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Review Article

A Possible Guide as a Tool to Complementary Effects of New Coronavirus

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ABSTRACT

At the end of 2019, Sars-CoV-2 was identified and has since spread in the world. Coronavirus is commonly caused by upper respiratory tract and severe acute respiratory syndrome in humans. Due to the novel nature of the virus and high mortality among high-risk people, today health care providers used several medications with different mechanisms to overcome this virus. The course of COVID-19 represents three stages that have different symptoms and used different drugs depends on each stage. Ultimately the minority of patients progress to stage III with high mortality.

The aim of this study is a comprehensive review of COVID-19 adjuvant therapies. We explained the current study on the use of Glucocorticoids, Interferon, Vitamin C, Tocilizumab, Anakinra, Pentoxifylline, IVIG, Allopurinol, Ivermectin, and Selenium in sepsis, pneumonia, and ARDS and we suggested a new protocol for prescribing each medication currently used in COVID-19 Outbreak.

Coronavirus is commonly caused by upper respiratory tract and severe acute respiratory syndrome in humans. At the end of 2019, Sars-CoV-2 was identified in Hubei province in China and has since spread in the world [1]. COVID-19 outbreak leading to relatively 51 million identified cases with 1.26 million deaths in over 200 countries.

Due to the novel nature of the virus and high mortality among high-risk people, today health care providers used several medications with different mechanisms to overcome this virus [2].

The course of COVID-19 represents three stages; after the incubation period, and in stage, I, constitutional symptoms including cough, headache, myalgia, fever,

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and diarrhea appear. In this stage, viral replication is highest through the disease. Therefore, antivirals with in vitro and in vivo activity against Sars-CoV-2 such as Remdesivir, Hydroxychloroquine, and Favipiravir can be useful in this stage [3]. With disease progression, a decrease has been reported in viral replication and subsequently constitutional symptoms. Then, dyspnea and mild hypoxia can be occurred, as a result of a significant increase in inflammatory markers. This phase usually begins one week after symptom onset. Due to an increase in plasma levels of inflammatory markers including IL-6, Ferritin, and CRP, anti-inflammatory medications such as corticosteroid and Tocilizumab may be useful [3-4]. Ultimately the minority of patients progress to stage III with high mortality [5].

The aim of this study is a comprehensive review of COVID-19 adjuvant therapies. Here, we explained the current study on the use of these drugs in sepsis, pneumonia, and ARDS. Also, the documentation of these medications in Covid-19 has been fully reviewed. Since these treatments may be associated with the risk of medication-related problems and costs, it is necessary to be careful in using them. Finally, we suggested a new protocol for prescribing each medication currently used in COVID-19 Outbreak.

Drugs

Glucocorticoids

Scientific reasons for using the drug in critically ill patients with COVID-19:

Glucocorticoids act solely as immunosuppressive agents. The mechanisms that underlie the immunosuppressive properties of these hormones have been intensely scrutinized, and it is widely appreciated that glucocorticoids have pleiotropic effects on the immune system. Due to their ability to stop or delay the progression of pneumonia, they have been used in the treatment of Acute Respiratory Syndrome (ARDS) [6-8]. In addition to immunosuppressive properties, these drugs have strong anti-inflammatory effects by reducing systemic inflammation, inhibiting exudate in lung tissue, improving the absorption of the inflammasome, and preventing alveolar diffuse injury. Through the mentioned mechanisms, these drugs can relieve hypoxemia and preserve lung tissue by preventing respiratory failure [9].

During the outbreak of SARS-CoV and MERS-CoV, the administration of glucocorticoids was associated with side effects such as cessation of the virus from the blood. Furthermore, there was a connection between corticosteroid therapy and increased mortality in patients with lung disease. Whether the administration of these drugs might be useful in controlling coronavirus infection still needs further investigation [10-12]. In some studies, the use of these drugs in ICU patients and SARS-CoV infection has been linked with benefits [13]. Reports from Chinese scientists suggest that many patients received glucocorticoid therapy during the SARS-CoV2 pandemic [14-15]. However, the routine recommendation of prescribing these drugs in COVID-19 positive cases is not appropriate and as a result, prescribing these drugs could bring clinical benefits to secondary outcomes, such as earlier reversal of shock, shorter duration of discharge from ICU, and weaning from mechanical ventilation [16].

The available information on the effectiveness of glucocorticoid adjuvant therapy in SARS-CoV2 infection in patients with lower lung infection is still insufficient. Based on the available evidence, appropriate use of low-dose glucocorticoids, especially in patients with ARDS, may be associated with improved survival in these patients [17]. Therefore, low doses of these drugs for a short time (less than 7 days) might be effective by monitoring side effects. Due to the risk of delayed complications in these patients, long-term follow-up (six months to three years) should be performed [16].

Scientific evidence showed in (Table 1). A-D

Recommendation: Currently, based on the available evidence, corticosteroids have a proven therapeutic role in COVID-19, and some studies have shown its beneficial effects.

Members of the Scientific Committee of the Ministry of Health and Medical Education suggest that corticosteroids could be used in low doses only if the patient's symptoms and the need for oxygen persist despite supportive therapies and SpO2 <90%.

Prescribe: Dexamethasone 8 mg daily intravenously for a maximum of 10 days; Or oral prednisolone tablets 0.5 mg/kg for a maximum of 10 days.

Interferon

Scientific reasons for using the drug in critically ill patients with COVID-19:

Interferons are broad-spectrum compounds used in the treatment of diseases such as hepatitis [28]. Interferons can be effective in improving SARS-CoV2 infection by improving innate immune responses [29-30]. Although there is no evidence to date that these drugs have beneficial effects on passive immunity, the use of interferon could theoretically be effective in treating these infections [31]. The combination therapy with interferon beta and interferon-gamma by their synergistic effect has been used in the treatment of SARS-CoV. The synergistic effects of ribavirin and interferon beta on coronavirus replication have been demonstrated in animal and human studies [32]. In addition, the effects of the combination therapy of lopinavir/ritonavir with interferon β1b have been expressed in patients with MERS-CoV. In several clinical studies, the effectiveness of this drug has been evaluated, which can help determine the effectiveness of this drug in the treatment of SARS-CoV2 [33]. To stimulate innate immune responses in

patients with COVID-19 infection, pegylated interferon α-2a and 2b can be used which is approved for the treatment of HBV and HCV. Various studies have shown that three virulence factors including Nsp1, Nsp3c, ORF7a are involved in the escape of coronavirus from the host immune system by interfering with innate immunity. Recent reports have shown that the Nsp1 factor has played a specific role on the host mRNAs through intervention with small ribosomal subunits and can inhibit the production of interferon subtype I [34-35]. The efficacy of synthetic alpha and recombinant interferon in patients with SARS infection has been demonstrated in clinical trials. This drug has been able to reduce lung damage in patients with SARS by 50%. Furthermore, it can reduce the proliferation of MERS-CoV. Accompanying, several studies have shown the effectiveness of this drug in COVID-19 [36].

