CÂMARA MUNICIPAL DE ARARAQUARA

INDICAÇÃO Nº 1754/2021

Dispõe sobre a realização de estudos junto ao Comitê de Contingência do Coronavírus, para que seja analisada a possibilidade de adoção pelo Município de Araraquara de protocolos de Intervenção Precoce para a Covid-19

Considerando o agravamento da situação pandêmica, com esgotamento iminente do sistema de saúde público e privado, apesar dos aportes de leitos já instalados.

Considerando a ausência de previsão concreta para que toda a população esteja imunizada através da vacinação, com projeções que superam um ano para a obtenção da imunidade coletiva por essa via.

Considerando que os mais recentes estudos médicos apontam diversas Drogas Reposicionadas (medicamentos já aprovados que apresentam efeitos desejados para alguma outra condição, além da inicialmente prevista) têm se mostrado eficientes no tratamento da doença.

Considerando estudos sobre exames clínicos que podem ajudar a avaliar o potencial de agravamento pela doença, possibilitando maiores chances de sucesso na prevenção de um desfecho mais grave.

Considerando os relatos de cidades e estados que adotaram as medidas para intervenção precoce na COVID-19 com bons resultados e diminuição da carga sobre os sistemas de saúde.

Considerando Carta enviada pelo Department of Pulmonary, Critical care and Sleep Medicine All India Institute of Medical Sciences (AIIMS) de New Delhi, India, e publicada em 19 de abril de 2021 no periódico Advances in Respiratory Medicine, em que os autores destacam que algumas medicações com efeito antiviral, devem ser administradas o quanto antes, na fase de replicação viral, para que produzam os efeitos clínicos desejados.

Considerando a introdução de número 32 da declaração de Helsinque, que dispõe:

"32. No tratamento de um paciente, quando métodos profiláticos, diagnósticos e terapêuticos comprovados não existirem ou forem ineficazes, o médico com o consentimento informado do paciente, deverá ser livre para utilizar medidas profiláticas, diagnósticas e terapêuticas não comprovadas ou inovadoras, se, em seu julgamento, estas oferecerem a esperança de salvar a vida, restabelecer a saúde e aliviar o sofrimento [...]"

Considerando que a relação médico-paciente deve ser aberta e de confiança, e que ambas as partes devem estar de acordo com o tratamento.

CÂMARA MUNICIPAL DE ARARAQUARA

Indico ao Senhor Prefeito Municipal, a necessidade de entrar em entendimento com o setor competente, para que seja analisada a possibilidade de adoção pelo Município de Araraquara, de protocolos de Intervenção Precoce para a Covid-19, buscando iniciar o tratamento com as medidas disponíveis, o mais rápido possível, visando reduzir o número de pacientes que progridem para fases mais graves da doença.

Sala de Sessões “Plínio de Carvalho”, 23 de abril de 2021.

LINEU CARLOS DE ASSIS

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Timing of anti-viral therapy in COVID-19: key to success

To the Editor

Since the onset of the current coronavirus disease 2019 (COVID-19) pandemic, there have been attempts to identify medications for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As there have been no antivirals available for the treatment of this disease, repurposing of drugs has started and various classes of drugs are being tried. Some of the candidate drugs include remdesivir (recently approved by Food and Drug Administration), ivermectin, and interferon β-1b. There is emerging evidence regarding the efficacy of these drugs; however, no definite conclusions are available. A recent study by Shi et al. reported results about the efficacy of antiviral therapies in patients with coronavirus disease 2019 (COVID-19) in China and found no significant impact on improvement [1]. Similar results were reported in a recently published randomized controlled trial (RCT) about the use of interferon β-1a in patients with severe coronavirus disease 2019 (COVID-19) and found no significant difference in the time to clinical response in the experimental arm as compared to the control arm [2]. However, there are a few aspects regarding the timing of the initiation of antivirals which require discussion. In both of these studies, the authors have not reported the timing of initiation of antiviral therapy, which is crucial to patient outcomes. We all understand that the host's immune response plays a crucial role in the prevention as well as containment of any infection; however, when an antiviral agent is sought for patients with disease or for patients who are at risk of severe disease, it should be done in a timely manner [3]. COVID-19 has an initial virological phase which leads the patients into a host inflammatory response phase where they tend to develop a cytokine storm [4]. Based on the report by Wölfel et al. [5] which states that the virus cannot be isolated beyond day 8, it is also likely that antivirals may not be efficacious beyond this time. Thus, it would be best to use antiviral medications relatively early in the illness and anti-inflammatory drugs later. Using antiviral drugs later in the disease course may add to the adverse effects rather than yielding clinical benefits. In the study by Effat *et al.* [2], the mean (standard deviation, SD) duration of starting treatment in the interferon arm was 11.7 (5.71) days. This late initiation of antiviral therapy may be the reason behind no difference in time to clinical response, which was the primary endpoint. However, there was a difference with respect to the percentage of patients being discharged by day 14, favouring the interferon group. Such a result may be owed to the properties of interferon, which endorses more than just an antiviral mechanism (i.e. decreasing vascular leakage and inflammatory biomarkers like IL-6) [6, 7]. They also reported that starting interferon treatment early in the course of the disease showed mortality benefit (odds ratio, 13.5; 95% confidence interval 1.5 to 118) which further emphasizes the importance of early initiation of therapy [2].

