 1 vez por día	Ídem	No	
36 mg oral (o su equivalente a 400 µg/kg), a repetir en una semana con dosis de caso leve	idem	Enoxaparina 1 mg /Kg de peso (100 UI/kg) dos veces al día	Oxígeno lavado a bajo flujo o concentrador de oxígeno
48 mg por SNG (ó su equivalente a 600 mcg/ kg), a repetir en una semana con dosis de caso moderado	Ídem o pulsos de corticoides	Ídem	Asistencia respiratoria mecánica

dos y objetivados en la primera consulta). Cada subgrupo recibirá el esquema y las dosis que correspondan a su categorización inicial. La evolución ulterior puede obligar a modificar dichas dosis, según esquema preestablecido.
Es menester enfatizar que la eficacia de estos medicamentos depende de la precocidad en la instalación del esquema, en relación estrecha y directa con la eficacia del mismo.

CRITERIOS DE EXCLUSIÓN

Mujeres gestantes. Niños menores a 5 años.

POSOLOGÍA, FORMA DE ASOCIACIÓN Y DOSIS

Las mismas se basan en un *score* de severidad desarrollado *ad hoc*.

Criterios menores	Criterios mayores
Fiebre inferior a 38,5°C. Episodios diarreicos aislados. Hiposmia o hipogeusia. Desaturación leve (entre 96 y 93%). Disnea *sine materia*. Polimioartralgias, cefalea persistente. Dolor abdominal. Lesiones dermatológicas tipo eritema pernio.	Fiebre mayor de 38,5°C. Diarrea (más de 3 deposiciones diarreicas/día). Conjuntivitis flictenular. Desaturación marcada (inferior a 92%). Taquipnea (FR >25/minuto). Urticaria gigante; livedo reticularis.

De ese *score*, se desprende el encasillamiento por severidad de cada caso.

INTERPRETACIÓN

Compromiso leve	Compromiso moderado	Compromiso severo
Criterios menores únicamente	3 hallazgos mayores o 2 mayores + 2 menores.	4 hallazgos mayores o 3 mayores + 2/3 menores.

Y, en función de los anteriores, se aplica la terapéutica (**Tabla 1**):

CONCEPTOS SOBRE BLOQUEO DE RECEPTORES ECA2 Y TMPRSS2:

RECEPTORES ECA2 Y SUS BLOQUEANTES

Los bloqueadores de los receptores de angiotensina (BRA) tienen efectos similares a los inhibidores de la ECA, pero los inhibidores de la ECA actúan evitando la formación de angiotensina II en lugar de bloquear la unión de la angiotensina II a los músculos en los vasos sanguíneos.
Los BRA se usan para controlar la presión arterial alta, tratar la insuficiencia cardíaca y prevenir la insuficiencia renal en personas con diabetes.
Por lo tanto, los BRA (losartán, valsartán, telmisartán, etc.) podrían constituirse en un enfoque terapéutico novedoso para bloquear la unión y, por lo tanto, la unión de SARS-CoV-2 RBD a las células que expresan ECA2, inhibiendo así su infección al huésped células.
Los últimos estudios retrospectivos no hallaron resultados alentadores en el uso de bloqueantes ECA2, y la hipotensión resultante limita su indicación en estos casos.

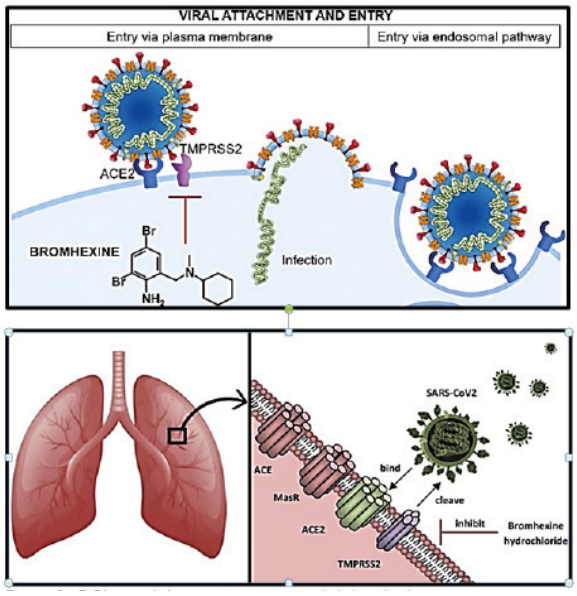
RECEPTORES TMPRSS2 Y SUS BLOQUEANTES

La sobreexpresión de estos receptores ha sido asociada con la mayor incidencia de cáncer de próstata.
TMPRSS2 sobreexpresa a ERG en respuesta a andrógenos.
Estructuralmente este reordenamiento se debe a una deleción intersticial y, en menor medida, a una translocación recíproca, y tiene un papel clave en el metabolismo celular. Casi todos los transcritos del gen de fusión producen una proteína ERG truncada, y la presencia de una determinada isoforma de este gen indica la clonalidad del tumor, de modo que la metástasis comparte isoforma de TMPRSS2-ERG con su localización primaria.
Así, mucho antes del comienzo de la actual pandemia se han venido ensayando distintos bloqueantes del receptor, como un intento para reducir el riesgo y/o la progresión de esa neoplasia.
Los distintos ensayos han encontrado varios bloqueadores: Tocilizumab. Anticuerpo monoclonal (IgG1) recombinante humano específico.

Mesilato de camostat. Aprobado en Japón para el tratamiento de la pancreatitis.
Y otros, pero cuyo costo haría insostenible un tratamiento a largo plazo de los pacientes afectados por COVID-19, tanto a nivel público como privado.

CONCEPTOS SOBRE LA BROMHEXINA EN PARTICULAR

La bromhexina es un fármaco sintético que ejerce efecto mucolítico y expectorante. Reduce la viscosidad de las secreciones bronquiales y aumenta el volumen del esputo al inducir despolimerización hidrolítica de las mucoproteínas fibrilares. Asimismo estimula la actividad ciliar del epitelio.
Algunos estudios sugieren que la combinación de bromhexina con antibióticos, en la misma formulación, es más eficaz que la sola administración del antibiótico para el tratamiento de infecciones respiratorias.
La bromhexina se absorbe bien a través de la mucosa gastrointestinal y alcanza concentraciones plasmáticas máximas en 60 min. Con el aporte oral de 4 mg, las concentraciones plasmáticas disminuyen a 0,14 µg/ml en las primeras 8 hsposteriores a la administracióndel fármaco.
Se metaboliza en el hígado.
Alrededor de 70% de una dosis oral del fármaco original se recupera en la orina en las primeras 24 hs.
La vida media de eliminación es de 6 hs.
Su indicación primaria es para facilitar la expectoración en casos de traqueobronquitis, bronquitis aguda, bronquitis crónica, neumonía.
Por su efecto mucolítico, se ha usado para reducir la viscosidad de las secreciones oculares en el síndrome de Sjögren.
Está contraindicado en casos de hipersensibilidad a la bromhexina, durante el embarazo y la lactancia.
Debe evitarse su uso en casos de úlcera gástrica.
Produce elevación sérica transitoria de la aspartato aminotransferasa.
Las reacciones adversas son poco frecuentes: náuseas, vómitos, gastritis, anorexia, diarrea, dolor epigástrico, vértigo, cefalea.
Excepcionalmente, se han reportado hepatotoxicidad y erupciones cutáneas.



Figuras 5 y 6. Bloqueo de receptores por parte de la bromhexina.

Recientemente, se ha demostrado que este fármaco, de amplio y antiguo uso en la farmacopea humana, es también un bloqueante de los receptores TMPRSS2 (**Figuras 5 y 6**)[24].

AGREGADO DE LA BROMHEXINA AL ESQUEMA TERAPÉUTICO I.D.E.A.

La bromhexina aporta una herramienta más al arsenal terapéutico para enfrentar al COVID-19; su uso no se contrapone con el resto de los fármacos empleados; su costo (al igual que el de los demás agentes terapéuticos) es muy bajo, y su posología sencilla[25-27].
Coincidiendo con los demás fármacos del Protocolo IDEA, esta medicación se halla incluida en la farmacopea desde hace décadas, y su eventual utilización es el indicado para bromhexina en la misma.
Su incorporación no modifica el protocolo antedicho, toda vez que el agregado de un mucolítico es una indicación precisa en cualquier paciente con tos productiva.
Ello redundaría en dos beneficios: la mejoría de los síntomas y el bloqueo de los receptores TMPRSS2, "cerrándole el camino" al COVID-19.

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Ivermectin in COVID-19 Patients a Multicenter: Retrospective Study.

Alonso Luis, Bracho Colina Wilmer, Carvallo Hector, Del Franco Haroldo, Hirsch Roberto, Salgado Antonio and Shaikh Sanjid Seraj.

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Ivermectin in COVID-19 Patients a Multicenter: Retrospective Study

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Abstract

During 2020, many Medical Centers and solo Practitioners have adopted the I.D.E.A. protocol (Ivermectin, Dexamethasone, Enoxaparin and Aspirin) as the only inexpensive, effective, safe means to fight COVID infection. We hereby summarize the experience of some of these endeavors, stressing the fact that -by providing their patients with this protocol they have saved thousands of lives that, if not, would have been put in an unnecessary danger, or simple lost. We take into consideration the percentage of COVID + patients that required ulterior admittance, and also the death rate amid those admitted.

Keywords: Ivermectin; COVID 19; Dexamethasone; Infection

Introduction

The COVID 19 (SARS COV2) pandemic implied a major challenge for Health Care. Though death rate amid those admitted at Medicial Centres has slightly declined (partly due to the lower ages now affected), it remains disturbingly high [1,2] (Figures 1 and 2).

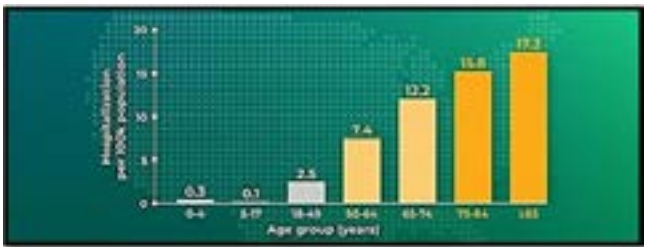

Figure 1: Rates of hospitalization for COVID, Related with patients age.

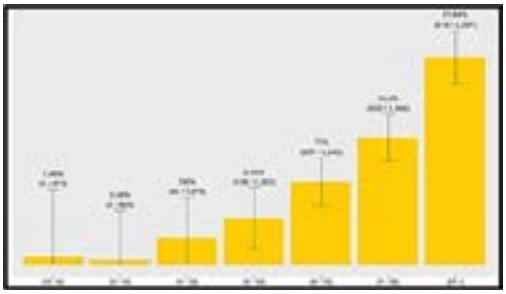

Figure 2: In-Hospital mortality related with patients age.

And, besides, the number of patients who test + and need ulterior admittance has stayed as high as it was at the beginning of the pandemic [3,4] (Figures 3 and 4).

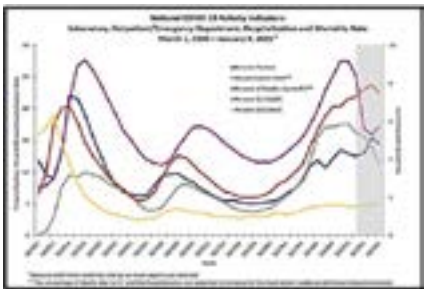

Figure 3: IOut-Patients and In-Patients indicators in USA during January 2021.

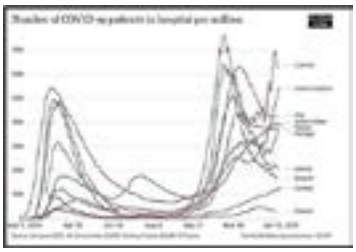

Figure 4: European COVID second wave.

What is more, the typical progress of those subjects admitted (Figure 5), and death rate among them is directly related to the type and magnitude of co-morbidities, the age of the patient, and the permanence in ventilator (Figures 6 and 7).

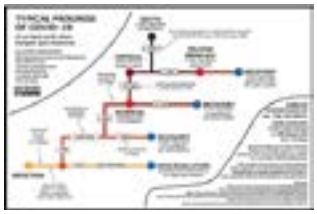

Figure 5: COVID evolution from early to final stages.

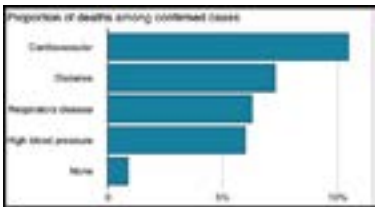

Figure 6: Deaths rates related to previous comorbidities.

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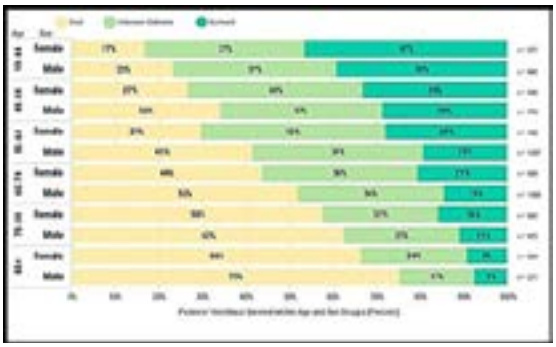

Figure 7: Ventilator survival.

Those facts have not only costed millions of lives, but have also spot lit an unpleasant reality: Health Authorities are not up to cope with this situation. From international entities (i.e.: W.H.O) to local ones (i.e.: NIH, CDC, NICE, and most national and minor offices) all of them have acted slowly, hesitatingly and –in many cases-prioritizing big pharma interests over ordinary people´s benefit. Thus, sanitary measures have come and go, with new concepts eclipsing old ones, over and over again. Expensive, unproven drugs have been preferred over repurposed, cheap ones. In this situation, new drugs have been greedily accepted, while repurposed drugs have been asked for more and more evidence, till the moment came when these last ones have almost 4 times more evidence that all other drugs, put together.

In this article, we gather the results obtained by a group of front-line Medical Doctors, working in different parts of the Argentina Republic, during the ongoing first wave of the pandemic. Ivermectin (IVM) is widely used all over the World as an anti-parasitic compound, and as a repurposed drug, it is proving to be more effective against COVID 19 than all the other drugs subjected to investigation [5-7] (Figure 8).

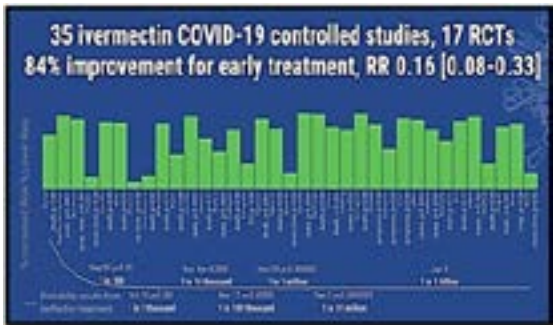

Figure 8: Ivermectin trials outcomes.