The effectiveness of this class of drugs in SARS-CoV2 infection has been demonstrated in various clinical studies. Some studies have used the inhaled form of the drug-aerosol for two weeks, while others have used the nebulizer form. Some studies have emphasized the synergistic role of interferon alfa and ribavirin in the early stages of SARS-CoV2 infection. Whether or not this drug is effective in SARS-CoV2 depends in particular on the time of onset of the drug [37].

Scientific evidence showed in (Table 2). A-D

Recommendation: The drug is recommended for COVID-19 only in clinical trials.

Vitamin C (Ascorbic Acid)

The rationale and evidence on the use of this medication in COVID-19:

Ascorbic acid or vitamin C as an antioxidant and cofactor of many physiological reactions, can strengthen the host's immune system against infection and protect cells against oxidative stress caused by infection [46-49]. On the other hand, the presence of infection may decrease the concentration of vitamin C [50].

Vitamin C deficiency is frequently observed in critically ill patients which are associated with a higher rate of mortality. Therefore, the rationale for the use of vitamin C in this population is to supplement an enhanced metabolic turnover of ascorbic acid [50-51]. In critically ill patients with sepsis or septic shock, a high dose of vitamin C may provide protective effects against oxidative-stress-mediated cell damage and organ dysfunction [52].

It is believed that IV vitamin C may be effective for the reduction of cytokines storm in ARDS by inhibiting the production of cytokines storm due to COVID-19 [53].

Many clinical trials are ongoing to systematically investigate the efficacy and safety of vitamin C in critically ill patients.

Scientific evidence showed in (Table 3). A-D

Recommendations: The current data is not specific to COVID-19, and many trials are underway. Therefore, additional studies are needed.

Studies of vitamins in critically ill patients with sepsis, septic shock, peneumonia, and ARDS have shown variable efficacy. We recommend against the routine use of vitamin C for COVID-19 in critically ill patients.

Tocilizumab

Scientific reasons for using the drug in critically ill patients with COVID-19:

IL-6 is mainly eliminated from the body through mediated IL - 6R clearance. Binding of TCZ to IL-6R inhibits the clearance of interleukin 6, resulting in its accumulation in serum. This is a possible explanation for the high levels of IL-6 in patients with COVID-19 treated with TCZ. Further treatment with a gradual decrease in IL-6 leads to stabilization or improvement of clinical outcome that may be due to inhibition of inflammatory activity by TCZ [57].

Given that large amounts of mononuclear inflammatory lymphocytes have been observed in biopsy specimens from autopsies of COVID-19 patients, it is believed that these pathogenic T cells and inflammatory monocytes may enter the pulmonary circulation in large numbers and provoke an inflammatory storm in COVID patients. Thus, these pathogenic Th1 cells (GM-CSF + IFN-γ +) and inflammatory monocytes (CD14 + CD16 +) with high levels of IL-6 are especially presenting in covid19 patients who have hospitalized with ICUs. It is for the sake of whether the IL6 is targeted or not, with the administration of tocilizumab potentially could be an effective and safe way to reduce mortality in patients with COVID-19 [58].

Tocilizumab blocks the binding of IL-6 to soluble IL-6 receptors and cell membrane receptors and it would inhibit consequently the inflammatory cascade signaling [59]. Tocilizumab appears to be a promising approach in the management of severe COVID-19 disease.

Scientific evidence showed in (Table 4). A-D

Recommendation: The drug may be recommended for COVID-19 only in clinical trials.

Anakinra

Scientific reasons for using the drug in critically ill patients with COVID-19:

Evidence suggests that SARS-CoV-2 activates the endothelial function, leading to the overproduction of D-dimer. The urokinase-type plasminogen activator receptor (uPAR) binds to the cell membrane of lung endothelial cells. As a result of caloricrin activation, uPAR cleaves and enters the systemic circulation as a soluble suPAR counterpart. Preliminary unpublished data from 57 Greek patients who addressed to Greek hospitals after March 1, 2020, due to pneumonia with confirmed SARS-CoV-2 infection, showed that individuals with a suPAR blood level above 6 ng/ml

within 14 days had a higher risk of developing serious respiratory failure (SRF). The sensitivity of suPAR in the diagnosis of these patients was 85.9% and the positive predictor was 85.9%. Noticeably, suPAR can detect the early onset of this type of inflammatory process in the lung parenchyma, which can get quickly intensifies. A recent publication has shown that this is due to the early release of interleukin-1α (IL-1α) from lung epithelial cells infected with the virus. This IL-1α acts as a promoting factor in the production of IL-1β and cytokine build-up of alveolar macrophages. Anakinra is the only product on the market that inhibits IL-1β and IL-1α. Therefore, it would be able to block an inflammatory response quickly and prevent downstream inflammatory signaling pathways. SuPAR can be used as a biomarker to identify patients with COVID-19 pneumonia at risk for SRF, and early onset of Anakinra may prevent SRF progression [69].

Scientific evidence showed in (Table 5). A-D

Recommendation: The drug is recommended for COVID-19 only in clinical trials.

Pentoxifylline

Scientific reasons for using the drug in critically ill patients with COVID-19:

Antiviral activity may be associated with a cytokine-modulating activity which has not known as an immunosuppressant such as corticosteroids. However, it reduces pro-inflammatory cytokines and led to maintain the function of the immune system. Other effects of PTX are discussed as bronchodilation [89]. In invitro, viral mRNA has not been shown to interfere with primary or delayed protein synthesis. Nevertheless, it is likely to act on virus assembly and/or release [90].

PTX can reduce the secretion of TNF, IL-1, and IL-6 IP-10 (CXCL10), as well as modulate the neutrophil function and macrophage activation. Beyond blocking the inflammatory function of IL-1 and TNF on neutrophils, it may reduce neutrophil-induced tissue damage. On the other hand, it can inhibit the release of cytokines from alveolar macrophages in pulmonary sarcoidosis. Additionally, It can also suppress the expression of ICAM-1 and the production of chemokines (IL-8 and MCP-1) induced by proinflammatory cytokines in human pulmonary epithelial cells. PTX was also able to prevents the IFN-γ and TNF-α, and cell proliferation with similar potency [91,92].

Scientific evidence showed in (Table 6). A-C.

Evidence and scientific documentation on the use of the drug in COVID-19: No study has been done so far.