Table 1 enlists some noteworthy trials in COVID-19 regarding the use of antiviral medications and timing of treatment initiation for the outcome reported. Remdesivir showed no benefit when treatment was started after ten days of illness. Instead, it was associated with higher

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Table 1. List of studies with use of antivirals and outcomes reported

Author	Drug	Number of patients	Study design	Day of initiation of treatment from symptom onset	Outcome in comparison to control or standard of care
Wang *et al.* [8]	Remdesivir	237	RCT	11	No benefit Patients started on treatment within 10 days had decreased mortality (11%) vs patients having treatment started after 10 days (14%)
Spinner *et al*. [9]	Remdesivir	584	RCT	8	Higher odds of a better clinical outcome with those randomized to standard care (OR 1.65; 95% CI 1.09–2.48; p = 0.02)
Beigel *et al*. [10]	Remdesivir	1063	RCT	9	The remdesivir group had a shorter time to recovery (median, 11 days, as compared with 15 days; rate ratio for recovery, 1.32; 95% CI 1.12 to 1.55; p < 0.001)
Cao *et al*. [11]	Lopinavir-ritonavir	199	RCT	13	No benefit
Hung *et al.* [12]	Interferon beta-1b, lopinavir–ritonavir, and ribavirin	127	RCT	5	Significantly shorter median time from start of study treatment to negative nasopharyngeal swab in treatment group (7 days [IQR 5–11]) than the control group (12 days [8–15]; HR 4·37 [95% CI 1.86–10.24], p = 0.0010) Clinical improvement was better in the combination group
Zhou *et al.* [7]	Interferon alpha	77	Non randomized	8	Significant accelerated viral clearance (p = 0.002), and reduced circulating levels of IL-6 ($p = 5.7 \times 10^{-10}$) and CRP (p = 0.002)

CI — confidence interval; CRP — C-reactive protein; HR — hazard ratio; Il-6 — interleukine 6; IQR — interquartile range; OR — odds ratio; RCT — randomized clinical trial

mortality than the control arm [8]. However, when used within ten days, it tended to show benefits in other trials [9, 10]. Most other trials tend to start antivirals late and have reported no clinical benefits with their use.

This brings us to essential questions of whether these drugs, if initiated early, can lead to clinical benefits, and whether or not these negative trials are giving us a false portrayal of their efficacy. Based on the available evidence, we suggest that antivirals should be initiated within the first ten days of illness, especially in research settings. In this COVID era, with the limited therapeutic options available to physicians, the appropriate and timely use of therapy can help save lives.

Conflict of interest

None declared.