This article is not only intended to increase the huge amount of evidence, but also (and mainly) as a tribute to those brave Professionals, that have prioritized patient´s health over theirs.

Materials and Methods

We will initially divide the outcomes according to the place where the cases were followed. Additionally, we will sum up all data, to reach a final, collective outcome. We include outcomes obtained in the Argentinian Provinces of Salta, Jujuy, Santa Fe and Buenos Aires, and the statistical treatment of that data, performed in the UK.

Salta, Argentina

Follow-up of 110 patients with COVID-19 (Figure 9).

Figure 9: Salta province (In Red) location in Argentina.

Dr. Antonio Salgado led a follow-up of 110 patients with COVID-19 (diagnosed by rt-PCR) from them, 18 were under 18 years of age, and 92 were over that, with a mean age of 52-55, 95% of patients used IVM according to previously consensual dosage. All underwent intra COVID craniological control before and immediately post discharge. Only one patient had mild pericarditis, discovered when studies were performed. In routine laboratory checks, all were studied for troponin-CPK MB. Only one patient had alterations of that parameter 100% of the patients 'evolution was favorable, without complications and without oxygen requirement, and/or need of admittance.

Jujuy, Argentina

Treatment of 130 patients with IVM (Figure 10).

Figure 10: IJujuy province (In Green) location in Argentina.

Dr. Wilmer Bracho Colina started treatment with IVM in a total of

130 patients 46 were Health Care Personnel, previously diagnosed by rt-PCR. Only 4 of them developed mild/moderate symptoms from them, 3 didn´t need to be admitted at Hospital, and the one who did, didn´t need ICU assistance, being discharged a week later. The remaining subjects had an average age of 84, and were living in 2 Senior Houses. Only 4 subjects developed symptoms, and one had to be admitted briefly, as she was discharged 2 days later.

Santa Fe, Argentina

The observational study consisted of conducting a comparative analysis between the first 60 days of the pandemic in Correa, Sante Fe Province, a period in which IVM was not used, and the second 60 days of said pandemic in which IVM was used at the same location. This retrospective observation consisted of evaluating the patients regarding the need for hospitalization, lethality, and disease avoidance in close contacts medicated in both periods, as it would have occurred with two different arms, one medicated with placebo and the other with IVM (Figure 11).

Figure 11: santa Fe province (In Red) location in Argentina.

The IVM treatments in Correa began on September 25th and the observational study of cases was cut off on November 25th. In those second sixty days, it was confirmed the death of an 87-year-old man with previous heart disease and severe comorbidities who had been diagnosed with COVID ten days before, and was medicated with IVM for humanitarian reasons six days after the onset of symptoms. The patient suffered a sudden death, without evidence of respiratory failure. The cause of death remains uncertain. Even so, it is included in the statistics as death from COVID. During this 60-day stage, 311 COVID (+) patients were assisted, and the above-mentioned case was the only fatality, with no other case of severe symptoms and/or need of admittance.

Buenos Aires, Argentina

Outcomes obtained in the Argentinian Provinces, Buenos Aires (Figure 12).

Figure 8: Ivermectin trials outcomes.

Scenery 1

The initial trial on IVM (I.D.E.A.) was created by Dr. Hector Carvallo and Dr. Roberto Hirsch, and applied on COVID 19 patients at A. A. Eurnekian Public Hospital (duly submitted to the National Library of Medicine USA, NCT04425863) between May and June, 2020 [8], with Ivermectin solution at a relatively high dose (maximum 4 times over usual dose) to lower the viral load in all stages of COVID 19.

The so-called IDEA protocol was composed of:

Ivermectin, in progressive doses according to severity of cases.

- Dexamethasone 4 mg injection, as anti-inflammatory drug to treat hyper inflammatory
- reaction to COVID-infection
- Enoxaparin injection as anticoagulant to treat hyper coagulation in severe cases.
- Aspirin 250 mg tablets to prevent hyper coagulation in mild and moderate cases.

Except for Ivermection oral solution, which was used in a higher dose than the one approved for parasitoids, all other drugs were used in the already approved doses and indications. Regarding Ivermectin safety, several oral studies have shown it to be safe even when used at daily doses much higher than those approved already. Results were compared with published data and data from patients admitted to the hospital receiving other treatments. None of the 131 patients presenting mild symptoms needed to be hospitalized.

From the 37 who had to be admitted at the time of first visit (because of the severity of their state), only one patient died (0.59% of all included patients vs. 2.1% overall mortality for the disease in Argentina). That meant 3.1% death rate of hospitalized patients vs. 26.8% mortality in published data. IDEA protocol proves to be a useful alternative to prevent disease progression of COVID-19 when applied to mild cases and to decrease mortality in patients at all stages of the

disease with a favorable risk-benefit ratio.

Scenery 2

Despite the B.A. Sanitary Authorities´ reluctance to incorporate IVM in the treatment of COVID 19 patients, Dr. Haroldo De Franco, between May and November 2020, applied IVM-based treatment on a total of 124 out patients with confirmed COVID infection at Mercante Public Hospital.

Average age: 61 years.

Women: 70; Men: 54

Without comorbidities: 18

Main comorbidities

Respiratory: 32

Obesity (with and without associated DM): 38

Cardiovascular (HTN): 31

Neurological: 3

Need for hospitalization after diagnosis and treatment: 1 (0.008%), whose evolution was benign.

Essex, United Kingdom

Dr. Sanjid Seraj performed a statistical investigation of all the above-mentioned data. Taking into account the number of subjects with confirmed diagnosed (mostly by rt-PCR, and some because of the epidemiological fact that they were close contacts to confirmed cases and had developed symptoms), there was a total of 806 patients. The average age was 57, 08.

From them, international literature mentions 10% need of ulterior admittance, due to worsening of symptoms and other risk factors. Morevoer, the same literature implies that –once admitted-the chances of a bad evolution and death arises to 25%. In the cases treated promptly with IVM, only 3 subjects had to be admitted (0.0037%), while the expected need would have been roughly 80. And there was just 1 sudden death (0.0011%), while the international figures speak of no less than 31 subjects.

Taken together, these figures account for a 95.5% reduction in the need of hospitalization, and also a 95.6% reduction in death rate, when IVM treatment was applied at the early stages of the disease [9-12].

Conclusion

From the statistical point of view, IVM has already proved its effectiveness against COVID 19 infection in all stages of the disease. The meta-analysis is also proved that an early treatment is far more effective than a delayed one. The amount of data supporting the need to incorporate IVM amid the options of treatment against COVID 19 is countless. We present a local part of these investigations, with the belief of having done what is best for our patients, and the wish to open the eyes of those in charge of public health. Our figures account for a 95.5% reduction in the need of hospitalization, and a 95,6 reduction in death rate, when IVM treatment was applied at the early stages of the disease, in consonance with existing data. According to ours and other international data, roughly 11,000 lives worldwide could have been saved daily, by simply adding IVM as the treatment offered to COVID 19 patients.

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Ivermectin and Herd Immunity in SARS COV2 Pandemic from Local Experience to Broader Possibility.

Hector E Carvallo and Roberto R Hirsch.

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Clinical Immunology & Research

Ivermectin and Herd Immunity in SARS COV2 Pandemic from Local Experience to Broader Possibility

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ABSTRACT

Immunity can be natural or artificial, and each of them –in turn- active or passive. Artificial active immunity is vaccine-induced (possibly long acting). Active natural immunity is that obtained by becoming ill (it is the longest, the most efficient, but also the most risky, if the disease in question is potentially lethal). When at least 70% of the population reaches immunity, we speak of "herd immunity", with which it is assumed that community transmission is reduced to a minimum. We have developed an ivermectin-based treatment for SARS COV2 infection, which has proven to reduce mortality on a 7:1 scale, in moderate and/or critical cases, and to prevent mild cases from progressing to more severe stages –thus staying as out patients- but, in all of them, humoral immunity was achieved in a reasonable amount.

If these procedures were applied on a larger, broader scale, we could achieve herd immunity, without waiting for the vaccines to be developed, and without the hazards their manufacturers haven´t yet disclaimed.

Keywords

Immunity, COVID 19, Resistance.

Description

In late April, 2020, the Authors developed and ivermectin-based treatment for COVID 19 infection [1]. It was duly submitted to the National Library of Medicine (USA), being the first one in the world to include results that were validated by clinicaltrials.gov. Those results showed a reduction of mortality rate from 23,5 % to 3,2 % of all moderate/critical cases admitted at hospital (reduction of 7:1), and no need of admittance of mild cases.

Nowadays, there are 43 trials on ivermectin, distributed worldwide, and with similar outcomes [2]. In July, 2020, we were called to treat an outbreak in a Senior Home, where both Directors had contracted the virus and through them 4 of the 50 inmates had got contagion. From these last ones, an 83-year- old female developed an ischemic stroke and died. All the participants (the remaining 49 inmates, and the 25 members of personnel), were treated according to our medication scheme [3].

Both the sick personnel and the affected inmates healed in less than one week, and no other inmates and/or personnel developed symptoms suspected to be related to COVID infection. 54 days after the outbreak, IgG for SARS COV2 was studied in both groups, and 85 % of all participants showed titers from 5 to 10 times higher than standard. That proved all of them had got in contact with the virus, in an asymptomatic way, but their immune system had been capable of producing antibodies.

In other words, all participants had contracted the infection, without even noticing it, and developed immunity. Further research should be needed in order to find out if this humoral response is long lasting, but –according to traditional evidence- active natural immunity obtained by becoming ill is the longest and the most efficient, if compared to vaccines.

Discussion

What is immunity?

It is resistance to contracting a disease. Immunity can be natural or artificial, and each of them in turn active or passive. Artificial

passive immunity is sera-mediated (short-acting). Artificial active immunity is vaccine-mediated (much longer acting). Passive natural immunity is that transmitted by the mother to the fetus, via umbilical cord (short lasting). Active natural immunity is that obtained by becoming ill (it is the longest, the most efficient, but also the most risky, if the disease in question is potentially lethal). When at least 70% of the population reaches this last form of immunity, we speak of "herd immunity", with which it is assumed that community transmission is reduced to a minimum. It is a "vaccine effect", but one hundred percent natural.

Let's look at two examples: Spain and the United Kingdom. Spain imposed a sui generis quarantine (called an “alarm state”), which did not prevent a large number of deaths, and did not achieve herd immunity (only 10% of the population is immunized) [4]. The United Kingdom is –after the USA and Brazil- the Country that has had the highest mortality in absolute numbers [5].

In relative numbers (number of inhabitants / number of dead and number of infected / number of dead), it exceeds the US by far. And it is not yet certain whether it has achieved herd immunity. If so, that would be a victory, but a pyrrhic one.

The logic would be trying to achieve herd immunity, but suffering as few casualties as possible. How to achieve herd immunity in Argentina (and the rest of the world), and live to see it?

By providing the population with the most effective medicines for their protection, and gradually releasing the quarantine.

Is that sustainable over time? The answer is yes, based both on outcomes and low costs. If vaccines are used, based on serious data, there is still a long way to go. In this last sense, we must differentiate the serious data from the interested parties, or the successful propaganda. If you apply medications that have proven (in a statistically acceptable way) their effectiveness, that are approved by most Health Authorities, that have a very low cost, it is POSSIBLE, even for economies as vulnerable as Argentina´s.

Why do we emphasize costs?

Human life cannot and should not be measured in monetary terms; but sustainability of health policies must.

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Ivermectin IN Long-Covid Patients: A Retrospective Study.

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Ivermectin IN Long-Covid Patients: A Retrospective Study

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Abstract

Long COVID convalescence has become a major issue in COVID infection. The variety and magnitude of sequelae has, so far, baffled scientific community, and no measure has proved to be both useful and reliable in diminishing and/or shortening it. We are summarising the outcomes in 856 patients previously admitted at a Public Hospital in the Province of Buenos Aires, due to moderate/severe COVID infection, who surmounted the infection and could be released later on.

We selected those whose symptoms, and mainly, the duration of them- could be attributed to long convalescence (long haulers).

In them, a simple post-COVID treatment with ivermectin (IVM) was applied, thus provoking a faster reduction of manifestations.

Keywords: long COVID, Ivermectin, long haulers.

Introduction

Current Knowledge on Long Covid:

There has been an increasing number of reports of COVID-19 symptoms extending beyond the acute phase of infection, named "long COVID"; and its sufferers are known as “long haulers”. A range of multiorgan complications following COVID-19 infection – including respiratory, cardiovascular, metabolic and renal impairments – have also been hypothesised [1].

In a survey by the UK Government's Office for National Statistics in November, 2020, around one in five people who tested positive for COVID-19 had symptoms that lasted for 5 weeks or longer, and one in ten people had symptoms that lasted for 12 weeks or longer. These figures equate to an estimated 186 000 individuals in England who had symptoms persisting between 5 and 12 weeks [2].

Adults with severe illness who spend weeks in intensive care, often intubated, can experience long-lasting symptoms, but that’s not unique to patients with COVID-19.

What’s unusual about the long haulers is that many initially had mild to moderate symptoms that didn’t require lengthy hospitalization-if any let alone intensive care.

In some organs, especially the lungs, those changes persist far past the point at which patients have stopped shedding the virus [3].