Recommendation: The drug is recommended for COVID-19 only in clinical trials.

IVIG

Scientific reasons for using the drug in critically severe patients with COVID-19:

Various studies have been performed on the use of this drug in patients with sepsis, and mechanisms have been proposed for its possible efficacy Including; 1- Complement ammonolysis 2- Immunophagocytosis, 3- Toxin neutralization, 4- Antibody-induced cytotoxicity [101].

Despite the theoretical efficacy, clinical studies have suggested conflicting effects on its efficacy. In a systematic review study, most studies that showed beneficial efficacy for IVIG in sepsis patients had a high risk of bias [102]. In infants, it didn't have significant effects on mortality [102]. However, in another study, a single administration of 15 g of IVIG had a more favorable effect on the inflammation and clinical condition of sepsis patients than the divided administration [103]. However, studies show the favorable effect of IVIG in treating coagulation disorders caused by sepsis [104].

Studies on the Efficacy of immunoglobulin therapy in influenza pneumonia have also been performed: In one study, NK cell activity as a marker of drug efficacy through antibody-dependent cellular cytotoxicity mechanism was used as a criterion that raised the possibility of treatment efficacy [105]. Another retrospective study found that IVIG administration to immunocompromised children with H1N1 had beneficial effects, including reduced mortality and hospitalization in the intensive care unit [106]. Moreover, a reliable role for IVIG in reducing the inflammatory response was found in a review study that examined the Efficacy of several immunomodulatory mechanisms on the severe form of influenza [107].

Regarding its effectiveness in non-viral pneumonia, in the Large-scale of studies (8264 patients) with VAP with septic shock, IVIG administration didn't show a good effect on mortality [108]. In 67-years-old with Good's Immune Deficiency Syndrome, routine IVIG administration has been shown to play a significant role in reducing the incidence of viral infections [109]. In another study in Iran, IVIG administration in children with common variable immunodeficiency (CVID) resulted in a significant reduction in the incidence of pneumonia [110].

Most studies on the Efficacy of intravenous immunoglobulin in treating of COVID-19 pandemic are case reports or case series. In one report of three patients, high doses of IVIG showed favorable effects in recovery from severe cases [111].

The above evidence suggests that IVIG may be used in patients with severe COVID-19, especially with coagulation disorders or hypogammaglobulinemia.

Scientific evidence showed in (Table 7). A-D.

Recommendation: The drug is recommended for COVID-19 only in clinical trials.

Allopurinol

Scientific reasons for using the drug in critically ill patients with COVID-19:

Since xanthine oxidase is activated in sepsis and can lead to the production of uric acid and oxygen radicals [14], some reports have been investigated the possible role of xanthine oxidase inhibitors, including allopurinol, in sepsis but haven't yielded promising results for allopurinol [112]. On the other hand, such shreds of evidence have been reported regards the role of uric acid in bleomycin-induced lung injury that has been found to make uric acid reducers an interesting subject for study [113]. No reliable control was found for the therapeutic role of allopurinol in viral and non-viral pneumonia, as well as sepsis. Also, no evidence has been found for the therapeutic effects of allopurinol as adjunctive therapy in COVID19.

Recommendation: The drug is recommended for COVID-19 only in clinical trials.

Ivermectin

Scientific reasons for using the drug in critically ill patients with COVID-19:

Ivermectin is an FDA-approved antiparasitic drug that is highly effective against many microorganisms including some viruses. Recently, there has been increasing evidence demonstrating that Ivermectin has a significant effect against RNA viruses such as Zika, dengue, yellow fever, West Nile, Hendra, Newcastle, Venezuelan equine encephalitis, chikungunya, Semliki Forest, Sindbis, Avian influenza A, Porcine Reproductive and Respiratory Syndrome, Human immunodeficiency virus type 1, and severe acute respiratory syndrome coronavirus [114]. Moreover, some reports are indicating antiviral effects of ivermectin against DNA viruses such as Equine herpes type 1, BK polyomavirus, pseudorabies, porcine circovirus 2, and bovine herpesvirus 1. Accordingly, Ivermectin plays a role in several biological mechanisms, therefore it could serve as a potential candidate in the treatment of a wide range of viruses including COVID-19 with an inhibitory effect on SARS COV 19 by acting on IMPα / β1 through membranes as well as other types of positive-sense single-stranded RNA viruses [115]. According to in vitro studies, it was able to stop coronavirus cell replication within 48 hours [114]. Up to date, FDA issued a statement regarding all self-administration of ivermectin against COVID19 has referred to a recently published in vitro study which is oriented around this subject. FDA indicated that this study could be just used in the early stages of drug development. Therefore, further trials are still needed to approve for the sake of safety and efficacy of ivermectin for human usage against COVID-19 to decipher all inhibitory features or therapeutic windows. According to studies, the dose that can have a therapeutic effect in humans and reach the appropriate level of treatment should probably be lethal doses for humans.

Scientific evidence showed in (Table 8). A-D.

Recommendation: The drug is recommended for COVID-19 only in clinical trials.

Selenium

Scientific reasons for using the drug in critically ill patients with COVID-19:

Viral pathogens caused oxidative stress by increasing ROS, and selenoproteinases, as common antioxidants, can be effective in controlling oxidative stress. Selenium deficiency weakened the body's defense system against infectious diseases by reducing the expression of selenoproteins [116-118].

Scientific evidence showed in (Table 9). A-D.

Recommendation: The drug is recommended for COVID-19 only in clinical trials.

Table 1- Scientific evidence of Glucocorticoids in sepsis (A), viral pneumonia (B), non-viral pneumonia (C), and COVID-19 (D)

Date	Authors	Type of study	Interventions	Outcomes	Results
A					
2019	Yue-NanNi	Systematic review and meta-analysis, 7035 people	Comparison of glucocorticoids versus placebo in severe sepsis	28-day mortality, recurrence of septic shock	Glucocorticoids reduced 28-day mortality in patients with severe sepsis or septic shock [18].
B					
2020	Lansbury,Louise	Systematic review and meta-analysis	Glucocorticoid administration	Mortality and nosocomial infections	Administration of glucocorticoids was associated with increased mortality and nosocomial infections. However, the available evidence includes high doses of corticosteroids and studies with low quality and potentially