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TRADUÇÃO

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Momento da terapia antiviral em COVID-19: a chave para o sucesso

Para o editor

Desde o início do coronavírus atual

pandemia de doença 2019 (COVID-19), houve

tentativas de identificar medicamentos para graves

síndrome respiratória aguda coronavírus 2 (SARSCoV-2). Como não há antivirais disponíveis

para o tratamento desta doença, reaproveitamento de

drogas começou e várias classes de drogas

estão sendo julgados. Algumas das drogas candidatas

incluem remdesivir (recentemente aprovado pela Food

and Drug Administration), ivermectina e interferon b-1b. Há evidências emergentes sobre

a eficácia dessas drogas; no entanto, nenhum

conclusões estão disponíveis. Um estudo recente de

Shi et al. resultados relatados sobre a eficácia de

terapias antivirais em pacientes com coronavírus

doença 2019 (COVID-19) na China e não encontrou

impacto significativo na melhoria [1]. Semelhante

os resultados foram relatados em um publicado recentemente

ensaio clínico randomizado (RCT) sobre o

uso de interferon b-1a em pacientes com graves

doença coronavírus 2019 (COVID-19) e encontrado

nenhuma diferença significativa no tempo para clínica

resposta no braço experimental em comparação

para o braço de controle [2]. No entanto, existem alguns

aspectos relativos ao momento do início do

antivirais que requerem discussão. Em ambos

esses estudos, os autores não relataram o

momento de início da terapia antiviral, que é

crucial para os resultados do paciente. Todos nós entendemos

que a resposta imunológica do hospedeiro desempenha um papel crucial

papel na prevenção, bem como contenção de

qualquer infecção; no entanto, quando um agente antiviral

é procurado para pacientes com doença ou para pacientes

que estão em risco de doença grave, isso deve ser feito

em tempo hábil [3]. COVID-19 tem uma inicial

fase virológica que leva os pacientes a

uma fase de resposta inflamatória do hospedeiro onde eles

tendem a desenvolver uma tempestade de citocinas [4]. Com base no

relatório de Wölfel et al. [5] que afirma que o vírus não pode ser isolado além do dia 8, também é provável que os antivirais não sejam eficazes além do

desta vez. Assim, seria melhor usar antivirais

medicamentos relativamente no início da doença e antiinflamatórios posteriormente. Uso de medicamentos antivirais

mais tarde no curso da doença pode adicionar ao adverso

efeitos ao invés de produzir benefícios clínicos. Dentro

o estudo de Effat et al. [2], a média (padrão

desvio, SD) duração do início do tratamento em

o braço do interferão foi de 11,7 (5,71) dias. Tão tarde

o início da terapia antiviral pode ser a razão

atrás de nenhuma diferença no tempo para a resposta clínica,
qual foi o endpoint primário. No entanto, há
foi uma diferença em relação à porcentagem de
pacientes recebendo alta no dia 14, favorecendo o
grupo interferon. Esse resultado pode ser devido a
as propriedades do interferon, que endossa mais
do que apenas um mecanismo antiviral (ou seja, diminuindo
vazamento vascular e biomarcadores inflamatórios
como IL-6) [6, 7]. Eles também relataram que começar
tratamento com interferon no início do curso do
a doença mostrou benefício na mortalidade (odds ratio, 13,5;
Intervalo de confiança de 95% 1,5 a 118) que além disso
enfatiza a importância do início precoce de
terapia [2].

A Tabela 1 lista alguns ensaios notáveis em
COVID-19 em relação ao uso de medicamentos antivirais e tempo de início do tratamento para
o resultado relatado. Remdesivir não mostrou
benefício quando o tratamento foi iniciado após dez dias
de doença.

HCQ is effective for COVID-19 when used early: real-time meta analysis of 235 studies

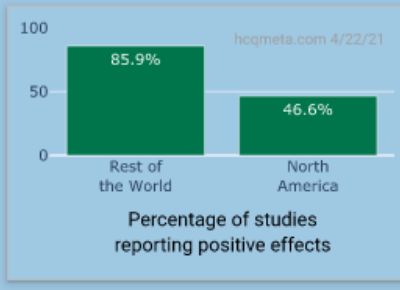
Covid Analysis, Oct 20, 2020 (Version 96, April 20, 2021)

@CovidAnalysis Share Tweet PDF Studies

- HCQ is effective for COVID-19. The probability that an ineffective treatment generated results as positive as the 235 studies to date is estimated to be 1 in 6 quadrillion (p = 0.00000000000000018).
- Early treatment is most successful, with 100% of 29 studies reporting a positive effect (13 statistically significant in isolation) and an estimated reduction of 65% in the effect measured (death, hospitalization, etc.) using a random effects meta-analysis, RR 0.35 [0.25-0.50].
- 92% of Randomized Controlled Trials (RCTs) for early, PrEP, or PEP treatment report positive effects, the probability of this happening for an ineffective treatment is 0.0017.
- There is evidence of bias towards publishing negative results. 88% of prospective studies report positive effects, and only 73% of retrospective studies do.
- Studies from North America are 3.8 times more likely to report negative results than studies from the rest of the world combined, p = 0.0000000015.
- All data to reproduce this paper and the sources are in the appendix.