The list of long hauler symptoms is long, wide and inconsistent. The most common long hauler symptoms include (Fig-1):

- Coughing
- Ongoing, sometimes debilitating, fatigue
- Body aches
- Joint pain
- Shortness of breath
- Loss of taste and smell-even if this didn’t occur during the height of illness
- Difficulty sleeping
- Headaches
- Brain fog

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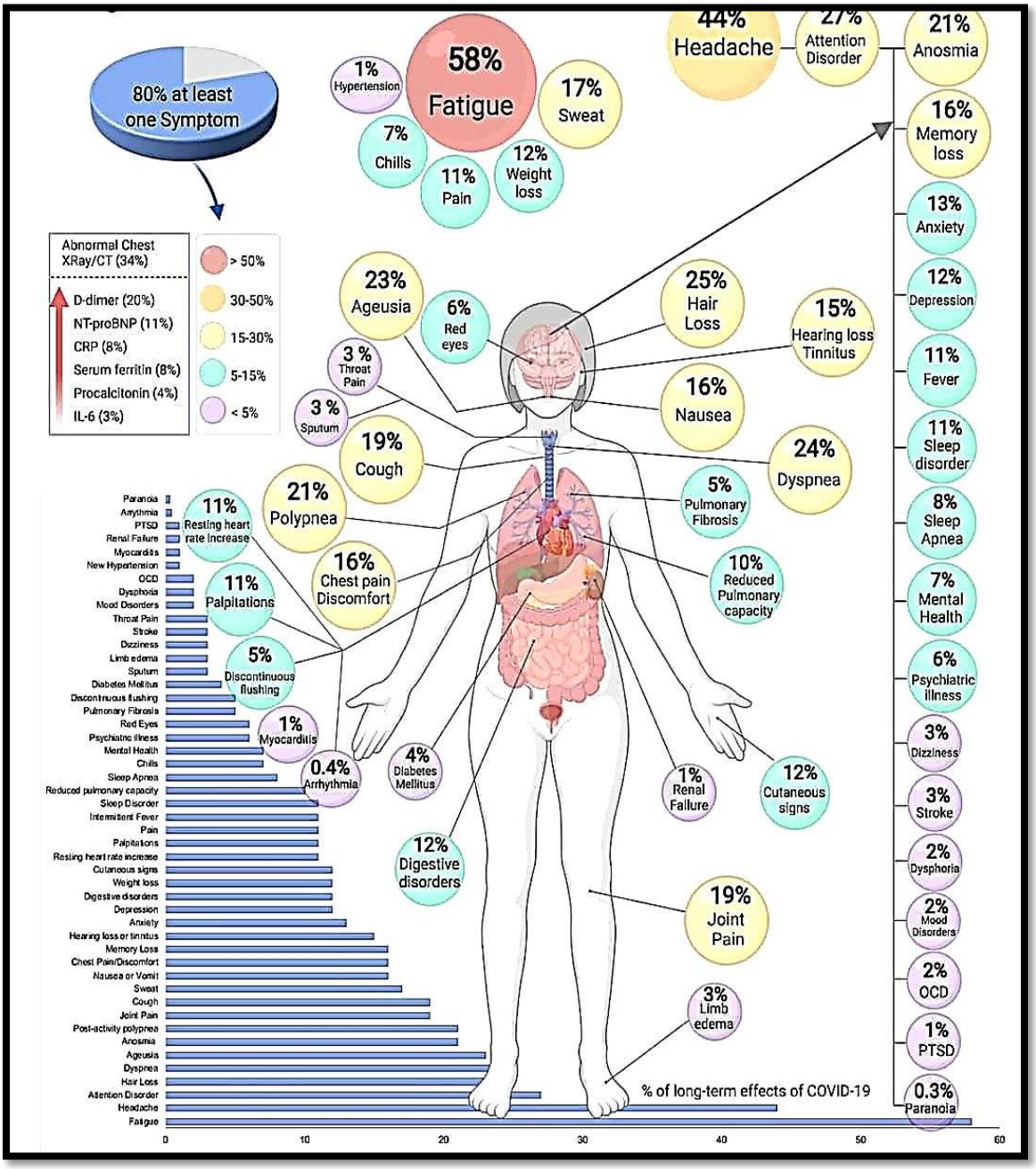

Figure 1: Long-Term Covid Effects (From Sonia Villapol: Long Term Effects of Covid 19. The Conversation. February, 2021)

Brain fog is among the most confusing symptoms for long haulers. Patients report being unusually forgetful, confused or unable to concentrate.

This can happen to people who were in an intensive care unit for a while, but it's relatively rare.

Any well-trained Medical Doctor can tell –from the way a COVID-patient talks- if he is still suffering a brain fog, as the voice sounds like that of a nearly drunken person.

There's not a lot of information on long haulers, who only recently received attention from experts because it's also so new.

The vast majority of long haulers test negative for COVID-19. One theory about patients with long-term COVID-19 symptoms is that the virus possibly remains in their bodies in some small form.

Another theory is their immune systems continue to overreact even though the infection has passed [4].

Based on the experience with other viral epidemics that are capable of causing a chronic-phase of the disease, COVID-19 is difficult because of the diversity it exhibits in:

a- Evading and affecting the human immune system.

b- The tissue tropism it exhibits based on ACE2 receptor density.

c- Its capability to run amok with multiple organ and systems.

Factors like the viral load, which may get eradicated or persist resulting from tissue budding of SARS-CoV-2, appear to be possibly playing the main role in long-haulers (Fig-2).

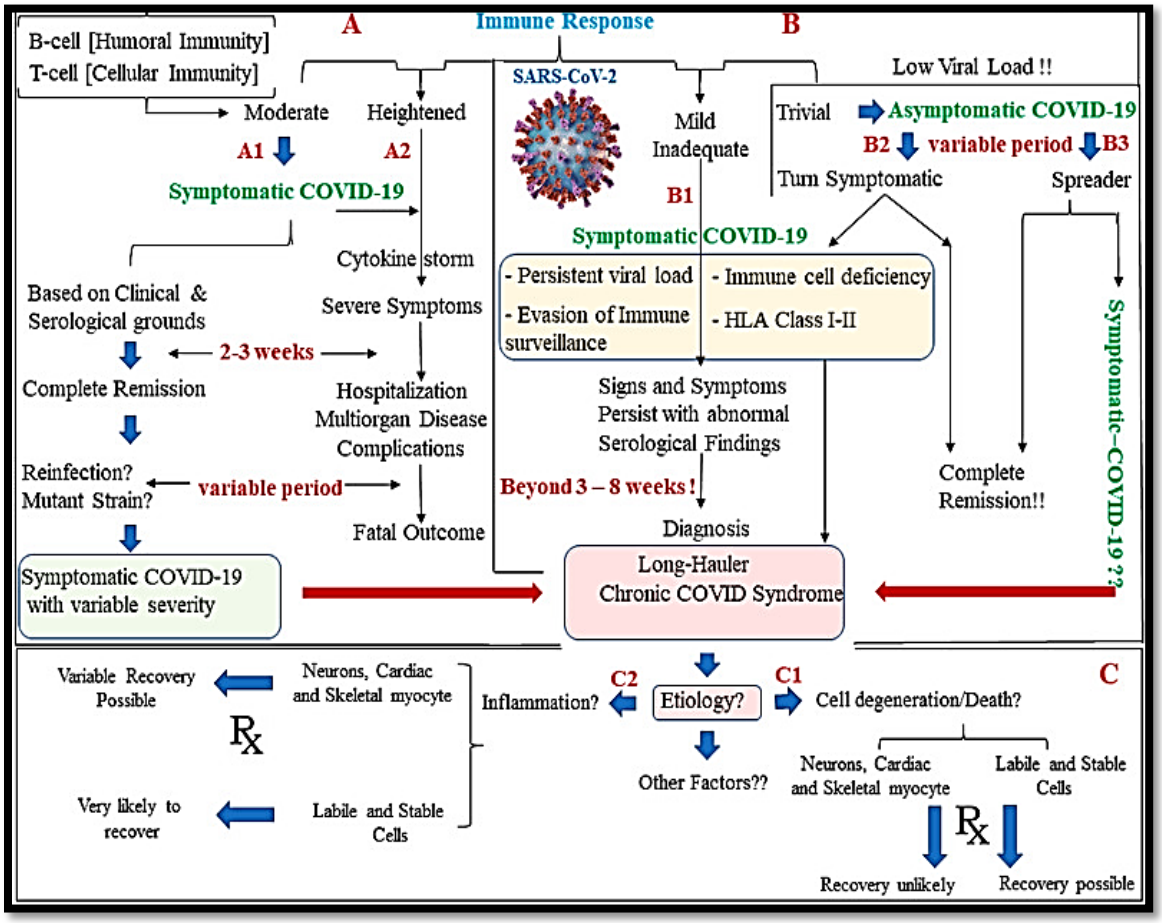

Figure 2: Phisiopathogenic Pathways towards long Covid (from: Abdul Mannan Baig: Deleterious Outcomes in Long-Hauler COVID-19)

Other factors like ACE2 density in tissues, vascular permeability, coagulation, and cytokine activation cascade appear to determine a progression to a prolonged, less lethal but more incapacitating clinical picture [5].

This could lead to a significant surge of people battling lasting illnesses and disabilities. Symptoms lasting several weeks and impairing a person's usual function should not be called mild, neither should the subject be considered up to returning to usual activities so quickly. Restoring such a subject to his ordinary labour tasks is a potential risk for both himself and his fellow co-workers.

Defining and measuring recovery from COVID-19 should be more sophisticated than checking for hospital discharge, or testing negative for active infection or positive for antibodies. Once recovery is defined, we can differentiate COVID that quickly goes away from the prolonged form [6].

The terms "COVID long haulers," "long COVID," and "Post COVID Syndrome," have all been used interchangeably in recent months to describe individuals who have been infected with the SARS-CoV-2 and continue to experience symptoms after "recovery."

However, these terms may be misleading, as they represent three different patient subsets with prolonged symptoms, usually defined as greater than one month after COVID-19 infection.

These subsets include:

a. Critically-ill patients, almost all who have been admitted to intensive care, who, are expected to have a lengthy recovery period (often months) and may have permanent organ damage, particularly in the lung.
b. An undetermined number of patients, following mild or severe infection, who have organ damage/dysfunction, such as myocarditis or an encephalopathy. The long-range consequences are unclear.
c. Many patients, in some series estimated up to 10%, have prolonged, multisystem symptoms with no evidence of organ damage or dysfunction.

These patients most often have severe exhaustion, headaches, myalgias, and mood and cognitive disturbances with normal physical and laboratory findings. This is the subset experiencing symptoms most similar to post-viral fatigue syndrome (PVFS), chronic fatigue syndrome (CFS) – also termed benign myalgic encephalomyelitis (BME) in the UK, fibromyalgia and other related, poorly understood disorders associated with chronic fatigue and pain. In these conditions, there has been no strong evidence for organ damage or persistent and significant immune/inflammatory abnormalities.

The confusion and controversy playing out online and among support groups for the third subset of patients mirrors the misunderstandings of CFS over the past 40 years in both the United States and the United Kingdom.

The symptoms are similar to those reported in PVFS or CFS. However, dyspnea and loss of taste and smell appear to be much more common in Post COVID Syndrome patients.
While PVFS is not new to the medical community, there is no clear path to treatment. More important, there is still not enough knowledge about the exact causes or repercussions of post-viral fatigue in recovering COVID-19 patients.

Ongoing symptoms reported by those recovering from COVID-19 infection should be taken seriously and addressed accordingly. Beyond doubt, there are a considerable number of individuals who have a post-viral syndrome that really, in many respects, can incapacitate them for weeks and weeks following so-called recovery and clearing of the virus, highly suggestive of myalgic encephalomyelitis/chronic fatigue syndrome [7].

A new study published in the Annals of the American Thoracic Society, experts concede they don't know why some people who develop COVID-19 experience persistent symptoms after the virus is no longer detectable in their body. When healthcare providers order chest X-rays, CT scans, or other tests to look for potential causes of long-haul symptoms, the results often come back negative.

Over 60 percent of the study participants said they had not yet returned to full health an average of 75 days after their diagnosis. However, only 4 percent showed signs of lung scarring on CT scans [8]. Those who emerged from life support at ICU, or beat severe cases of COVID-19 in the hospital, are being home- visited and/or receive virtual house calls tend to post-hospital diagnoses, medical checks as well as physical and occupational therapy for patients dealing with symptoms impacting cognitive function as well as anxiety or depression [9].

Outpatient clinics that are dedicated to following up on lasting disabilities in the large number of patients who previously had COVID-19 are opening in many hospitals, especially in areas where large SARS-CoV-2 outbreaks have occurred. However, this initiative implies a further burden on the health-care system in terms of human and economic resources, in addition to conventional health-care services. Unfortunately, these clinics are largely unaffordable in most low-income or middle-income countries that have also been severely affected by the COVID-19 pandemic. This is consistent with the syndemic nature of the COVID-19 pandemic, and has implications for the long-term follow-up of COVID-19 sequelae, which in most instances should be interpreted against a background of an array of non-communicable diseases and social and income inequalities that exacerbate the adverse effects of each of these diseases in many communities [10].

On the other hand, trying to make these patients recover by just prescribing "vitamins, deep breath and plenty of rest" brings us back to the XIX century methods [11].

J. George characterized a group consisting of mostly outpatients: 90% of their cohort experienced only a mild COVID-19 illness, yet one-third continue to have lingering effects. Many of those individuals were young and have no pre-existing medical conditions,

indicating that even relatively healthy individuals may face long-term impacts from their illness.

Early in 2021, Wuhan studies of non-hospitalized patients have shown that anywhere from 35% to 50% of non-hospitalized patients had symptoms 2 to 4 months later.
Fatigue, breathing issues, and cardiac concerns like chest pain are common findings, as are neurologic symptoms. Of patients at the Center for Post-COVID Care at Mount Sinai with neurology referrals, about 65% come in with cognitive complaints or brain fog. Brain fog means different things to different people, but usually it's some combination of short-term memory issues, attention issues, and word-finding difficulty.

The University of Washington study followed 177 people with laboratory-confirmed SARS-CoV-2 infection who completed questionnaires from August to November 2020, 3 to 9 months after their COVID-19 onset (median 169 days).

Mean age was 48 and 57% were women. Hypertension was the most common comorbidity (13%).

Across the cohort, 6.2% of participants were asymptomatic, 84.7% were outpatients with mild illness, and 9.0% were hospitalized with moderate or severe disease. Patients completed followup questionnaires a median of 169 days after COVID-19 onset.

Overall, 32.7% of outpatients and 31.3% of inpatients reported at least one persistent symptom, most commonly fatigue (13.6%) and loss of sense of smell or taste (13.6%). In addition, 13.0% reported other symptoms, including brain fog (2.3%).

Among outpatients and hospitalized patients, 30.7% reported worse health-related quality of life compared with baseline; this figure was 12.5% for patients who never had overt COVID symptoms.

About 8% of all participants said at least one activity of daily living suffered long-term consequences, most commonly household chores.

Study limitations include small sample size, single study location, and potential bias from self-reported symptoms [12].

a. Putting all the above-mentioned facts and theories in perspective, some obvious certainties arise: The real number of long-COVID patients is not clear.
b. There is no close relation between the severity of the illness and the long COVID.
c. The origin of this syndrome may be related to the permanence of the virus in tissues either tan blood.
d. There is no current treatment for reducing long COVID.

Current Knowledge about Ivermectin (IVM)

Ivermectin (IVM) is an antiparasitic (endodecticide), with nematicidal and ectoparasiticidal properties. It is a macrocyclic lactone derived from avermectins, a group of highly active endodecticidal antiparasitic agents isolated by fermentation of the soil microorganism Streptomyces avermitilis.

It was discovered in 1960 in Japan by Satoshi Omura.
In 1981, William C. Cambell began the studies that allowed its veterinary use.

Both received the Nobel Prize in Physiology and Medicine in 2015.

In 1985, the French proved its usefulness in onchocerciasis in Africa. It was approved in 1997 by the FDA for treatments of: strongylidiasis and crusted scabies, in patients with AIDS.

In Human Medicine, it has been used in children from 5 years of age onwards, for the management of ecto and enteroparasitosis.

Orally, in humans, it does not cross the blood-brain barrier. It is contraindicated in pregnancy and lactation.

Recently, its viricidal effects on flaviviruses, dengue, Zica, Chikungunya, among others, have been compiled.

Ivermectin is an inhibitor of the causative virus (SARS-CoV-2).

This activity is due to the dependence of many RNA viruses on IMPα / β1 during infection. Recently, another mechanism of action has been proposed, assuming its role as an ionophore agent.