					confounding factors that affect the results of the study [19].
2019	Yue-Nan Ni	Systematic review and meta-analysis, 6548 patients	Glucocorticoid administration	Mortality, days of mechanical ventilator support, length of stay in ICU	In patients with influenza pneumonia, administration of glucocorticoids had been associated with increased mortality [20].
C					
2015	Christophe Marti	Systematic review and meta-analysis 2077 patients	Glucocorticoid administration	Length of hospital stay, time of stable clinical condition of the patient, severe complications, 30-day mortality	Adjuvant use of glucocorticoids in CAP has associated with severe complications, reduced length of hospital stay, stable clinical condition, but its effects on mortality were unclear [21].
D					
2020	WHO REACT Working Group	Meta-analysis On 1703 critically ill	Group 1: systemic dexamethasone, hydrocortisone, or methylprednisolone (678 patients), Group 2: usual care or placebo (1025 patients).	all-cause mortality at 28 days after randomization	systemic corticosteroids were associated with significant lower 28-day all-cause mortality in comparison to standard of care or placebo [22].
2020	Christiane Maria Prado Jeronimo	Clinical trial 416 people	patients were randomized 1:1 ratio to receive intravenous methylprednisolone (0.5 mg/kg) or placebo (saline solution)	28-day mortality	The short course of methylprednisolone in hospitalized COVID-19 patients could not reduce 28-day mortality [23].
2020	Chen Zhenshun	Clinical trial 75 people	Group 1: Early administration of glucocorticoids Group 2: Delayed administration of glucocorticoids Group 3: No administration of glucocorticoids	Time to improve clinical symptoms, improve imaging, the incidence of complications during hospitalization, duration of hospitalization in ICU, connection to a mechanical ventilator, 21-day mortality, side effects	Ongoing [24].
2020		Clinical trial 80 people	Group 1: standard treatment Group 2: Methylprednisolone 40 mg twice for 5 days	PaO2 / FiO2 difference between the two groups, SOFA score, Support with ventilator, Mortality	Ongoing [25].

2020	Ronghui Du	Clinical trial 100 people	Group 1: standard treatment Group 2: standard treatment and methylprednisolone	ECG - Chest imaging - Complications - vital signs - NEWS2 score	Ongoing [26].
2020	W Horby	Clinical trial 6425 people	Group 1: standard treatment Group 2: Standard treatment and dexamethasone 6 mg daily	Mortality	Dexamethasone was able to significantly reduce 28-day mortality in patients undergoing mechanical ventilation or oxygen therapy; But not in patients who did not receive respiratory support [27].

Table 2- Scientific evidence of Interferon in sepsis (A), viral pneumonia (B), non-viral pneumonia (C), and COVID-19 (D)

Date	Authors	Type of study	Interventions	Outcomes	Results
A					
No clinical trial was found.					
B					
2006	Lauren J Stockman	Systematic review	A systematic review of treatments available in SARS	Effectiveness side effects	In in vitro studies, interferon administration has been effective, but the results of clinical studies were inconclusive [38].
C					
No study found					
D					
2020	Hamid Rahmani	Clinical trial 80 people	Group 1: Standard treatment along with β 1b- 250 micrograms subcutaneously every other days for 14 days Group 2: standard treatment	Duration of hospitalization, clinical response, need for admission in ICU and invasive mechanical ventilation and side effects of treatment	IFN β-1b effectively shorten the duration of clinical improvement, need for admission in ICU and invasive mechanical ventilation without causing serious adverse events in severe cases of COVID-19 [39].
2020		Clinical trial 328 people	Group 1: Long-acting interferon-alpha-2b and standard treatment Group 2: standard treatment	Percentage of side effects,Percentage of patients without dyspnea,Percentage of patients without cough, Percentage of patients without oxygen,Percentage of hospitalized patients	Ongoing [40]
2020		Clinical trial 328 people	Group 1: Standard treatment with interferon α1β at a dose of 10 micrograms twice daily as a nebulizer for ten days	Incidence of side effects such as dyspnea, cough, SPO2≤94%, increase in a respiratory rate more than 24	Ongoing [40]

			Group 2: standard treatment	Improvement of clinical symptoms, negative PCR, the incidence of side effects, percentage of patients in need of hospitalization	
2020	Ivan Fan-Ngai Hung	Clinical trial 86 people	Group 1: Kaletra and ribavirin and interferon Beta-1B and standard treatment Group 2: Kaletra and	PCR test negative time, Time to improve clinical symptoms Hospitalization rate, Mortality Immune reactions, side effects	Early triple antiviral therapy was better than Kaletra alone in relieving clinical symptoms, reducing viral shedding, and duration of hospitalization in mild to moderate disease [41].
2020	Effat Davoudi-Monfared	Clinical trial 81 people	Group 1: Standard treatment and interferon β 1a 44 micrograms subcutaneously three times weekly, for 14 days Group 2: standard treatment	Duration of hospitalization Clinical implications side effects	The addition of interferon to standard treatment did not significantly change the clinical response time between the two groups. On the fourteenth day, a significant higher percentage of the interferon group were discharged and had a lower mortality rate on day 28 in the interferon group [42].
2020		Clinical trial 94 people	Group 1: Nebulized Recombinant Interferon (rSIFN-co) Group 2: Nebulized Interferon α	Clinical signs, biochemical and myocardial enzymes, Inflammatory cytokines,CT Scan,Vital signs,Procalcitonin,ESR,CRP,ABG, O2 Saturation,side effects	The time of radiological and clinical improvement was significantly higher in in the rSIFN-co arm on day 28. In Combination of rSIFN-co with antiviral was safe and more effective in the management of moderate-to-severe COVID-19 [43].
2020		Clinical trial 300 people	Group 1: Human recombinant interferon α1b eye drops Group 2: placebo drops	Improve clinical symptoms, Temperature, O2 Saturation,Respiration rate,CT scan of the lungs,Frequency of dyspnea Cough, recovery time,Dyspnea recovery time,PCR negative time	Ongoing [44].

2020		Clinical trial 450 people	Group 1: Interferon α1b human recombinant spray Group 2: placebo spray	blood test,CT scan of the lungs,O2 Saturation,Fever, Cough,incidence of pneumonia in imaging and adverse reaction	Ongoing [45].
2020		Clinical trial 328 people	Group 1: Standard treatment = human interferon recombinant α 1beta as a nebulizer for ten days Group 2: standard treatment	Incidence of side effects	Ongoing [46].
2020	FarzanehDastan	Clinical trial 20 people	Group 1: ydroxychloroquine + Kaletra for 5 days with interferon beta-1a every ther day subcutaneously for ten days Group 2: ydroxychloroquine + Kaletra for 5 days	Response to treatment, Time of hospitalization and discharge from the hospital Lung radiological changes in the baseline, day 7 and day 14 side effects	The findings of this study were in favor of administration of interferon beta-1a in combination with hydroxychloroquine and Kaletra in the patients positive for COVID-19 [47].
2020	Pooya Payandemehr	Single- arm Clinical trial 20 people	Standard antiviral therapy with subcutaneous Interferon beta-1a for 5 days	Routine lab tests, patients' vital signs and O2 saturation, the need for ICU admission and intubation	The result of this study support Interferon beta-1a in combination with antiviral treatment in Covid-19 [48].
2020		Clinical trial 100 people	Group 1: Arbidol, for two weeks Group 2: Arbidol + Interferon PegIFN-α-2b 45 micrograms for two weeks	The rate of disease remission Cessation of fever and respiratory symptoms Improved pulmonary imaging rate CRP rate	Ongoing [49].