Total	235 studies	3,740 authors	359,862 patients
Positive effects	179 studies	2,743 authors	251,797 patients

Early treatment	65% improvement	RR 0.35 [0.25-0.50]
Late treatment	23% improvement	RR 0.77 [0.71-0.83]



Fonte: https://hcqmeta.com/

Ivermectin for COVID-19: real-time meta analysis of 52 studies

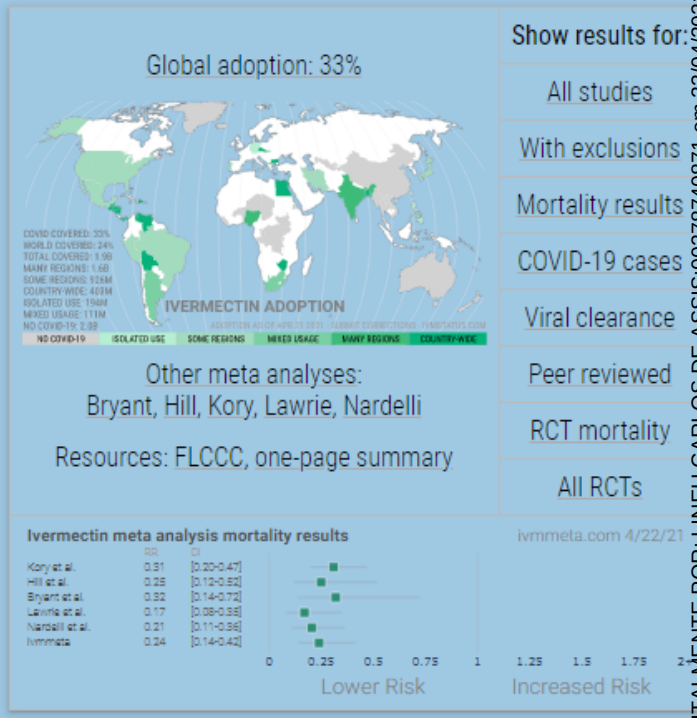
Covid Analysis, Nov 26, 2020 (Version 61, Apr 18, 2021)

@CovidAnalysis Share Tweet PDF Studies Adoption

- 98% of the 52 studies to date report positive effects (25 statistically significant in isolation). Random effects meta-analysis for early treatment and pooled effects shows an 81% reduction, RR 0.19 [0.09-0.38], and prophylactic use shows 85% improvement, RR 0.15 [0.09-0.25]. Mortality results show 76% lower mortality, RR 0.24 [0.14-0.42] for all treatment delays, and 84% lower, RR 0.16 [0.04-0.63] for early treatment.
- 96% of the 27 Randomized Controlled Trials (RCTs) report positive effects, with an estimated 65% improvement, RR 0.35 [0.24-0.52].
- The probability that an ineffective treatment generated results as positive as the 52 studies to date is estimated to be 1 in 85 trillion (p = 0.000000000000012).
- All data to reproduce this paper and the sources are in the appendix. See *[Bryant, Hill, Kory, Lawrie, Nardelli]* for other meta analyses, all with similar results confirming effectiveness.

	Improvement	Studies	Authors	Patients
Early treatment	**81%** [62-91%]	18	175	1,942
Late treatment	**43%** [27-56%]	20	143	6,831
Prophylaxis	**85%** [75-91%]	14	108	8,789
Mortality	**76%** [58-86%]	18	155	7,267
RCTs only	**65%** [48-76%]	27	246	4,854
All studies	**72%** [64-78%]	**52**	**426**	**17,562**

WHO ivermectin approval status				
Indication	Studies	Patients	Effect size	Status
Scabies	6	613	35% [22-46%]	Approved
COVID-19	52	17,562	72% [64-78%]	Pending



Completo em: https://ivmmeta.com/