Ionophores have many oxygen atoms internally, and are essential for binding cations and transporting them through phospholipid bilayers (cell membranes; phospholipid capsid of the virus). As a consequence, it determines an ionic imbalance between the external and internal environment, with the consequent osmotic

These results, as a whole, demonstrated that ivermectin possesses antiviral action against SARS-CoV-2 in vitro, with a single dose capable of controlling viral replication in 24-48 hours, and the possibility of repeating it periodically.

Research has been added on other forms of action of IVM in the face of COVID disease, not directly on the causative agent, but on the pathophysiological mechanisms through which its deleterious activity develops (hyperinflammation and hypercoagulability). All of the above is summarized in Figure 3.

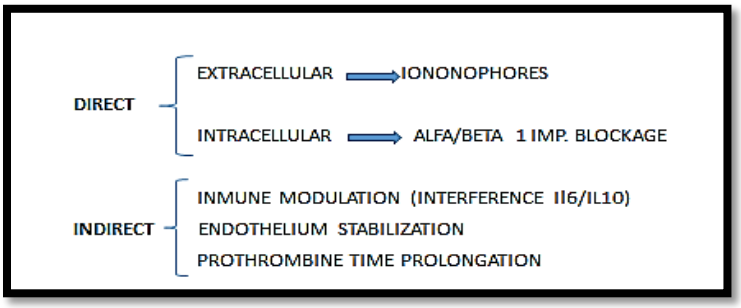

Figure 3: IVM Mechanisms of Action (from Hirsch Roberto R, Carvallo Hector E.: COVID 19 and Ivermectin Prevention and Treatment Update)

The effectiveness of IVM on pre and intra COVID have already been proved in all our essays [13, 14, 15]. Though still neglected by the W.H.O., from the statistical point of view, IVM has already proved its effectiveness against COVID 19 infection in all stages of the disease. A meta-analysis also proved that an early treatment is far more effective than a delayed one. The amount of data supporting the need to incorporate IVM amid the options of treatment against COVID 19 is countless, and –little by Little- more Countries and regions around the World are including it in their schemes (Fig-4).

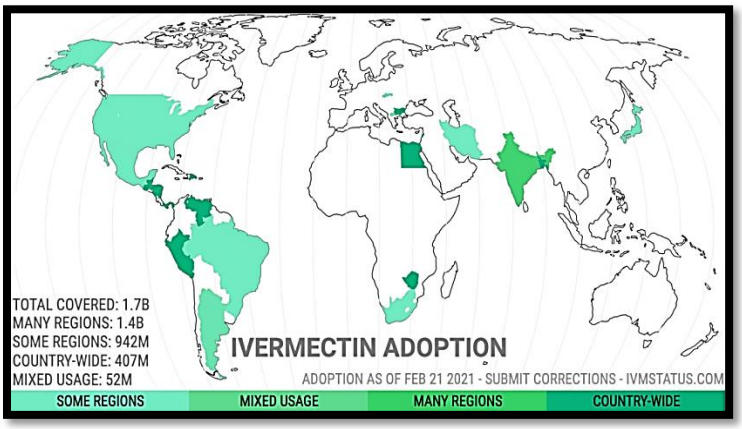

Figure 4: IVM use against COVID 19 in the World, February 2021 (from IVM Meta)

Our figures account for a 95.5 % reduction in the need of hospitalization, and a 95,6 % reduction in death rate, when IVM treatment was applied at the early stages of the disease, in consonance with existing data. According to ours and other international data, roughly 11,000 lives worldwide could have been saved daily, by simply adding IVM as the treatment offered to COVID 19 patients [16].

Statistically speaking, up to 10% of mild cases, and up to 40% of moderate cases, require hospitalization. For this reason, avoiding this instance is crucial, not only to decompress health systems, but also to drastically lower their costs, which will result in the possibility of sustaining these health policies indefinitely. We also carried out a cost-survey to support what has been stated so far: Hospitalization Costs, in Europe: Daily hospitalization (average): 2,932 euros this figure doubles, if the ICU admission is considered. IVM presentation of 20 ml (for two weeks): 5 euros [17].

Material and Method:

We conducted a follow-up of 856 patients discharged from hospitalization at a Public Hospital in Buenos Aires (Argentina), starting on July 2020 and still continuing. All the patients included had not received IVM either before or during hospitalization. Instead, they had been treated with corticosteroids, antibiotics, blood-thinners, convalescent's plasma, etc.

The follow-up lasted as long as the patients were found to be free from symptoms and/or sequelae. Thus, some of them remain in weekly observation. For that reason, we divide this cohort into two groups:

a- Those patients who could finally be discharged even from ambulatory control (799).

b- Those patients who still have to be controlled, or referred to different subspecialties (57).

Beginning by this Second Group, the long-lasting symptoms have been:

1) Stress and/or paranoid disorders (39 from a total of 57).
2) Memory loss (8 from a total of 57).
3) Dysgeusia, defined as alterated sense of taste, mainly mixing salad and sweet sensations (6 from a total of 57).
4) Fatigue (4 from a total of 57).

All these 57 patients had been at ICU for over 10 days.

Now turning to the FIRST GROUP (799 subjects) it was composed of 411 male (51.44 %) and 388 female individuals (48.56 %). (Figure 5)
The average age was 52,3 years, ranging from 21 to 82 years. (Figure 6)

a. The prevailing symptoms were:
b. Coughing (not related to previous history of COLD)
c. Brain fog (not related to previous circulatory diseases and/or dementia)
d. Headaches (not related to high blood pressure or other common causes)
e. Persistent fatigue (not related to anemia and/or other causes)
f. Loss of taste and smell
g. Shortness of breath (same as "a" group)
h. Body/joint aches (not related to previous history of arthritis) (Figure 7)

Some patients had two or more simultaneous symptoms.
All of the above-mentioned patients received IVM, ranging from 12 up to 18 mg per os, on a weekly basis, until the symptoms disappeared, but no longer than 8 weeks (what happened first).
Some of them also received polivitaminic compounds (the exact number lacking, because it was an auto-prescription, but not exceeding from 12 patients).
The average time needed to get rid of those disturbing symptoms were 36 days, ranging from 21 to 69 days. (Figure 8 and 9)

The side effects reported by the IVM-treated patients were:
1) Diarrheic episodes in 5 patients
2) Abdominal pain in 2 patients

No cases of allergy were reported; neither were pregnant or lactating women among those treated, thus IVm contraindications could be disregarded.

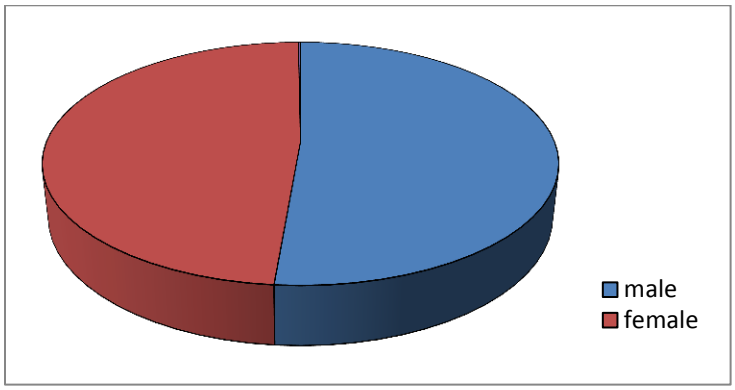

Figure 5: Sex-Related Distribution

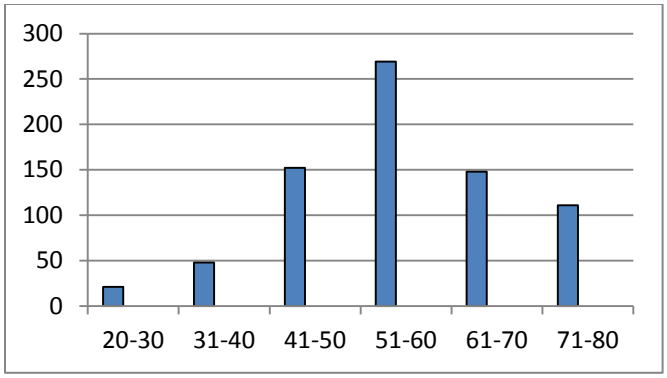

Figure 6: Age-Related Distribution

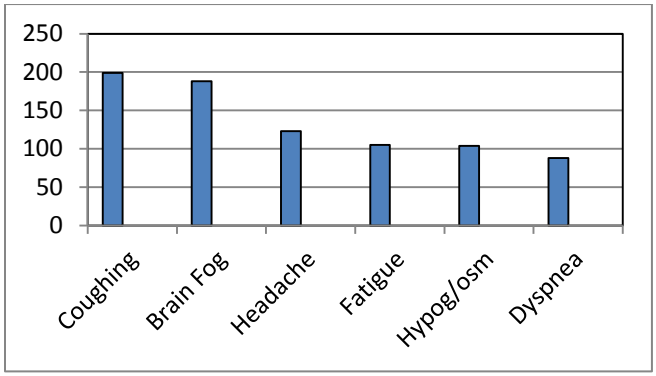

Figure 7: Symptoms Referred by Post-COVID Patients

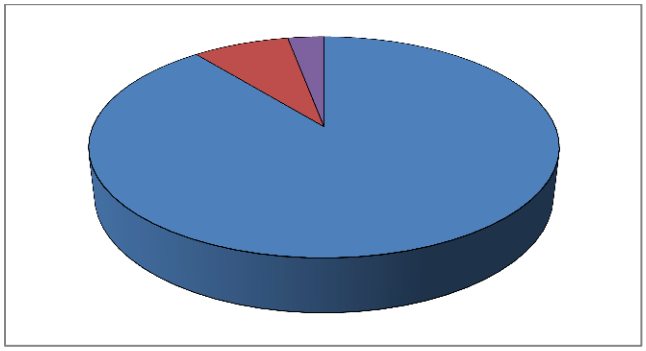

Figure 8: Days to make symptoms disappear in IVM-Treated and Untreated Patients (in red and violet: patients on IVM; in blue: collected data from different surveys of untreated patients)

Conclusion

Long COVID includes a constellation of symptoms, that may be caused by the unobtrusive persistence of virus in different tissues, and the subsequent persistence of inflammatory and coagulation disorders. Since IVM has already proved to impair virus capacity to invade cells, and also to have immune and clotting modulatory effects, there is a reasonable chance to diminish, shorten and even completely correct almost all the symptoms by using IVM in the post COVID.

Consent for Publication: Written informed consent was obtained from the patient for the publication.

Conflicts of Interest: The authors declare no conflict of interest.

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COVID-19 and Repurposed Drugs: How Much is A Human Life?.

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Research Article

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COVID-19 and Repurposed Drugs How Much is A Human Life?.

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ABSTRACT

The current pandemic due to COVID 19 (SARS COV2) has revealed a disturbing reality most of the world's health systems, and the organizations that govern health policies at a global level, have not been able to meet the expectations that were set on them. On the one hand, W.H.O has shown hesitations, orders, counter-orders, delays and errors that have made it lose credibility. The terrible images of corpses piled up in the corridors of healthcare centers (from underdeveloped countries to the most powerful ones in the planet); will remain forever in our memory. The enormous financial effort made was not always well targeted, and rarely benefited the patients. The cost / benefit ratio was inverted, contributing fortunes in the final monitoring of severe cases, when logic indicates that emphasis should be placed on not reaching severe stages, and must be solved earlier. In this article, we establish a comparison between what is done and what - in our opinion - should be done.

Keywords

Repurposed drugs, Ivermectin Azithromycin, Vitamin D, Bromhexine, COVID 19.

Introduction

The answer to the question in the subtitle, about the value of a human life, is simple: a human life, all-human lives, any human life, are priceless. However, if we refer to the cost of healthcare for that human life, there are values that must always be taken into account, not to lower costs, but to optimize benefits. The sustainability of health policies over time is what differentiates utopia from reality. The current pandemic has confirmed a truism: the more advanced a clinical stage, the greater the resources that must be applied (Figure 1).

We are seeing that - during the current pandemic - health services (primary care, general hospitalization and admission to the ICU) are overcrowded, personnel in charge are at the limit of their strength, and the population does not find a response in time. The division of those infected into mild, moderate, severe and critical forms is not tight, since even the most serious cases began as mild, because a percentage of them will inevitably evolve into severe and even lethal forms (Figure 2).

In addition to the lethality of this virus, there are those due to exacerbation of pre-existing comorbidities, and the appearance of new entities, associated with the methods used in its attempt to mitigate it (Figures 3 and 4).

Also, the attention of all pathologies other than COVID are being put off, in an unprecedented neglectfulness (Figure 5).

A very important point is the level of contagion between Health Care Agents. This is far from being an abundant resource; rather, it is disturbingly rare (Figure 6). The higher the level of hospitalization of COVID cases, the greater the risk of contagion from Health Agents, which, in turn, will negatively affect the quality of care of those hospitalized (whatever the cause of their admission). Nor is it a minor or isolated detail the stigmatization to which Health Agents working in the first line of defense against the pandemic have been subjected, who are rewarded in public and rejected or avoided in private (Figure 7).

In another aspect, quarantines have yielded most contradictory results, but -in general terms- it has been shown that their prolonged duration has caused more damage (to the physical and mental health of populations and to the economy of the population

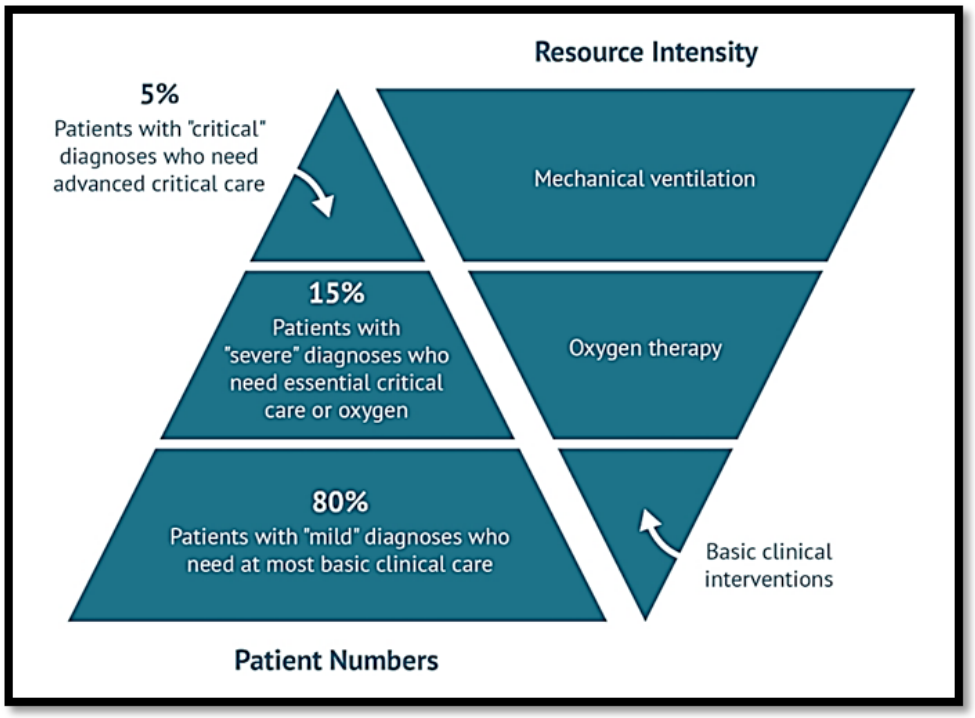

Figure 1: Relation between severity of cases and need of health measures [1].