Table 3- Scientific evidence of Vitamin C in sepsis (A), viral pneumonia (B), non-viral pneumonia (C), and COVID-19 (D)

Date	Authors	Type of study	Interventions	Outcomes	Results
A					
2020	Chang P, et al.	A single-blind, randomized controlled trial on 80 patients with sepsis or septic shock (The HYVCTTSSS trial)	Hydrocortisone (50 mg every 6 h for 7 days), vitamin C (1.5 g every 6 h for 4 days), and thiamine (200 mg every 12 h for 4 days) vs placebo (normal saline)	28-day all-cause mortality Organ protection Procalcitonin reduction, Adverse events related to hydrocortisone,vitamin C, and thiamine	No difference in 28-day all-cause mortality, More incidents of hypernatremia in the treatment group, A significant improvement of 72-h ΔSOFA score The study was terminated after the mid-term analysis [54].
2020	Iglesias J, et al.	A randomized, double-blinded,	Hydrocortisone, ascorbic acid,	Resolution of shock	Astatistically significant difference

		placebo-controlled trial on 137 patients with sepsis or septic shock (The ORANGES trial)	thiamine (HAT) therapy	Change in Sequential Organ Failure Assessment (SOFA) score 28-day mortality ICU mortality Hospital mortality Hospital length of stay ICU length of stay	in the time patients required vasopressors, indicating a quicker reversal of shock in the HAT group compared with the comparator No statistically significant change in SOFA score between groups No significant differences between study arms in ICU and hospital mortality, ICU and hospital length of stay, ventilator-free days, and procalcitonin clearance [55].
2018	Jing Li	A meta-analysis of several small studies	Use of IV vitamin C in patients with sepsis	Mortality rate ICU length of stay Duration of vasopressor administration	Reduction in mortality and duration of vasopressor administration following vitamin C administration in septic patients.
2019	Fujii T, et al.	A multicenter, open-label, randomized clinical trial on 216 patients with septic shock in 10 ICUs (The VITAMINS trial)	Intervention group: IV vitamin C (1.5 g every 6 hours) plus thiamine (200 mg every 12 hours) plus hydrocortisone (50 mg every 6 hours) until shock resolution or up to 10 days Control group: hydrocortisone (50 mg every 6 hours) alone	Duration of time alive and free of vasopressor administration up to day-7 90-day mortality	Not significant improvement in duration of time alive and free of vasopressor administration over 7 days. Not leading to a more rapid resolution of septic shock
2019	Fowler AA, et al.	A double-blind, placebo-controlled, multicenter trial on 167 patients with sepsis and severe acute respiratory in 7 medical ICU (The CITRIS-ALI trial)	Vitamin C group: IV infusion of vitamin C of 50 mg/kg in dextrose 5% in water every 6 hours for 96 hours Placebo group: dextrose 5% in water every 6 hours for 96 hours	Change in organ failure as assessed by SOFA score from baseline to 96 hours, Plasma biomarkers of inflammation (C-reactive protein levels) and vascular injury (thrombomodulin levels) measured at 0, 48, 96, and 168 hours	Not significantly improvement of organ dysfunction, and markers of inflammation and vascular injury
B					
2016	Bharara A, et al.	A case report of a patient with recurrent ARDS	Intravenous vitamin C administration of 50 mg/kg every 6 hours for 96 hours as adjunctive therapy	Chest imaging via AP chest X-ray PaO2: FiO2 (PF) ratio duration of intubation	Improvement of chest imaging Improvement of PF ratio Successful extubation
C					

2013	Harri Hemilä	Review on several small studies	Prophylactic effects of vitamin C on pneumonia Therapeutic effects of vitamin C on pneumonia	The rate of improvement of symptoms Duration of hospitalization Mortality rate	Reduction in pneumonia incidence in the vitamin C group Lower mortality rate reduced severity A dose-dependent reduction in the duration of pneumonia
D					
2020	Baladia E, et al.	Systematic Review	Administration of vitamin C in the treatment of patients with COVID-19		No studies met the inclusion criteria No evidence to support or refute the use of vitamin c in the treatment of patients with covid-19 [56].

Table 4- Scientific evidence of Tocilizumab in sepsis (A), viral pneumonia (B), non-viral pneumonia (C), and COVID-19 (D)

Date	Authors	Type of study	Interventions	Outcomes	Results
A					
2020	Yasmine F.Ibrahim, Rabab A. Moussa	Rat Model	Evaluation of the effect of tocilizumab in patients with ALI, AKI caused by sepsis	Evaluation of creatinine and urea level in the serum, survival rate, evaluation of total protein in BALF	Decreased level of creatinine and urea, decreased total protein in bronchoalveolar fluid, increased survival [60]
2018	Robert Q. Le, Liang Li	45 Patients	The dose of 8 mg/kg for the treatment of CRS	Improve fever and tachycardia and hypotension and organ disorders	Early improvement in fever and tachycardia and delayed improvement in hypotension and organ dysfunction[61]
B					
2017	L.C.Welch,K. A.radigan,	Rodent model	Pretreatment in In vitro and In vivo studies	Check the diameter of myotubes	Preventing the reduction of the diameter of myotubes [62]
2020	Binqing Fu, Xiaoling Xu	Single-arm, Human	One or two doses of 400 mg	Oxygen requirement, fever improvement, ventilator dependence, CRP changes	Reduce oxygen demand, reduce ventilator dependence within 5 days, reduce CRP, improve fever [58]
C					
2016	Asami Masui-Ito	Case study	8mg / kg intravenously once every two weeks for up to 5 months then every 4 weeks	CRP changes, ferritin, lung photo changes	Decreased CRP, ferritin, improved lung image [63]
D					
2020	Hoffmann-La Roche	Phase 3 Clinical Trial (COVACTA)	Administration of 400 mg of the drug and placebo to 450 patients	Duration of ventilator dependence - duration of ICU hospitalization, mortality rate, serum concentrations of interleukin-6 and ferritin and CRP,	September 25 completed. Not published yet [64]

				improvement of clinical symptoms	
2020	Emanuele Focà Malattie Infective,	ChiCTR2000029765 Interventional clinical trial	21 patients with COVID 19 were prescribed 400 mg	Improves fever and lung function	Recovery of patients [65]
2020	Xiaoling Xu	retrospective	21 patients	Improving clinical and laboratory symptoms and lung imaging	Improvement of hypoxia and lung opacity [66]
2020	YIKAI YU, Tongji	NCT04306705	Retrospective Study on 120 patients	Improve fever and oxygen saturation, positive changes in CBC, negative PCR, mortality, change in interleukin levels 6 and 8	ongoing[67]
2020	Armando Gabrielli, Università Politecnica	Intervention Open Label,NCT04315480	38 patients in phase 2 clinical trial	Improving lung function, requires intubation and death	Ongoing [68]

