**Description of the Condition:**

COVID-19 is a highly contagious respiratory disease which has reached pandemic levels worldwide in 2020, and it is caused by the SARS-Cov-2 virus. The mechanism of transmission of this virus is from person to person, via droplets that are released by an infected person through sneezing, coughing or even during normal conversation (National Cancer Institute, 2020).

The transmission can also occurred when touching any kind of surface that has received an infected droplet and then touching one's eyes, mouth of nose if no sanitization through washing the hands or using alcohol hand sanitizer with a minimum of 70% of alcohol content.

Signs and Symptoms of COVID-19 commonly appear between 2 and 14 days after being exposed to the virus. These symptoms include troubled breathing, cough, fever, as well as headaches, muscle pain and chills. Many patients also report a loss of the sense of smell and taste.

Empirical evidence shows that COVID-19 tends to have more serious consequences among the older population, and although some patients are asymptomatic or present very mild symptoms, they can still spread the disease. Although some patients can recover quickly and easily, other patients such as the elderly and people with chronic conditions may be at a much higher risk, and could develop life-threatening conditions such as pneumonia and general organ failure (National Cancer Institute, 2020).

SARS-Cov-2 may cause widespread infection and even possibly the destruction of lung cells, which in turn triggers a local response from the immunity system using different mechanisms such as the release of cytokines and adaptive T and B cell responses. Often times this response resolves the problems but other times a dysfunctional immune response is observed, which leads to the most severe complications observed in patients with COVID-19. The most common approach used to control the disease is the use of therapies that have the objective of inhibiting the viral infection as well as regulating any potential dysfunctional immune responses, as well as controlling the inflammatory response observed among patients (Tay, Poh, Rénia, MacAry & Ng, 2020).

**Description of the intervention :**

Although some patients may have COVID-19 and have no symptoms, a relatively percentage of patients will need some degree of hospital intervention, and in some cases some urgent care is needed. This hospital intervention serves as a controlled setting for keeping inflammation at bay and monitoring the evolution of the condition.

No effective vaccine or proven effective antiviral therapy has been approved as of yet. Still, most patients with medium to severe conditions will receive some sort of therapeutic antibody treatment. A commonly used antibody therapy is the monclonal therapy, which has been used commonly for other acute respiratory conditions (Shanmugaraj, Siriwattananon, Wangkanont & Phoolcharoen, 2020).

**How the intervention might work :**

While an effective vaccine or treatment is not yet approved, the intervention consists of using some type of monoclonal therapy and to keep inflammation under control. The selection of the therapy is associated to the specific patient, due to the potential existence of harmful side effects.

**Pico question being explored:**

 Are any of the existing antiviral treatments and antibody therapies effective at treating COVID-19 and safe for its use in humans?

**Methods**

|  |  |
| --- | --- |
| **Types of studies included** | The studies included in this analysis are all randomised control trials (RCT). |
| **Types of participants** | The analysis is restricted only adults, who are older than 18 years. |
| **Types of interventions (include intervention and control)** | * Standard of Care ( control group) * Antiviral or anti inflammatory drug ( intervention group) |
| **Types of outcome measures (i.e. Visual analogue 10-point scale)** | Primary outcome  Evaluation of how effective the treatment is compared to the control group |

## **Inclusion Criteria**

* Only Randomised controlled trials were included.
* Studied that had maximum comparison of two methods.
* Patients with COVID-19 with no previous terminal diseases or asymptomatic subjects with exposure to a confirmed COVID-19 case.
* Patients older than 18 years of age.
* Only studies no older than 2 years were used.
* Only cases were intervention was needed were included
* Only articles with literature in English were included.

## **Exclusion Criteria**

 For this review any study that was a reviews or a letters was excluded. Also, the following elements were excluded as well.