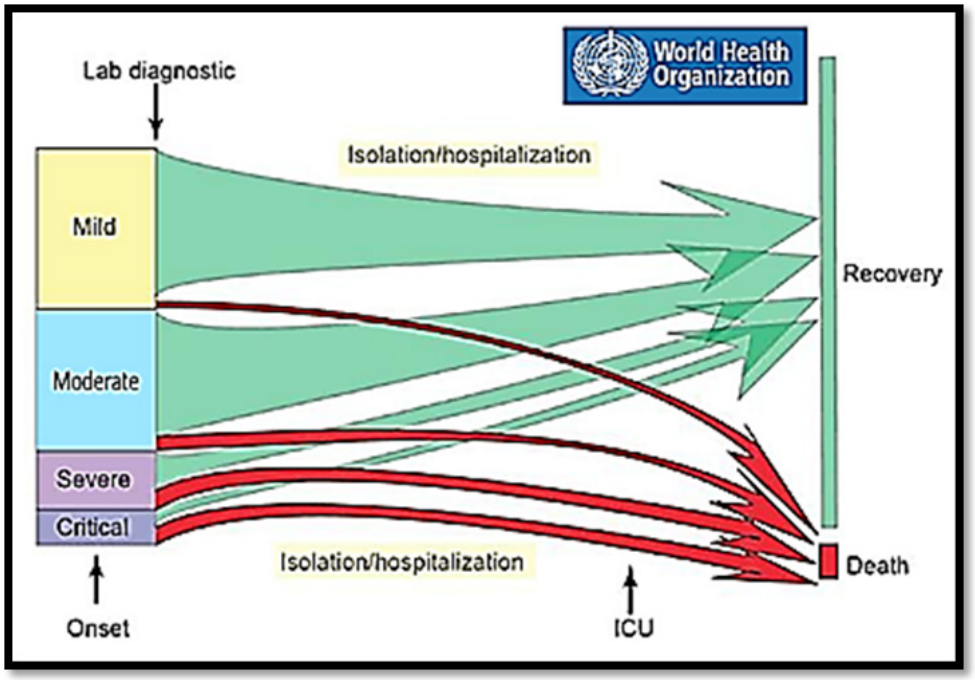

Figure 2: Evolution of confirmed cases [2].

and Countries), than the eventual and hypothetical benefit that was initially expected from them (Figure 8). Last but not least, restrictions on free movement have caused not only a limitation on human rights, but also a fatal blow to local economies, mainly those that depend on tourism (Figure 9). Therefore, we want to warn the World Health Authorities that these inequities cannot and should not continue, and that there is a way to avoid them.

Material and Method

THE REPURPOSING OF DRUGS we propose pharmacological alternatives that can be applied with immediate results (waiting for the vaccines to demonstrate - after the necessary time - their respective efficacy and safety). **A. I.D.E.A. PROTOCOL** The IDEA protocol, consisting of the sequenced use of Ivermectin (IVM), Aspirin (ASA), Dexamethasone (DM) and Enoxaparin

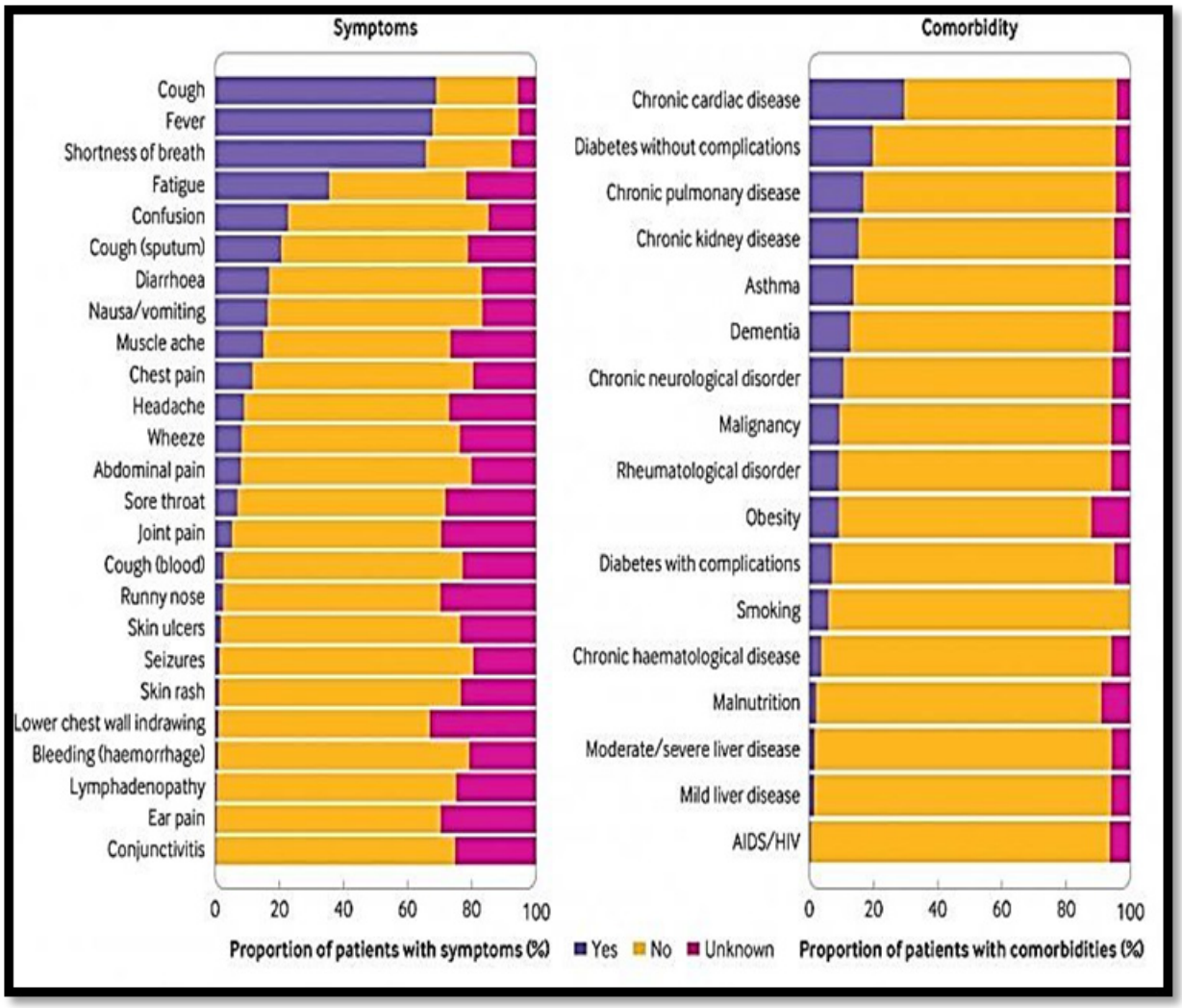

Figure 3: Comorbidities, which worsen prognosis [3].

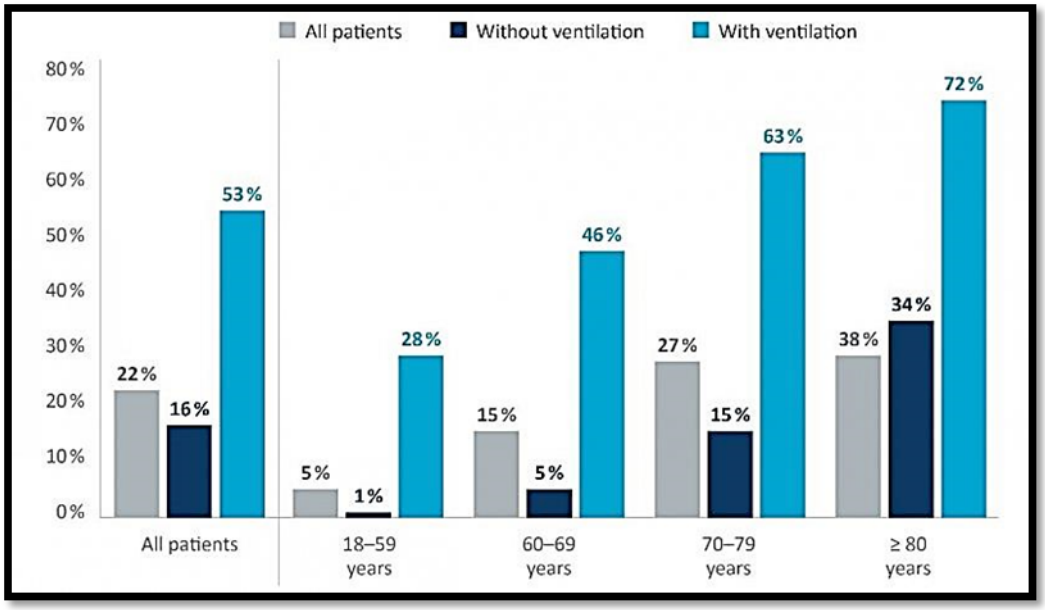

Figure 4: Ventilator-related deaths [4].

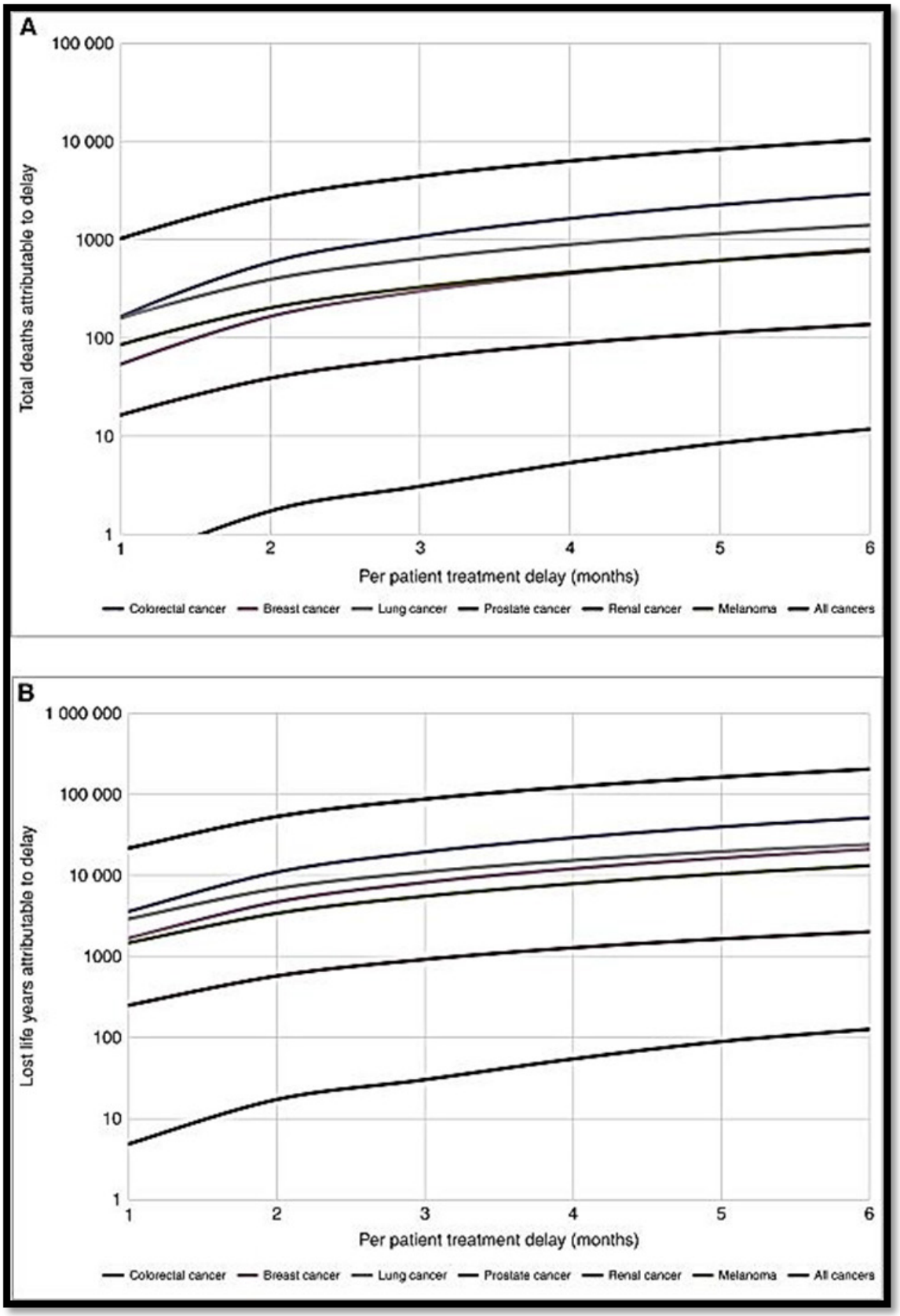

Figure 5: Delays in the assistance of breast cancer cases.

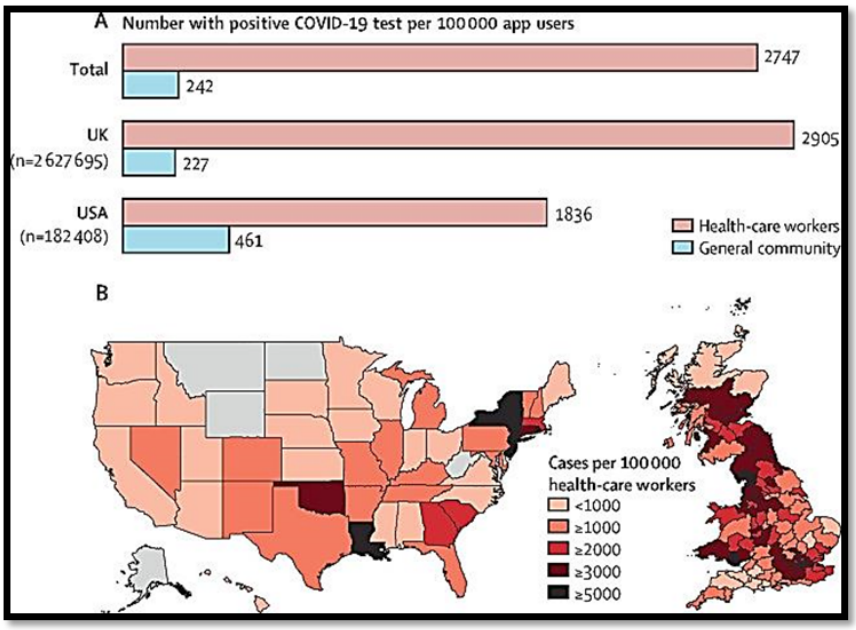

Figure 6: Relation between contagion of patients and health care workers in two different scenarios [5].