Table 5- Scientific evidence of Anakinra in sepsis (A), viral pneumonia (B), non-viral pneumonia (C), and COVID-19 (D)

Date	Authors	Type of study	Interventions	Outcomes	Results
A					
2017-2019	Evangelos J. Giamarellos	A Personalized Randomized quadruple blind clinical Trial	On 36 patients with sepsis,The first group of Anakinra 200 ml three times a day for up to 7 days.The second group: placebo.The third group: receiving interferon-gamma	Mortality, 50% reduction in SOFA, number of secondary infections, length of in-hospital stay	ongoing [70]
2014	Hassan, Nabil E. MD1	Retrospective case series	On eight children as first-line of treatment with corticosteroids	Evaluation of changes in CRP, fibrinogen, ANC, ALC, dependence on the ventilator and vasoactive agents	67% reduction in CRP, 63% reduction in ferritin, 42% reduction in fibrinogen, no change in ANC, ALC and no secondary infection [71]
2016	B. Shakoory, M.D., J.A. Carcillo, M.D	Re-analysis of the identified data from the phase III randomized interleukin-1 receptor antagonist trial	763 adult patients receiving Anakinra 2mg/ kg/h for 72 hours and a placebo	28-days mortality	Improving survival rate [72]
B					
Lack of study in this area					
C					
Lack of study in this area					
D					
2020	University Hospital, Tours	French multicentre, open-label, randomized, controlled	The intervention group on days 1, 2, and 3 of treating with Anakinra with a dose of 100mg 6h, then on days 4 to 10	Recovery of the patient without any needs for ventilator or ECMO and reduction of morbidity and reduction of ICU	Suspended (Efficiency and safety reasons) 27 October [73]

		superiority trial	with a dose of 100mg every 12 hours, and the control group receiving routine treatment on 71 patients	hospitalization time, change of inflammatory parameters including CRP, ferritin, fibrinogen, lymphocyte count on days 3, 10, 14, 28, reduction of vasopressor requirement, evaluation of Spo2 / Fio2 changes	
2020	de Toulon La Seyne sur Mer	Open-label, randomized, controlled clinical trial	54 patients with COVID were selected and based on the severity of the disease if it is in stage 2 or 3, the drug is given at a dose of 300 mg intravenously and if it is at stage 3 or higher, then Anakinra will be advisable at a dose of 300 mg intravenously with Ruxolitinib 5 mg x 2	Including at least three of the following cases: 50% reduction in CRP, 1.3% reduction in ferritinemia, 1.3% reduction in serum creatinine, 50% reduction in AST / ALT, eosinophil> 50, lymphocytes> 1000, fever recovery time, duration of its dependency on the ventilator	[74]
2020	Hellenic Institute for the Study of Sepsis	The SAVE Open-label, Non-randomized Single-arm Trial	For 100 volunteer patients, Anakinra is given at a dose of 100 mg subcutaneously with cotrimoxazole once daily for up to 10 days in combination with other protocol drugs.	On the 14th day of the visit, there are no signs of worsening of the disease, improvement of clinical symptoms and improvement of respiratory function, evaluation of SOFA changes on days 1 to 14, change of inflammatory mediators on days 1 to 7	Ongoing [69]
2020	Pedro Abizanda, Complejo	Retrospective observational	576 volunteer patients with Adults older than 70 years hospitalized for COVID-19 disease between 09/03/2020 and 20/04/2020 in the "Perpetuo Socorro" Hospital of Albacete [Spain]	Evaluation of lung graph changes, mortality, Kant lymphocyte changes, CRP, ferritin, D-dimer	Ongoing [75]
2020	Swedish Orphan Biovitrum	A Phase 2/3, Randomized, Open-label, Parallel Group, 3-arm, Multicenter Study	On 54 volunteer patients consisting of three groups: the first group Anakinra 400 mg/day in total, divided into 4 doses given every 6 hours, the second group without intervention, the third group Emapalumab Day 1: 6mg/kg. Days 4, 7, 10 and 13: 3 mg/kg for totaly 5dose	Evaluation of ventilator dependence, improvement of Spo2, improvement of Po2 / Fio2, evaluation of changes in pH, Pco2, hemoglobin, ferritin, lactate, LDH, Platelet count, fibrinogen, CRP, ALT, AST, bilirubin levels	Ongoing December 2020 [76]
2020	Hellenic Institute for	Interventional non-	On 40 volunteer patients, one group without	Decrease of at least 25% SOFA on day 8,	[77]

	the Study of Sepsis	randomized open-label	intervention and the second group with tocilizumab 8mg / kg single dose and Anakinra 200 mg intravenously 3 times a day for 7 days	increase of at least 50% Po2 / Fio2, the mortality rate on days 28 and 90, change of serum/plasma protein changes on days 0 and 4,	
2020	Assistance Publique - Hôpitaux de Paris	Interventional randomized open-label	On 240 patients with one non-intervention group and the second group Anakinra 200 mg intravenously twice daily on days 1, 2, and 3 and then 100 mg twice daily on the fourth day and then 100 mg on the fifth day	Increased survival without ventilator on day 14, WHO progression scale ≤ 5, on day 14 for 48 hours without need for NIV or ecstobia, length of hospital stay and ICU, improvement of Po2 / Fio2, improvement of respiratory acidosis	Ongoing [78]
2020	W Winn Chatham,	Interventional randomized triple-blind	On 30 patients in the non-intervention group and the second group of Anakinra with a dose of 100 mg subcutaneously every 6 hours to 5 days	Within 48 hours, the oxygen demand to maintain Sato2 > 90% is reduced or unchanged, 25% reduction of ferritin, D-dimer, LDH, CRP, discharge from the hospital without the need for a ventilator	March 2021 [79]
2020	Bart N. Lambrecht	A Prospective, Randomized, Factorial Design, open-label Interventional Study	0n 342 patients: Group 1= Usual Care Group 2=anakinra SC 100 mg for 28 days or until hospital discharge Group 3= Siltuximab will be given via single IV infusion at a dose of 11 mg/kg Group 4= Anakinra + Siltuximab Group 5= Tocilizumab will be given via single IV infusion at a dose of 8 mg/kg with a maximum infusion of 800 mg/injection Group 6= Anakinra + Tocilizumab	Improve at least two of the following six: mortality, ventilator or ECMO dependence, supplemental oxygen requirement, no supplemental oxygen requirement, discharge, etc.	Ongoing december 2020 [80]
2020	Safia Barber	Randomized Interventional Open Label study	For 5 patients: 1-Subcutaneous Arm: 100mg anakinra, there is a minimum 8 hours and maximum 16 hours between administrations. 2-Intravenous Arm: 100mg anakinra in 100mL 0.9% NaCl will be administered intravenously four times a day every 6 hours	1-Plasma IL-6 levels from Day 1 to Day 7 following administration of SC anakinra in patients with SARS-CoV-2 2-Plasma markers including IL-6,CRP,IL1,2,33, CXCL9, HMBG-1 from Day 1 to Day 14 in all participants	Suspended (Lack of patients in the trial population from which to recruit and lack of funding) [81]