* Multiple methods
* Studies that included subjects under the age of 18
* Studies that were more than 2 years old.
* Articles that were of poor evidence and/poor methodological approach.
* Literature written in a language other than English.

|  |  |  |
| --- | --- | --- |
| **Name of database** | **Detailed search terms / strategy** | **Number of results obtained** |
| **Pubmed** | Covid 19  "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR "covid 19"[All Fields] OR "sars cov 2"[All Fields] OR (("coronavirus"[All Fields] OR "cov"[All Fields])  Covid 19 randomised control trial  "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR "covid 19"[All Fields] OR "sars cov 2"[All Fields] OR (("coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])  covid 19 intervention, full text, from 2019 - 2020  ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR "covid 19"[All Fields] OR "sars cov 2"[All Fields] OR (("coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND ("intervention s"[All Fields] OR "interventions"[All Fields] OR "interventive"[All Fields] OR "methods"[MeSH Terms] OR "methods"[All Fields] OR "intervention"[All Fields] OR "interventional"[All Fields])  covid 19 monoclone  "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR "covid 19"[All Fields] OR "sars cov 2"[All Fields] OR (("coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND ("monoclonal"[All Fields] OR "monoclonality"[All Fields] OR "monoclonally"[All Fields] OR "monoclonals"[All Fields] OR "monoclone"[All Fields] OR "monoclones"[All Fields])  Covid 19 antiviral therapy  ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR "covid 19"[All Fields] OR "sars cov 2"[All Fields] OR (("coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND ("antivir ther"[Journal] OR ("antiviral"[All Fields] AND "therapy"[All Fields]) OR "antiviral therapy"[All Fields]) | * 55860 * 50 * 44 * 1 * 11 |

## PRISMA Flow Diagram (edited version)

Full-text articles assessed for eligibility  
(n = 10)

Records screened  
(n = 40 )

Records after duplicates removed  
(n = 107 )

Additional records identified through other sources  
(n = 1 )

## Identification

## Eligibility

## Included

Records identified through database searching  
(n = 106 )

## Screening

Records excluded, for being reviews or letters  
(n = 67 )

Full-text articles excluded, based on meeting any of the other exclusion criteria  
(n = 30)

Studies included in quantitative synthesis  
(n = 4)

## **Discussion – Critical appraisal and interpretation**

The COVID-19 pandemic has taken the world by storm, causing havoc in all aspects of life. Confinement, dramatic economic slowdown, COVID-19 came to put an halt to all of the world's daily common activities: commerce, schools, entertainment, sports and essentially the way humans relate. Covid-19 proved to be extremely easy to spread and it showed rapid exponential growth, until epidemiological measures were taken.

A race for the production of a vaccine and an effective treatment has been on since the beginning of the pandemic, in China, while the emergency rooms in the world keep being saturated with Covid-19 patients (although the pressure of emergency rooms beds due to Covid has somewhat decreased in many countries, thanks to the measures of social distancing taken).

Results from the database searched were analysed were screened and the four ones that best represent the topic being study and those which had potential to provide sufficient information to answer the PICO questions were selected. Due to the recent nature of this phenomenon, only articles from years 2019 and 2020 were considered, because that short span is the time period of the pandemic.

The study of (Cao, Wang, Wen, et al, 2020) was published on March 18, 2020. The paper describes the results of a randomized controlled trials of Lopinavir-Ritonavir in adults who were hospitalized, who were presenting severe Covid-19 symptoms. For a total of 199 patients, randomization was conducted to assign 99 to the lopinavir–ritonavi, and 100 to the standard care group. Notice that the lopinavir–ritonavi group had this treatment (400 mg and 100 mg respectively) plus the standard care. The output to be measured was the time to clinical improvement, from the time of the randomization. Results did not show significant difference between the treatment and control group. Indeed, the hazard ratio for clinical improvement was 1.31, with a 95% confidence interval of (0.95, 1.80). Since 1 is contained by the 95% interval, then there is not a significant difference between the Lopinavir-Ritonavir group and the standard care group.