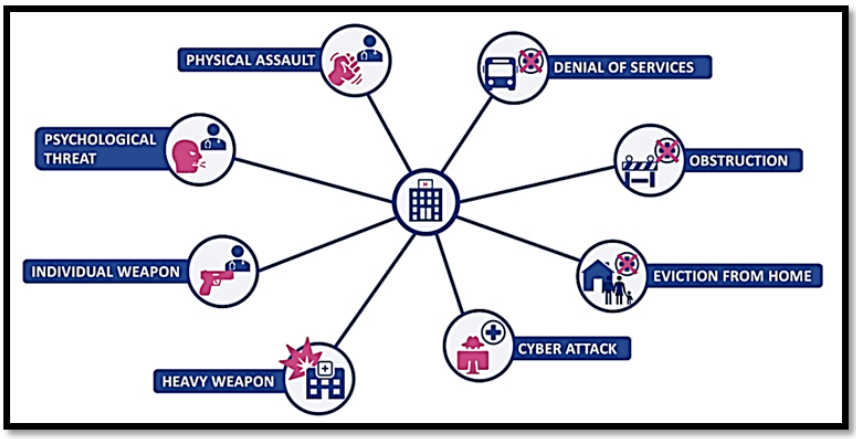

Figure 7: Attacks suffered by health care workers during the pandemic [6].

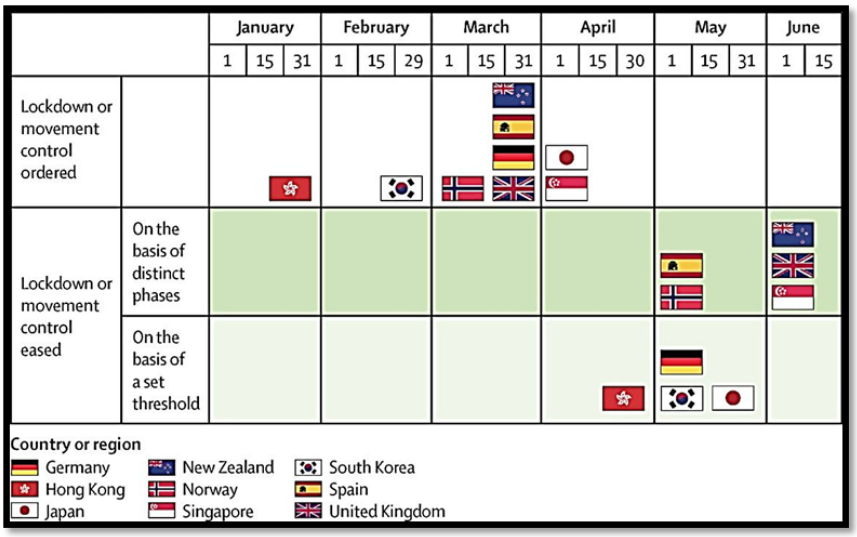

Figure 8: Lockdowns in different countries [7].

Figure 9: Travel restrictions in different scenarios (multiple sources).

DISEASE SEVERITY	IVERMECTIN	CORTICOID		VENTILATION
Confirmed Mild case (and close contacts)	24 mg orally at a dose of 300 ug / kg in a single dose, to be repeated a week later	No	Aspirin 250 mg orally, on a daily basis	No
Moderate clinical stage	36 mg orally at a dose of 450 ug / kg in a single dose, to be repeated a week later	Dexamethasone 4 mg (parenteral)	idem	Low Flow Oxygen or Oxygen Concentrator
Severe case with bilateral pneumonia	48 mg via gastric cannulae, at a dose of 600 ug / kg to be repeated a week later	idem	Enoxaparin 100 UI/kg (1 mg/kg)	Mechanical Ventilation

Figure 10: I.D.E.A. PROTOCOL [8,9].

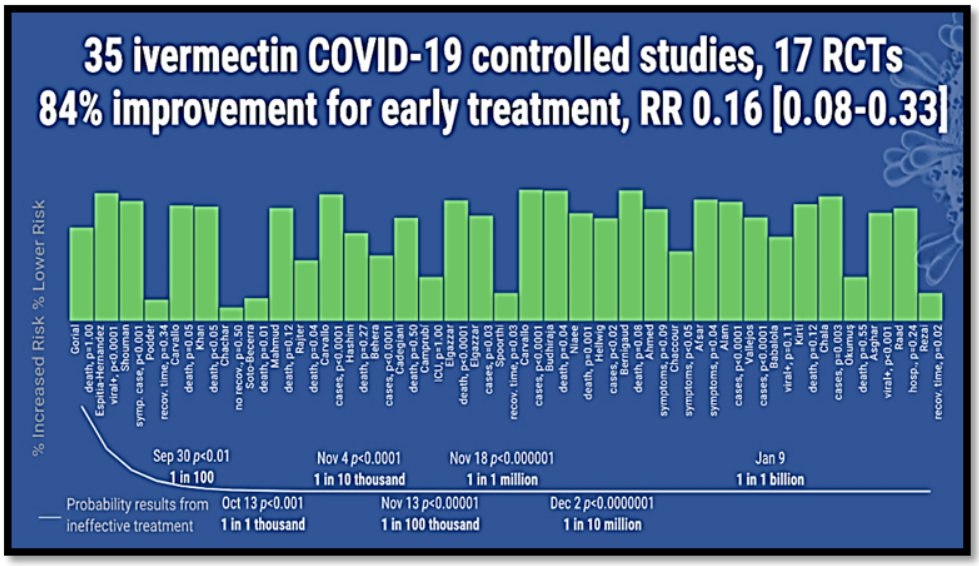

Figure 11: Effectiveness of IVM on COVID 19 [10].

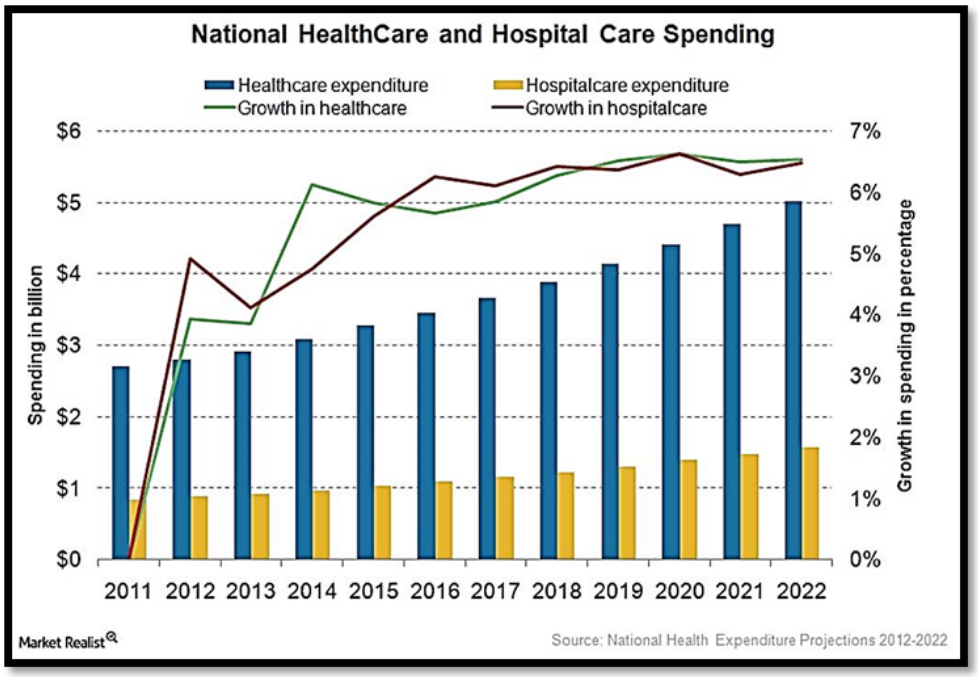

Figure 12: Permanent increase in hospital costs [11].

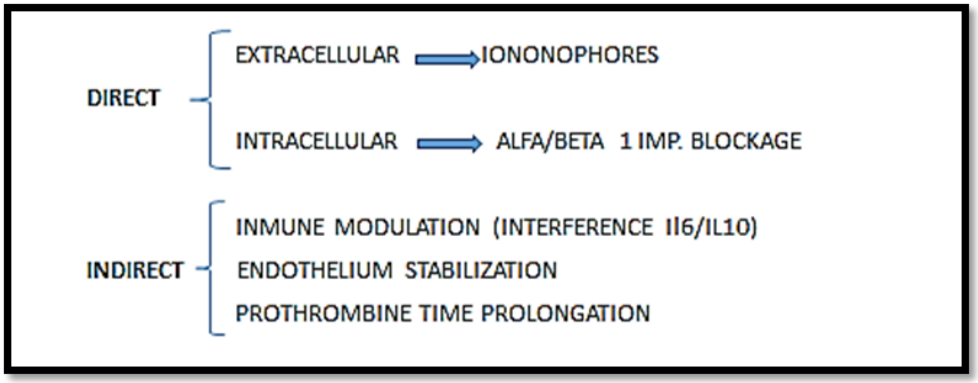

Figure 13: IVM Mechanisms of action on COVID 19 [8,9]

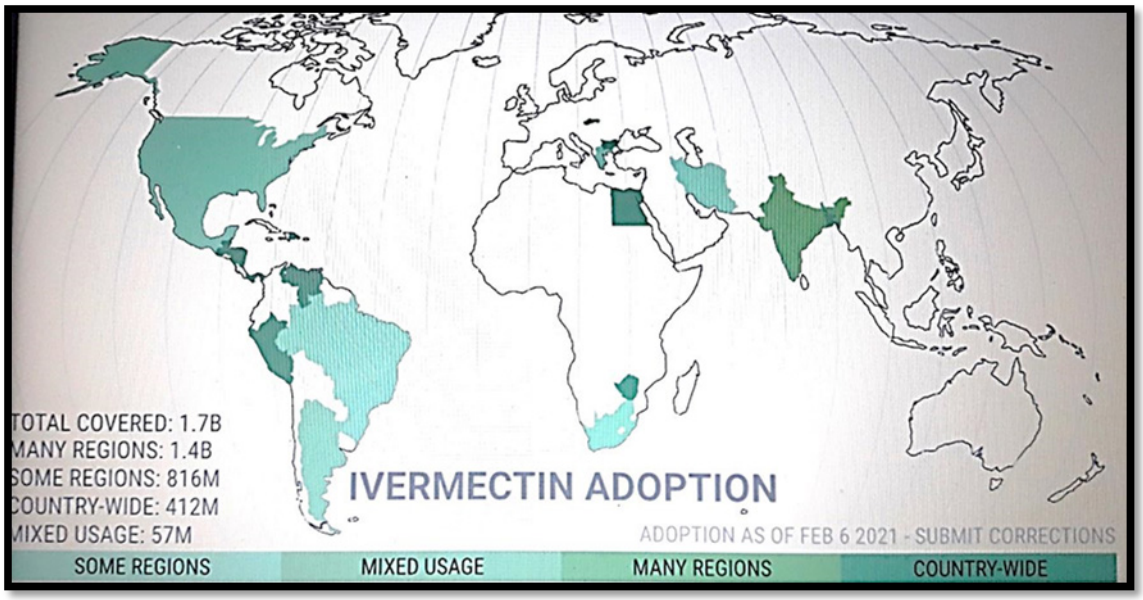

Figure 14: Regions, which adopted IVM as treatment against COVID 19 at february 2021.

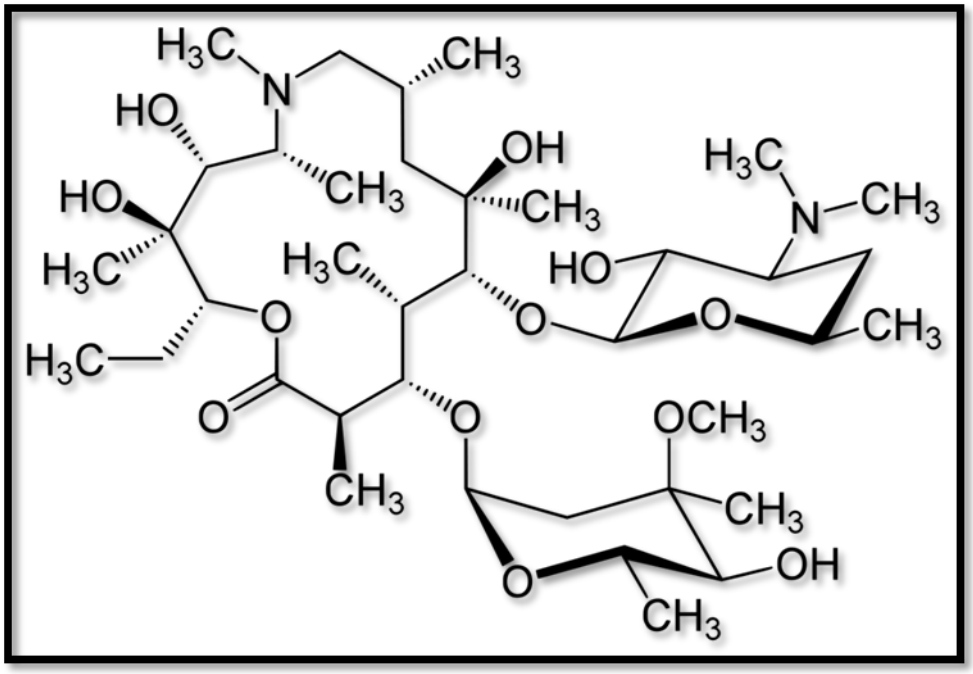

Figure 15: Azithromycin chemical structure.

(ENP), implies a clear advance in the management of COVID patients, particularly in mild patients with recent diagnosis, but also in all its stages (Figure 10).

The present protocol, as all medical interventions, has proved to be more effective if applied at early stages of disease (Figure 11).

There, the rapid improvement and resolution of the COVID 19 pictures has allowed the early discharge of affected patients, while avoiding the need for hospitalizations, which has a crucial impact in the following areas: bio-psycho-improvement of patients and their affective environments, reduction of the potential risk of contagion among participating Health Personnel, cutting the chain of transmission / contagion, and lower health costs. The latter, which continues to grow, is summarized in figure 12.

In mild patients, and even in early moderate ones, only IVM, ASA and DM will be used, and this will mean –in most cases- that there will be no need to hospitalize them. Statistically speaking, up to 10% of mild cases, and up to 40% of moderate cases, require hospitalization. For this reason, avoiding this instance is crucial, not only to decompress health systems, but also to drastically

lower their costs, which will result in the possibility of sustaining these health policies indefinitely (Figure 14). We carried out a cost survey to support what has been stated so far: **Hospitalization Costs, in Europe**: Daily hospitalization (average): 2,932 euros this figure doubles, if the ICU admission is considered. **IDEA Protocol costs**: IVM container for 20 ml (for two weeks): 5 euros AAS, 200 mg / day (for two weeks): 5 euros Dexamethasone (1 shot / day, for 10 days): 45 euros ENP (2 shots / day, for 10 days: 1800 euros. It should be reiterated that mild cases will only require IVM and ASA, and DM will be added to moderate cases, all of which can be treated on an outpatient basis, with which the daily costs of outpatient management of such patients will be approximately 20 euros, on average.