				3-IMP related severe laboratory abnormalities in 2 weeks	
2020	Fundacion Miguel Servet	A phase 2/3, randomized, open label, parallel group, 2-arm, multicenter study investigating the efficacy and safety of intravenous administration	On 180 patients:1- Standard of care plus Anakinra (100mg) administered as 4-times daily i.v. infusions for a maximun of 15 days 2- No Intervention: Control Arm	Treatment success, defined as number of patients not requiring mechanical ventilation by Day 15. Number of patients not requiring mechanical ventilation Time to mechanical ventilation And oxygen saturation normalization. Stay in ICU and hospitalization	Ongoing [82]
2020	Jonas Sundén-Cullberg,	A Single-center, Randomized, Open-label Study	On 120 patient: Standard-of-care Treatment (SOC) Anakinra 100 mg iv every 6 hours] for 7 days Tocilizumab: 8mg/kg for a single infusion iv up to max 800 mg. If no clinical response is obtained, another dose of 8mg/kg may be administered after earliest 2 days SOC	-in Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care -in not hospitalized, limitation on activities and/or requiring home oxygen -Number of Days on mechanical ventilation and supplemental oxygen use 4-mortality	February 2021 [83]
2020	Swedish Orphan Biovitrum,	phase II double-blind, placebo-controlled, multicentered trial	anakinra IV (N=50) 4 times a day for 7 days. The investigator will follow up with patients for up to 60 days. normal saline IV (N=50] 4 times a day for 7 days,follow up 60 days	-Number of subjects who need mechanical ventilation - 28-day and 60-day mortality - The number of days of hospitalization - Patient Mechanical Ventilation	Not yet recruiting [84]
2020	Toulon La Seyne sur Mer	Open Label, Randomized, Interventional	On 54 patients: - Experimental: Anakinra +/- Ruxolitinib :Stage 2b or 3 : Anakinra 300 mg IV ,Overcome stage 3 : Anakinra 300 mg IV and Ruxolitinib 5 mg x 2 -SOC	- Biological criteria: CRP: decrease > 50% Ferritinemia: decrease > 1/3 Serum creatinine: decrease > 1/3 AST/ALT: decrease > 50% Eosinophils > 50 /mm3 Lymphocytes > 1000 /mm3	Not yet recruiting [74]
2020	Groupe Hospitalier Paris Saint Joseph	Observational Retrospective cohort study	126 patient Under Treatment With Anakinra	Evaluation of the netosis process at day 1 and 3. Link between this marker (DNA-MPO)	Not yet recruiting [85]

				and the clinical course of patients	
2020	Guy's and St Thomas' NHS Foundation Trust	Observational, Retrospective, Case-Control study	On 50 patient: Angiotensin II and Angiotensin II control Anakinra and Anakinra control	Proportions of patients with mean arterial pressure ≥ 65 mmHg or an increase of mean arterial pressure ≥10 mmHg at 3 hours, Noradrenaline dose, SOFA score, RRT-free days, PaO2/FiO2 ratio, Change in serum C-reactive protein and serum ferritin	Recruiting [86]
2020	Anna Cruceta, Fundacion Clinic per a la	Multicenter open label randomized controlled clinical trial	On 116 patients: Group 1=Plasma exchange + Anakinra 200mg/ 12h SBC first day, 200mg / 24h SBC two more days + Standard medical treatment Group 2= Standard medical treatment+anakinra	Number of exitus at 28 days after plasma exchange	On going [87]
2020	Memorial Sloan Kettering Cancer Center	A Phase II Non-Randomized open label interventional Study	On 90 patients:Arm 1 (CART Cell Group): Cohort 1 Patients will receive anakinra 100mg s.c. every 12 hours starting on day 2 for 10 days. Cohort 2 anakinra 100mg s.c. daily on day 0 of T cell infusion, for 7 days, Experimental: Arm 2 (COVID-19 Group) anakinra 100mg IV q6h for 7 days.	Arm 1 (CAR T Cell Group) Rate of Severe Neurotoxicities Arm 2 (COVID-19 Group) proportion of patients able to avoid death or mechanical ventilation	Octber 2022 [88]

Table 6- Scientific evidence of Pentoxifylline in sepsis (A), viral pneumonia (B), non-viral pneumonia (C), and COVID-19 (D)

Date	Authors	Type of study	Interventions	Outcomes	Results
A					
2000	Douglas J.KooB.A,P eterYooB. A	Spragu Dawley male rats	Intravenous administration of 50mg/kg infusion for 90 minutes	Measurement of inflammatory cytokines during sepsis, vascular response to ADM	Pentoxifylline inhibits the reduction of vascular ADM responses at the macro and microcirculation levels and in turn reduces the expression

					of TNF-α, IL-1β, and IL-6 during the delayed phase of sepsis [93]
2000	Richard J.Krysztopik FRCS	Male Wistar rats kidney	Intravenous administration of 25mg / kg	Renal vascular resistance and renal arachidonic acid production	Pentoxifylline reduces the production of arachidonic acid. However, it has a slight effect on renal vascular resistance [94]
1998	Karl-Hermann Staubach	Randomized, Double-blind, Placebo-Controlled	1 mg/kg of body weight per hour	multiple organ dysfunction scores Mortality, PaO2 / FIO2, Serum endotoxin levels, tumor necrosis factor α, and interleukin 6	Reduction of mortality and improvement of PaO2 / FIO2, improvement of organ function, no significant change of interleukin 6 and endotoxin [95]
2017	Şahin Hamilçıkan	cross-sectional observational	5 mg/kg/h for 6 hours	Neonatal morbidity and mortality and side effects	Decreased the level of CRP and HR. Besides increased blood pH, without side effects or significant effect on mortality [96]
B					
1993	Philippe Montravers	Pilot Study 6 patients	1-mg/kg bolus, followed by infusion of 1.5 mg/kg/h over 6 h	Hemodynamic changes and gas exchange of the lungs	Increase in heart rate without deterioration of gas exchange [97]
1995	Moriuchi, Hiroshi	Prospective trial contains 48 guinea pigs	5 or 20 mg/kg	PaO2, PaCO2, and pH and systolic blood pressure	Reduction of pulmonary vascular permeability and improvement of hypoxemia [98]
C					
2002	Michael J.Myers	In Vitro & In Vivo	Dose less than 25 mg / kg	The effect of the drug on inflammatory cytokines	Decreased band neutrophils, decreased in vitro inflammatory cytokines but no in vivo effect [99]
2011	Priscila Aikawa	mechanically ventilated 57 male Wistar rats	25 mg / kg	Lung mechanical changes, mesenteric blood flow, leukocyte-endothelial interactions, MAP changes	The inflammatory response to high VT with high PEEP [and excessive lung distance] decreases during mechanical ventilation [100]
D					
No study found					

Table 7- Scientific evidence of IVIG in sepsis (A), viral pneumonia (B), non-viral pneumonia (C), and COVID-19 (D)

Date	Authors	Type of study	Interventions	Outcomes	Results
A					
2015	Ishikura H, Nakamura Y, Kawano Y,	Research article	Evaluation of the effectiveness of IVIG on coagulation disorders and inflammatory factors caused by sepsis	Inflammatory and coagulation factors indicated a decrease in patients receiving the drug	This drug can be useful in this case

2015	Ohlsson A , Lacy JB.	Systematic Review	Review and analysis of studies on the Efficacy of IVIG in neonatal infections	Much of the critical reports in this review did not show much effect in reducing mortality and length of study	Routine administration is not recommended in infants
2013	Alejandria MM, Lansang MA, Dans LF,	Systematic Review	Review and analysis of studies on the Efficacy of IVIG in neonatal infections		Studies showing beneficial effects had a higher risk of error.
B					
2018	Hui DS, Lee N, Chan PK,	Review	Evaluation of the effects of several immunomodulatory drugs on severe influenza	Some medications, including systemic corticosteroids, were more likely to have harmful than beneficial effects. Some of them, such as macrolides, showed conflicting efficacy. Injected immunoglobulin had shown favorable effects.	Immunoglobulin can be helpful in this regard
2017	Morrison BJ, Roman JA, Luke TC,	Original article	Investigation of antibody-dependent NK cell degranulation assay as a marker in influenza pandemic to evaluate the cytotoxic effects of influenza-vaccinated transchromosomal bovine intravenous antibody-mediated immunoglobulin	Led to a decreased level of marker	
2016	Gokturk B, Pekcan S, Guner SN,	Original article; 37 children with the flu	Evaluation of the effectiveness of immunoglobulin in the period of the disease in retrospective children	It was effective in patients with immunodeficiency in mortality and prevention of hospitalization in the intensive care unit.	Intravenous immunoglobulin, in this case, especially in children with immunodeficiency, can be considered as an adjunctive therapy.
C					
2015	Tagami T, Matsui H, Fushimi K,	Original article; 8264 patients out of 1014 hospitals	Patients under ventilator with ventilator-induced pneumonia with septic shock were divided into two groups receiving and not receiving IVIG	Showed no effects on mortality	No effect
2015	Wang CH, Chan ED, Perng CL,	Case study	A patient with a history of Good's Immune Deficiency Syndrome, who repeatedly had a respiratory infection, was prescribed periodic immunoglobulin.	The incidence of infection had a significant decreased	It is useful in preventing recurrent respiratory infections in patients with immunoglobulin deficiency.
2006	Pourpak Z, Aghamoham madi A,	26 children with Common variable	Administration of injectable immunoglobulin and its	The annual incidence of pneumonia decreased from 80% to 35%, and	Significant effects

	Sedighipour L,	immunodeficiency (CVID)	role in reducing the incidence of respiratory infections	the hospitalization rate from 88% to 46%	
D					
2020	Shi H, Zhou C, He P, Huang S,	Case study	Plasma replacement and subsequent intravenous immunoglobulin administration in a patient with severe covid19	Clinical and radiological improvements	No need for ventilation
2020	Cao W, Liu X, Bai T,	Case series	Intravenous immunoglobulin administration in three patients with severe disease	Accelerating in recovery speed	Effective [47].

Table 8- Scientific evidence of Ivermectin in sepsis (A), viral pneumonia (B), non-viral pneumonia (C), and COVID-19 (D)

Date	Authors	Type of study	Interventions	Outcomes	Results
A					
2015	Florent Montini	Case report	Patient with septic shock due to corticosteroid-induced strongyloids treated with ivermectin	The patient died.	It was not prescribed for the treatment of sepsis. It is supposed to be prescribed for the treatment of estrogeloids, and the patient eventually died of encephalopathy due to the disease [16].
B					
1991	John Randall Thomps	Case report	Administration of ivermectin in the treatment of pulmonary estrogeloids	ARDS has no application in treatment. This study investigates the incidence of ARDS following ivermectin use.	The patient has ARDS.
C					
No evidence has been found					
D					
2020	Leon Caly	In Vitro study	Prescription of ivermectin	After 48 hours, more than 5000 times viral load decreased but after 72 no further reduction in hours was observed!	Ivermectin can dramatically reduce the viral load of the coronavirus in cell culture media.

Table 9- Scientific evidence of Selenium in sepsis (A), viral pneumonia (B), non-viral pneumonia (C), and COVID-19 (D)

Date	Authors	Type of study	Interventions	Outcomes	Results
A					
2015	Legese Chelkeba	Randomized clinical trial	Administration of selenium in treating severe sepsis	The incidence of VAP in ICU patients reduced.	No changes in mortality improvement [119].
2016	Rhodes, Andrew	Meta-analysis	Administration of selenium in treatment sepsis	It's an effect on mortality, incidence of infections Pulmonary and length of stay in ICU	No beneficial effect in any of the mentioned cases [120].

B					
No study available					
C					
2019	Mahmoodpoor	Clinical trial	Intravenous selenium administration	Evaluating the effect of venous selenium on inflammatory factors and duration of hospitalization of patients in ICU	No effect on improving the patient's shelf life and even overall survival [121].
D					
2020	Amin Gasmi	Review article	-	-	Suggests that selenium can help improve the immune system against viral infections [122].

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