The study of (Plaze, Attali, Petit, et al., 2020) is based on a clinical observation from Sainte-Anne Hospital, Paris, France, a hospital specialized in Psychiatric and Neuroscience, with a very large prevalence of patients using psychotropic drugs. It has been observed in recent months that there is a clear lower incidence of COVID-19 forms among patients than among staff of clinic. This suggests that psychotropic drugs may be some sort of prophylactic effect against the SARS-CoV-2 virus, which leads to a lower incidence of COVID-19 symptoms among patients. Indeed, this hypotheses is supported by the fact that Chlorpromazine (one of the active ingredients of many psychotropic drugs) has been shown to have certain antiviral effects (diverse studies have shown it provides a degree of inhibition of viral replication in an in-vitro setting). A RCT was proposed to repurpose Chlorpromazine (CPZ) as a potential Covid-19 therapy, due to its good tolerance profile and it antiviral properties . For the RCT, subjects are randomized to the CPZ + standard care group, or to the standard care group. The output to measure and compare between the treatment and standard groups is degree of clinical improvement and level of decrease in the biological markers of viral attack by SARS-CoV-2 (Plaze, Attali, Petit, et al, 2020). Overall, the design includes a randomized, single-blinded, controlled trial. This trial is still being conducted.

This study (Miller, Bruen, Schnaus, et al. 2020) includes a total of 30 adult patients with severe or critical Covid-19 pneumonia. The purpose of the study is to assess the results of a randomised controlled trial to determine whether or not calcium release-activated calcium (CRAC) channel inhibitors have positive stabilizing effects on a patient's pulmonary endothelium and to contribute to reduce inflammation caused by the Covid related pneumonia. A 2:1 randomisation was used to assign patients to three doses of Auxora (plus standard care), and to the standard care alone. Auxora is a new CRAC that is administered intravenously to COVID-19 patients exhibiting severe pneumonia cases. When comparing Auxora with standard care, it was found that there was a similar proportion of adverse events (with 75% and 80% respectively), but when comparing serious adverse events, Auxora showed significantly lower rates (30% versus 50% for standard care alone). Although when comparing time to recovery from pneumonia, Auxora showed a median of 5 days versus 12 days for standard care, the recovery ratio with 1.87, with a 95% CI of (0.72, 4.89), which shows no significant difference (because the 95% confidence interval includes the value of 1). Now, when comparing results in the 8-point ordinal scale that indicates condition, the Auxora group showed significantly improved scores.

Finally, the study of (Boulware, Pullen, Bangdiwala, et al., 2020) was carried across United States and Canada, to test the effects of hydroxychloroquine as SARS-CoV-2 post-exposure prophylaxis. A 1:1 randomized controlled trial, that was double-blind as well as placebo-controlled. This study used 821 asymptomatic adult participants who were known to have had household or occupational exposure to a confirmed Covid-19 case, within a distance of 6 feet. Recruitment occurred mainly via social media out, on top of the normal media platforms (newspapers, etc). Out of the 821 participants, 414 were randomly assigned to the hydroxychloroquine treatment, and 407 participants we assigned to the placebo group. Overall, 107 out of the 821 participants developed Covid-19 symptoms within 2 weeks of randomisation. It was found that the incidence rate of Covid-19 did not different significantly between the hydroxychloroquine group and the placebo group, *p = .35 > .05*).

Analysing and comparing these four studies, it can be observed that none of the existing antibody therapies that were analysed had much success at proving that they were effective at treating Covid-19. Only the CRAC channel inhibitors study showed significant improvement for the treatment, but only in one of many outcomes. Possibly the small sample

**Randomisation**

Randomisation is one of the key elements to reduce biases and allows to attribute any potential effects (if any) to the treatment and not to any lurking variable. Randomisation serves as a way of balancing the different characteristics of both groups in a controlled trial. In the case of this analysis, all four studies had randomisation.

### **Concealment**

Only the Hydroxychloroquine therapy study and the Lopinavir-Ritonavir treatment used concealment. The other two studies did not report concealment, as far as it can be read in the corresponding papers.