B. Azithromycin Recent publications by French and Italian researchers have raised interest in azithromycin as a treatment for SARS-CoV-2 infection. In one of these articles, the efficacy of combined hydroxychloroquine and azithromycin therapy in patients with COVID-19 is evaluated. In addition, hopes of successfully finding an effective causal therapy against COVID-19 rose after the comment of the co-author of the article, Professor Didier Raoult of the Mediterranean Infection University Hospital Institute, who announced a "significant reduction in the number of positive cases" before the official publication of the study results. It included 42 patients with laboratory-confirmed SARS-CoV-2 infection (RT-PCR) with different clinical symptoms (asymptomatic infection, rhino pharyngitis symptoms, pneumonia), mainly adults in need

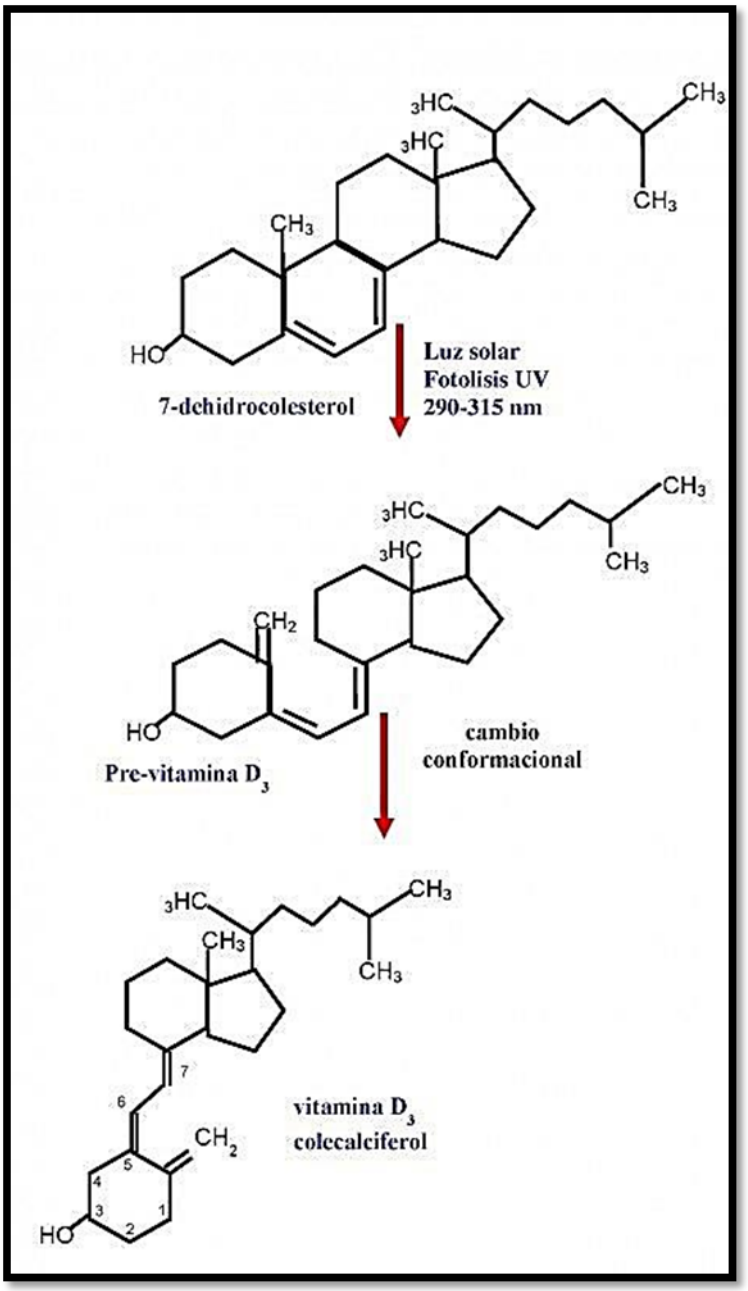

Figure 16: Vitamin d progressive reactions.

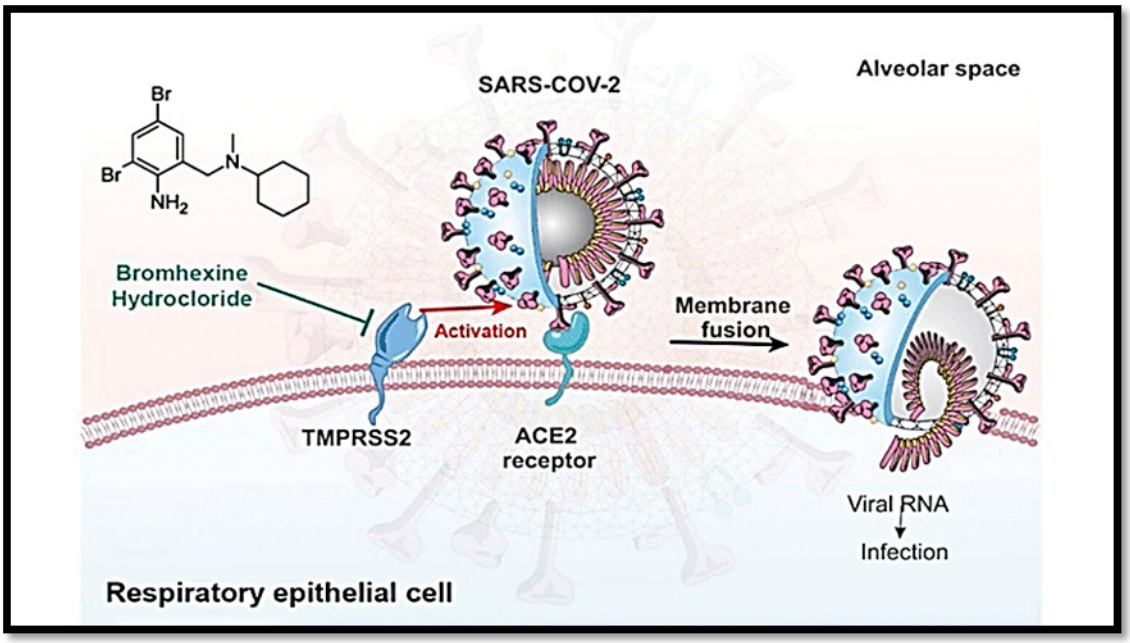

Figure 17: Bromehine interference with virus/tmprss2 membrane receptors.

of treatment or hospital isolation. The authors of the current guidelines of the Polish Association of Epidemiologists and Physicians of Infectious Diseases have also commented on reports on azithromycin, stating that in COVID-19 patients, administration of azithromycin may be considered in justified situations with concomitant bacterial infections and following the general protocols of antibiotic therapy. In this framework, considering the results, and facing the reality that is presented to us in this year 2021, it is possible to recommend the treatment of patients diagnosed positive for coronavirus and before the first symptoms of disease with oral administration of azithromycin, to mitigate the damage induced by said condition, giving them a 500 milligram tablet from the first day until the seventh day of treatment. Always recording the clinical evolution of patients for statistical purposes of clinical research. It should be remembered that this antibiotic is available as a generic drug in the world pharmaceutical market, at an affordable price (Figure 15).

C. Vitamin D (VD): VD has antiviral, anti-inflammatory and lung protection properties, demonstrating that it could play a role in enhancing the immune response.

Hypovitaminosis D is associated with a higher prevalence of diseases that increase the risk for COVID-19: diabetes, hypertension, obesity, cardiovascular diseases, and has a high incidence in the risk group of older adults. The endocrine system of vitamin D can have a variety of actions on the cells and tissues involved in the progression of COVID-19.

The administration of calciferol or 25-hydroxyvitamin D to hospitalized patients with COVID-19 significantly reduced their need for admission to United Intensive Care.

Calciferol seems to be able to reduce the severity of the disease, again to a value so low that it would be sustainable indefinitely in time (Figure 16).

An open-label randomized controlled trial (RCT) in institutionalized but asymptomatic adults older than 60 years is evaluating the effect of 2000 IU (50 µg) of vitamin D plus 30 mg of zinc gluconate per day for two months versus usual care. The primary outcome measure is mortality; the incidence of COVID-19 infection is a secondary outcome.

A trial is testing whether a single oral dose of 25,000 IU (625 µg) of vitamin D (form not specified) improves mortality in SARS-CoV-2 infected patients without severe symptoms, compared to usual care.

Another RCT compared single doses of vitamin D3, 50,000 IU to 200,000 IU (1250 vs 5000 µg) in people with COVID-19 pneumonia who are older than 75 years or older than 70 with low oxygen saturations; the primary outcome measure is mortality at 14 days.

D. Bromhexine (BMH): Bromhexine is a mucolytic drug used in the treatment of respiratory disorders associated with viscid or excessive mucus. It has also proved to be a potent inhibitor of COVID 19 binding to TMPRSS2 membrane receptors, which is crucial for further virus interaction with ACE2 receptors, in order to invade host cells (Figure 17).

Its oral, early administration reduces the ICU transfer, intubation, and the mortality rate in patients with COVID-19. This affordable medication can easily be administered everywhere with a huge positive impact(s) on public health and the world economy.

Discussion / Conclusions

The early application of repurposed drugs, whose primary and secondary effects are widely known, whose efficacy in the current pandemic is being accepted worldwide, and whose costs make them accessible to any health policy over time, forces us to rethink the strategy applied so far, where test drugs have been prioritized, almost invariably with disappointing results.

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SARS COV2, Emerging, Reemerging and Potentially Emerging Diseases in Argentina.

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SARS COV2, Emerging, Reemerging and Potentially Emerging Diseases in Argentina

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Abstract

The SARS COV2 (COVID 19) pandemic has become a tremendous challenge to mankind. In our Country, this pandemic gets associated to other emerging, re-emerging and potentially emerging diseases, which means an augmented risk, as it requires from Internists, Pediatricians and Infectologists to be well acquainted with all those illnesses, their similarities, differences and differential diagnosis and treatment. In the brief list below, we summarize these diseases.

INTRODUCTION

Brief History of SARS CoV2 (Covid 19)

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

PCR (Polymerase Chain Reaction) studies found a coronavirus, which was> 85% similar to a SARS-like CoV of bats (bat-SL-CoVZC45).

This species was initially named nCOV19 and later renamed SARS-CoV-2 due to its structural similarity with the homonymous species.

Its origin is still uncertain, and is the subject of many conjectures.

The early association identified between SARS-CoV with SARS-CoV-2 was supported by the analyzes made later to the protein S (spike) that characterizes these two viruses, where an important similarity in these transmembrane structures was made clear, making them practically superimposable with each other.

What distinguishes them is a furin-binding domain in the SARS-CoV-2 protein S, which expands the tropism and increases virus transmission, compared to the 2003 SARS-CoV.

Studies on SARS-CoV proteins have revealed a potential role for IMPα / β1 during infection in the signal-dependent cytoplasmic nucleus closure of the SARS-CoV nucleocapsid protein, which can affect host cell division.

The predilection and competitiveness of the virus over the ACE2 and TMPRSS2 cell receptors has already been demonstrated, and its subsequent need for the importin described above is also confirmed [1].

These functional receptors are found in multiple tissues, including lung alveolar epithelium, arterial and venous endothelium, smooth muscle, renal tubular epithelium, oropharyngeal mucosa, and small intestine epithelium, largely explaining the clinical presentation of COVID-19 patients.

This also explains the higher incidence of severe symptoms in patients with over-expression of TMPRSS2 receptors (androchronogenetic alopecia, prostatic hyperplasia, etc.), and the predilection of the virus for establishing its first replication site in salivary glands (these contain more receptors TMPRSS2 than ACE2) [2].

However, it is unavoidable to bear in mind that the clinical forms of the infection are due to two processes triggered by the virus: hyperinflammation and hypercoagulability.

Both originate from endothelitis caused by COVID 19, which results in cytokine storm (in relation to hyperinflammation), and alteration of Virchow's triad (in relation to hypercoagulability) [3].

To seek an effective treatment that is exclusively oriented to antivirals is to ignore the pathophysiology of SARS

COV2, and to appeal to the utopian "silver bullet", instead of reorienting the therapy with a synergistic and coadjuvant criteria.

HOW MANY COVID CASES ARE THERE REALLY IN ARGENTINA?

In order to answer that question, we must start from official data.

As of today (03/10/2021), the total number of confirmed cases throughout the country amounts to 2,250,000 and fatalities total 52,000.

Based on data from The Lancet journal, it is deduced that less than 50% of those infected will know about their condition, as they are asymptomatic or oligosymptomatic [4].

Likewise, the Argentine Authorities have publicly acknowledged that it is not being tested as much as it should.

It follows that-in Argentina-only 1/3 of the people consult (and much less, in the samples taken at random); they will be tested and-therefore-confirmed.

From both facts, it is concluded that-following the current work methodology-only less than 30% of the cases will be confirmed.

Therefore, if there are 1,450,000 confirmed cases, the reality must be a number close to 4,000,000 infected people.

The serious things about these figures is that the asymptomatic, presymptomatic, oligosymptomatic, does not confirmed and/or awaiting confirmation, are as contagious as the rest. Similarly, in Spain it was observed that the number of deaths from COVID had a major underreporting, according to a reliable data collector: funeral homes.

This stems from the incongruity between the expected death rate by region and by year (a statistical data based on multiple retrospective variables), and the one actually found. The highest number obtained is called Excess Deaths.

The excess of deaths-in the countries initially hit by the pandemic - has implied no less than 50% of total deaths.

In Spain, funeral homes reported thousands of cases of bodies from geriatric institutions, nursing homes, hospices, etc., which were included in "natural death" (because there had been violence), but without specifying the causes that ended in death.

"Non-traumatic cardio-respiratory arrest" is the medico-legal name used in all these cases.

It has been speculated that the underreporting reached 50% of COVID deaths.

It should be understood that deaths were not overlooked, but the real cause of them: pneumonias due to COVID, cerebrovascular accidents due to COVID, acute renal failure due to COVID, catastrophic antiphospholipid syndrome due to COVID, disseminated intravascular coagulation due to COVID, etc.

Applied to our Country, it could be inferred that deaths from COVID, to date, would amount to approximately 78,000. All of the above has two readings.

On the one hand, that the infectivity of the virus is much greater than it is supposed; likewise, that the underreporting is much larger than is evident.

CONCEPT OF EMERGING, RE-EMERGING AND POTENTIALLY EMERGING DISEASES

An emerging infectious disease is one caused by a recently identified and previously unknown infectious agent capable of causing public health problems at the local, regional or global level [5] (Table 1).

Re-emerging diseases are defined by the reappearance and increase in the number of infections of an already known pathology that, due to the few cases registered, was no longer considered a public health problem, but which cause an alarming return [6].

Finally, the denomination of "potentially emerging" is proposed to all those nosological entities for which-although they are considered "exotic" and there are currently no confirmed cases-the conditions for their appearance are given: climate change, presence of vectors adequate, socio-sanitary predisposition, frequent trips, etc.

All the above nosological entities have in common an imbalance in the man-domestic species-fauna interrelation, generating situations that threaten the health and well-being of the three populations involved [7].

Human activities and environmental disturbances have created new patterns for infectious diseases, favoring the spread of pathogens between different species and previously uncorrelated geographic areas.

New social trends such as the acquisition of exotic species for pets, food products from wild animals and plants or ecotourism contribute to their development and propagation.

Regarding food consumption, the terms "free of pesticides" should not be confused with "lacking in phytosanitary controls".

Table 1: We outline-below-a list with the pathologies. Despite its being a succinct enumeration, we emphasize the imperative need to know the differential diagnoses, the form of confirmation, and their eventual therapeutics.

AGENT	CLASSIFICATION	DISEASE	E / RE / PE
VIRUS	Arenavirus	Argentinian Hemorragic Fever	RE
VIRUS	Arenavirus	Chapare	PE
VIRUS	Hantavirus	Hantavirus	E
VIRUS	Flavivirus	Dengue	RE
VIRUS	Flavivirus	Yellow Fever	RE
VIRUS	Flavivirus	Zica	E
VIRUS	Togavirus	Chikungunya	E
VIRUS	Flavivirus	West Nile Encephalitis	PE
VIRUS	Rhabdovirus	Rabies	RE
VIRUS	Filovirus	Ebola	PE
VIRUS	HIV	AIDS	RE
VIRUS	Herpesvirus	Dissemitnated Herpes simplex	RE
VIRUS	Paramyxovirus	Hemorrhagic measles	RE
VIRUS	Ribovirus	Flu	RE
VIRUS	Paramyxovirus	Nipah	PE
VIRUS	Paramyxovirus	Hendra	PE
VIRUS	Poxvirus	Smallpox	PE
BACTERIA	Escherichia	Hemolytic uremic syndrome	E
BACTERIA	Lestospira sp	Leptospirosis	E
BACTERIA	Salmonella	Typhoid fever	RE
BACTERIA	Corynebacterium	Diphtheria	RE
BACTERIA	Bordetella	Whooping cough	RE
BACTERIA	Mycobacterium	T.B.	RE
BACTERIA	Vibrio	Colera	RE
BACTERIA	Legionella	Legionelosis	E
BACTERIA	Borrelia	Lyme´ disease	E
BACTERIA	Helicobacter	Gastric Ulcer	E
BACTERIA	Chlamydia	Psittacosis	RE
BACTERIA	Brucella	Acute brucellosis	RE
BACTERIA	Micobacteriae	Landouzy typhobacillosis	RE
BACTERIA	Meningococo	Acute meningococcemia	RE
BACTERIA	Treponema	Herxeimer in Syphilis	RE
BACTERIA	Mycobacterium	Leprosy syndrome	RE
BACTERIA	Cocos	Sepsis by Gram –	RE
BACTERIA	Pasteurella	Bubonic plague	PE
BACTERIA	Bacillae	Anthrax Inhalation anthrax	RE
BACTERIA	Campylobacter	Food poisoning	RE
PARASITE	Plasmodium	Malaria	RE
PARASITE	Strongyloides	Estrogyloidiasis	RE
PARASITE	Tripanosoma	Acute Chagas	RE
PARASITE	Entamoeba	Acute amebiasis	RE
PARASITE	Triquinella	Trichinosis	RE
PARASITE	Toxocara	Larva migrans	RE
PARASITE	Taenia	Cysticercosis	RE
PARASITE	Cestoda	Hydatidosis	RE
FUNGI	Cryptosporidium	Cryptosporidiosis	RE
FUNGI	Blastomices	Blastomicosis	RE
FUNGI	Histoplasma	Histoplasmosis	RE
CA	Combined Agents	Erythema polymorphous	RE
CA	Combined Agents	Kawasaki´s Disease	RE
RE: reemergent E: emergent PE: potentially emergent CA: combined Agents			

Likewise, the growing conditions of impoverishment, overcrowding, lack or fear of accessing health systems, and self-medication (folkloric or induced by the media), favor the serious situation.

In the same way, bioterrorism must be taken into account because it leads to the resurgence of diseases that are now considered eradicated, such as smallpox [8].

In humans, more than 1,415 pathogens are known, of which 868 species are zoonotic (61%), and 80% of the latter have the capacity to affect different species of animals [9].

The control of zoonoses is a highly complex process, and each case needs to be approached differently.

We outline-below-a list with the pathologies.

Despite its being a succinct enumeration, we emphasize the imperative need to know the differential diagnoses, the form of confirmation, and their eventual therapeutics.

MATERIAL AND METHODS

Surgical Procedure

Prone position, asepsis and antisepsis, longitudinal linear incision in posterior aspect of left thigh, interfascial dissection, localisation of common sciatic nerve dependent tumour, continuous neurophysiological monitoring, proximal and distal electrode placement on sciatic nerve, mapping with bipolar stimulator during resection. Extracapsular tumour dissection, fascicle-dependent tumour mapped and silent, complete enbloc resection.

No drop in nerve action potential detected at any time during surgery. Haemostasis. Closure by planes. Tumour sent for PA.

Two Recording Modalities for Intaroperative Monitoring were Used

Bipolar probe mapping of the tumour looking for silent areas without CMAPs (compound muscle action potentials) for resection. Gastrocnemius, Tibialis anterior, Extensor digitorum brevis and Abductor hallucis left were used as recording muscles.

During resection, the structure was mapped to look for silent areas with no CMAPs recorded in the recording muscles and these areas were used to respect the lesion. Fascicles with muscle response were not resected.

ANATOMOPATHOLOGICAL DIAGNOSIS

“Left sciatic nerve: SCHWANNOMA (neurilemoma).

RESULTS

The entire tumour was excised.

The patient was discharged after 48 hours without any neurological deficit with disappearance of his previous pain.

LIMITATIONS

The presentation of a single case does not allow us to generalise the results, but it can serve as a guide for other neurophysiologists to use this simple and very useful technique.

As the sciatic nerve is a very thick nerve, there were difficulties in keeping the electrode in place and the electrode had to be repositioned on occasion. After these relocations, the initial recording was the same as the final recording, with no evidence of changes in latency or amplitude.

CONCLUSION

The mapping of muscle structures dependent on the peripheral nerve provides security for the resection of tumours dependent on nerve fascicles that without this tool it would not be possible to determine whether they are functional or not and could produce a transient or definitive partial or total paresis of the structure that it preserves.

The preservation of the NAP until the end of the surgery ensures that the nerve will be functional even if it presents post-surgical paresis.

Al ser el nervio ciático un nervio de gran grosor hubo dificultades en mantener el electrodo en el teniendo que recolocar en alguna ocasión. Tras etas recolocaionesle registro inicial fue el mismo que el registro final no evidenciándose cambios de latencia o amplitud.

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Ivermectin and Sars Cov 2 Pandemic: The Right Time to Start.

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Ivermectin And Sars Cov 2 Pandemic: The Right Time To Start As Evidenced By The Statistics Of The Pandemic

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Abstract

The ongoing pandemic has become the major challenge to all mankind. Since its very beginning, huge economic resources have been used in order to fight against it. But not always in the right direction. Repurposing drugs have proved to be more useful than recently investigated ones. Yet, they are not used in the massive and strong way they should be. More expensive doesn´t mean better. There are currently 53 international trials on ivermectin, with 100 % of good outcomes. In this article, we review the evolution of IVM, from its early in vitro studies to our final Clinical Trials. Despite it, ivermectin keeps awaiting its turn to be included in WHO, NIH, NICE and other national and international guides.

Keywords: Ivermectin; SARS COV2; repurposing drugs

Introduction

Since its outbreak in China on December 2020, the SARS COV2 pandemic has already provoked over 2 million deaths. During 2020, huge efforts have been made worldwide to reduce the impact of this virus on public health. New compounds and repurposed drugs have been tried, with variable outcomes. One of the most promising results came from the use of ivermectin (IVM) [1, 2]. Ivermectin is an FDA-approved anti-parasitic agent which in recent years has shown to have in vitro anti-viral activity against a broad range of viruses, from dengue to recently-included SARS COV2 (Figure 1).

IVM is in a class of medications called anthelmintics. It is widely used for treating scabies, ongyloidosis and onchocerciasis. There are currently 53 international trials on IVM/SARS COV2, with 100 % of good outcomes, ranging from 2:1 reduction of death rate to 8:1, depending on methods, doses, time of application, etc. Despite its having been presented to all international Health Organizations, after a whole year of death and sorrow, it isn´t still included in the potential arsenal against the disease. We summarize its effects, the way we investigated its efficacy, and the huge international literature that supports its potentialy-benefitial massive use.

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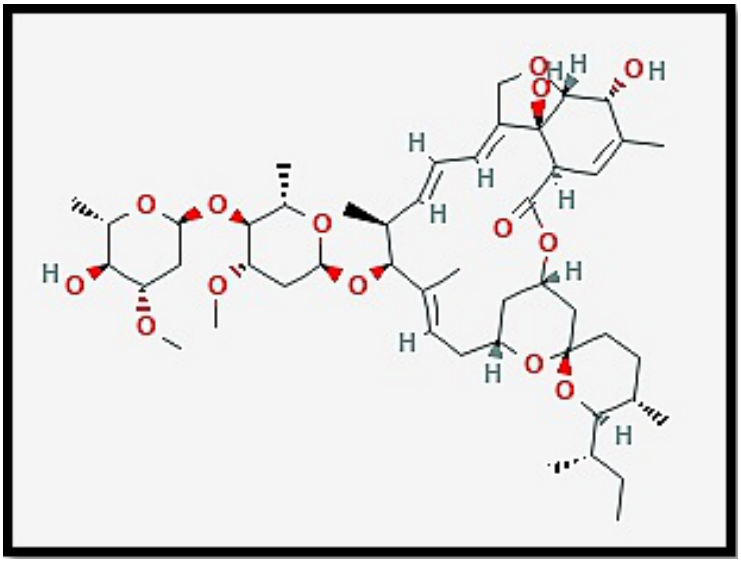

Figure 1: IVM Structure

Ivermectin and SARS COV 2, from in *Vitro* to in *Vivo* Studies

IVM is widely used in Human Medicine as an anti-parasitic compound. Its efficacy and safety have been proved worldwide. Its introduction by Omura and Campbell was awarded with the Nobel Prize. Since then, IVM has shown different aspects of activity on other microorganisms, such us virus (dengue fever, West Nile Encepahlitis, etc) [1]. Caly and Wagstaff [2] proved the efficacy of ivermectin (IVM) to dramatically reduce viral load in a matter of 48 h. Those studies were held in vitro. We transferred the use of IVM to human beings 3,4,5,6,7 with equal results. Those results were duly submitted to the National Library of Medicine (USA), being the first ones in the world to be released. Since then, loads of evidence has been mounting in the same direction, but with scarce luck in order to attract the attention of international Health Organizations. Even locally, the Argentinian Health Authorities have failed to give IVM a preferential treatment. Those Professionals who have adhered to the use of IVM have, so far, saved thousands of human lives. IVM has becomes the silent, neglected silver bullet against SARS COV2. It can be used either for prevention or treatment. In the first situation (pre-exposure use), we prescribe 1 drop of IVM per kilogram of weight, on a weekly basis. So far, its efficacy in protecting subjects from contagion has ranged from 99 to 100 % [3]. For treatment, we suggest the following scheme (Table 1).

Disease Severity	Ivermectin	Corticoid		Ventilation
Confirmed Mild Case (and close contacts)	24mg orallyat a dose of 300ug/kg in a single dose, to be repeated a week later.	No	Aspirin 250mg orally	No
Modrate Clinical Stage	35mg orallyat a dose of 450ug/kg in a single dose, to be repeated a week later.	Dexametha sone 4 mg (parenteral)	Idem	Low Flow Oxygen or Oxygen Concentrat or
Severe Case with Bilateral Pneumonia	48mg via grastric cannulae, at a dose 600ug/kg in a single dose, to be repeated a week later.	Idem	Enoxaparin 100 UI/kg (1 mg/kg)	Mechanical Ventilation

TABLE 1: Scheme of IVM as Treatment in COVID 19 Patients

The efficacy of treatment if compared to all other treatments- was 7:1 when considering mortality, in our series [4]. The mechanisms of action of IVM on SARS COV2 are summarized in Figure 2.

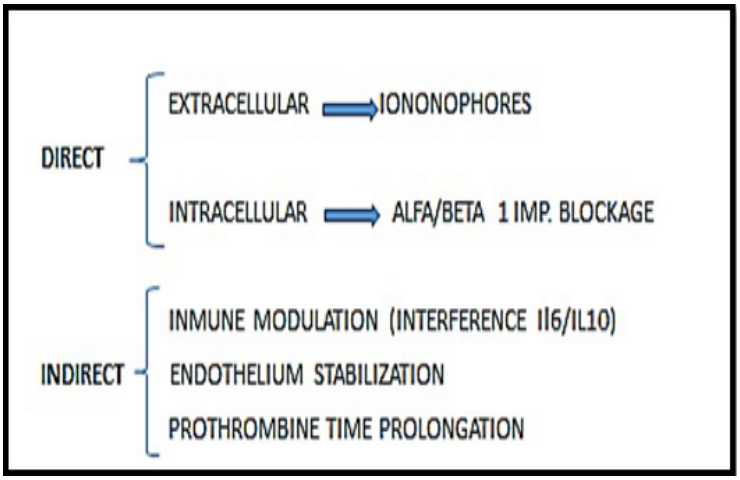

Figure 2: IVM MECHANISMS OF ACTION AGAINST SARS CVO2

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Discussion

Having performed a meta-analysis of the 35 international trials, the outcomes of which have already been submitted to the National Library of Medicine (USA), we have found that all of them have positive results. There are still on-going 18 Trials; but the chance of bias in the 35 finished ones is 1 in 4 billion, thus proving the efficacy of IVM on SRAS COV2, and the urgent need to include this compound in the list of international alternatives against the current pandemic.

Conclusions

As IVM is a worldwide attainable drug, with many years of use that stand for its safety, low cost all over the World, and many new and promising effects that have been proved beyond doubt, we strongly support its being used against SARS COV2 [5-7]. Every human life count; 2 million death is a massacre and –what is worse- an avoidable massacre. Up till now the scepticism of World Health Organizations has been paralyzing. But enough is enough. As A. Camus quoted [8], it is just a matter of common sense, and it only requires common decency.

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PROFILAXIS y TRATAMIENTO