### **Baseline similarity**

All four studies used some level of baseline similarities. The first study used participants that were already exhibiting COVID-19 symptoms and were undertaking hospital treatment. The second study used participants who also were psychiatric patients. For the third study, CRAC channel inhibitors were to used among COVID-19 already affected by a severe pneumonia, and for the fourth study, the study used participants that have known to be exposed to a confirmed Covid-19 case.

### **Blinding**

Blinding means that the subjects did not know what treatment they were assigned to, which is known to eliminate certain potential biases. In this case only three of the four studies used blinding, as the lopinavir–ritonavir study did not use it, and also, the hydroxychloroquine study was double blinded.

**Completeness of reporting and follow-up :**

Both the Lopinavir–ritonavir study and the Hydroxychloroquine study had clear follow-up mechanism, and the Auxora had a kind of a follow-up procedure. All studies except for the CPZ therapy study showed completeness of reporting. Indeed, the Auxora study is still being undertaken, so it does not have a complete report that has been presented as of yet.

### **Intention-to-treat analysis (ITT) :**

Based on the analysis conducted on the papers that were review, all four studies were intention-to-treat analysis, except for the Auxora study.

### Summary of risk of bias

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Lopinavir–Ritonavir** | **CPZ** | **Auxora** | **Hydroxychloroquine** |
| **Randomisation** | + | + | + | + |
| **Concealment** | + | - | - | + |
| **Baseline similarity** | + | + | + | + |
| **Blinding** | - | + | + | + |
| **Follow-up** | + | - | + | + |
| **Intention-to-treat analysis** | + | - | + | + |

**Key**  **+** Low risk of bias **-** High risk of bias **?** Unclear risk of bias

## **Chance**

In all four studies that had results provided (all of them except for the CPZ, which was still being conducted), the sample difference between the therapy chosen and the standard of care was better explained by chance. Only for one possible outcome in the Auxora study positive significant differences were found between Auxora and the control .

## **Confounding**

The existence of confounding variables impedes the assignment of causality in a study. In this case, randomisation was present in all four studies and it is expected that randomised controlled nature of them minimizes/eliminates potential confounders, especially considering that all four studies had some degree of baseline similarity

## **Results**

None of the studies showed conclusive evidence that the treatment being studied was significantly better at treating the complications derived from Covid-19 than the standard or care being used. Only Auxora showed some degree of significance for one possible output, which was clinical improvement, as measured by a 8-point ordinal scale.

**External validity**

All four studies had a relatively low external validity because none of the studies selected their participants via a random sampling procedure. All of them were convenience samples from a specific location, except for the case of the that did recruitment though social media outreach as well as using other traditional media platforms, and the Auxora study that corresponded to an open clinical trial.

## **Limitations**

One of the biggest limitation of this study is that only four studies were used. In order to conduct a successful meta-analysis, probably more than 4 studies need to be analysed. Another limitation is that the COVID-19 events are very recent, and many of the largest randomised controlled trials are still being conducted, which mainly rules them out from the reporting of results (except for those who reported initial results or had some sorted of founded suspect of its efficacy). Something that could be considered as a limitation is the required formatting and maximum length for this paper that may not be conducive to get in depth into each of the studies.

# **Conclusion**

The main conclusion from the analysis that the use and repurpose of known antibody therapies or other anti-inflammatory agents may have only marginal effect, and no statistical significance was shown. Perhaps the most effective therapy found was the Auxora treatment, that showed some degree of significance for one possible output, which was clinical improvement, as measured by a 8-point ordinal scale. Perhaps the Auxora study required a larger sample size to increase its statistical power and show potentially existing effects that were not significant.

# **Audit**

I used large medical/scientific databases for the best potential sources for analysing my PICO question. Four studies were conducted and met the requirements of what was specified for my PICO question. This process has brought lots of experience and learning, which I will certainly be using in future research .

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# **Extension approval**:



