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Pharmacological therapy with azithromycin, hydroxychloroquine and ivermectin increased gastrointestinal side effects in a population in northeast Brazil.

Terapia farmacológica com azitromicina, hidroxicloroquina e ivermectina aumentou os efeitos colaterais gastrointestinais em uma população do Nordeste do Brasil.

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RESUMO

O surgimento da pandemia de COVID-19 impulsionou o consumo de combinações de medicamentos como o Kit COVID Brasileiro composto por azitromicina, hidroxicloroquina e ivermectina. Os efeitos dessas drogas no trato gastrointestinal permanecem incertos, motivando este estudo. Foi realizado um estudo epidemiológico transversal analítico e quantitativo em pacientes (n=124) da macrorregião costeira do estado do Piauí, Brasil, com diagnóstico confirmado de COVID-19, no período de fevereiro e agosto de 2021. Os sintomas gastrointestinais foram avaliados por meio do questionário Gastrointestinal Symptom Rating Scale (GSRS). A renda mostrou-se um fator na escolha do tratamento. Entre os 15 domínios do GSRS, os escores de dor abdominal, dor de fome, diarreia e urgência defecar foram significativamente maiores ($p<0,05$) no grupo de tratamento do que no grupo não tratado. Em relação às síndromes avaliadas, apenas as síndromes diarreicas apresentaram diferença significativa de frequência entre os grupos. O uso de medicamentos do Kit COVID associado ao desenvolvimento de sintomas gastrointestinais destaca a importância de considerar os potenciais efeitos adversos dos medicamentos em pacientes diagnosticados com COVID-19.

Palavras-chave: Covid-19; Diarréia, Prescrição de medicamentos; Gastroenterologia.

ABSTRACT

The emergence of the COVID-19 pandemic has fuelled the consumption of drug combinations such as the Brazilian COVID Kit composed of azithromycin, hydroxychloroquine and ivermectin. The effects of these drugs on the gastrointestinal tract remain uncertain, prompting this study. An analytical and quantitative cross-sectional epidemiological study was conducted in patients (n=124) of the coastal macroregion of the state of Piauí, Brazil, with a confirmed diagnosis of COVID-19. Interviews were conducted between February and August 2021. GI symptoms were assessed using the Gastrointestinal Symptom Rating Scale (GSRS) questionnaire. Income proved to be a factor for treatment choice. Among the 15 GSRS domains, the scores for abdominal pain, hunger pain, diarrhoea and defecation urgency were significantly higher ($p<0,05$) in the treatment group than in the untreated group. Regarding the evaluated syndromes, only diarrhoea syndromes exhibited a significant difference in frequency between the groups. The use of COVID Kit drugs was associated with the development of gastrointestinal symptoms, mostly diarrhoea. This sheds light on, the importance of being careful with gastrointestinal adverse effects of medications in patients with COVID-19.

Keywords: Covid-19; Diarrhoea; Drug prescriptions; Gastroenterology.

INTRODUÇÃO

COVID-19 is a respiratory disease caused by a species of coronavirus known as severe acute respiratory syndrome virus 2 (SARS-CoV-2). The disease quickly spread to all continents, leading to a pandemic (WHO, 2019), and the absence of adequate therapy has become a major challenge for treating the infection (VELAVAN, MEYE, 2020; WU *et al.*, 2020). Thus, the identification of therapeutic and preventive tools has become a major objective of global science (CIOTTI *et al.*, 2020).

Because of the uncertainty associated with the disease, many drugs have been applied in the treatment of COVID-19 despite a lack of proven scientific effectiveness. Azithromycin, hydroxychloroquine and ivermectin are examples of drugs that have been highly disseminated in Brazil as therapeutic solutions in patients infected with SARS-CoV-2 based on guidelines from the Ministry of Health (BRASIL, 2020; FONSECA *et al.*, 2020). Some in vitro studies demonstrated that these drugs can inhibit the replication and intranuclear transport of viral proteins (ANDREANI *et al.*, 2020; KING *et al.*, 2020).

Although these drugs have demonstrated antiviral effects in vitro, their use in vivo has many limitations. In addition, the possibility of adverse effects exists, especially with indiscriminate use. The excessive use of these drugs has been demonstrated to cause heart failure and kidney and liver problems (GÉRARD *et al.*, 2020; WONG *et al.*, 2021). When used individually, these drugs cause changes in the morphology of organs in the gastrointestinal tract, as well as dyspepsia, diarrhoea, abdominal pain and vomiting (LOFGREN *et al.*, 2020; SRINIVASA, TOSOUNIDOU, GORDON, 2017).

Thus, the consumption of medicines for the treatment of COVID-19, as well as the absence of studies providing concrete information about their unwanted effects, especially on gastrointestinal tissues, highlights the importance of clarifying the efficacy and safety of these drugs. Therefore, this work evaluated the adverse effects of the Brazilian COVID Kit on the gastrointestinal tract in a population of northeast Brazil.

METHODS

This was an analytical, quantitative, cross-sectional epidemiological study. The data were collected through questionnaires performed by telephone, and the contacts and information of the participants were obtained from the Municipal Health Foundations of

the cities of the coastal macroregion of the state of Piauí, Brazil. Interviews were conducted between February and August 2021. Patients were eligible if they had tested positive for COVID-19 and they were residents of cities in the coastal macroregion of the state of Piauí. A confirmed diagnosis for COVID-19 was defined as the PCR-confirmed presence of the SARS-CoV-2 genome in a nasopharyngeal swab or a positive rapid or quantitative serological test result. Patients with mild or moderate COVID-19 who remained in home isolation or who were hospitalised in clinical beds were included.

Patients who reported frequent symptoms or chronic diseases of the gastrointestinal tract were excluded. Other exclusion criteria were as follows: younger than 18 years, asymptomatic for COVID-19, not residing in the region established by the survey, and refusal to participate or unable to be contacted. Informed consent was obtained for the use of voluntary information for research purposes and for sharing relevant privacy policies and terms of use.

Two questionnaires were applied. First, for all eligible patients, we collected the following data: sex, age, education, marital status, family income, place of residence, skin colour, use of medication, pre-existing diseases and the type of COVID-19 diagnostic test. Second, an assessment was performed using the Gastrointestinal Symptom Rating Scale (GSRS) questionnaire for gastrointestinal symptoms in patients with COVID-19 who received treatment in comparison to patients who did not receive pharmacological treatment. The questionnaire consisted of 15 items with a seven-point Likert-type scale ranging from one (no discomfort) to seven (very severe discomfort). Items were divided into five subscales that included reflux (heartburn and acid regurgitation), abdominal pain (abdominal pain, hunger pain and nausea), indigestion (abdominal noises, eructation, abdominal distension and increased flatulence), diarrhoea (diarrhoea, soft stools and urgent need to defecate) and constipation (constipation, hard stools and rectal tenesmus). The GSRS has been considered a useful tool with demonstrated reliability for the assessment of gastrointestinal disorders (SOUZA *et al.,* 2016; ASAI *et al.,* 2019).

Statistical analysis

The chi-squared test was used to assess the associations between socio-demographic aspects and gastrointestinal symptoms in patients with COVID-19 as evidenced by the GSRS questionnaire. The significance of differences in the total score

and domains of the GSRS questionnaire between patients who did and did not receive pharmacological treatment was examined using the Mann–Whitney U test. With the stratification of the pharmacological treatment covariate, we implemented an analysis of differences using the Kruskal–Wallis test.

Statistical adjustment was considered at the 95% confidence interval for the dependent variables. A probability of 5% for type I error was adopted in all analyses ($p < 0.05$), with alpha-Bonferroni correction performed when necessary. Analyses were performed using SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL, USA).

Ethics approval

This study has been approved by the Federal University of the Parnaíba Delta (UFDPar) Research Ethics Committee (approved on 11 November 2020 and certification number 4.455.806). Verbal informed consent was obtained from all participants before applying the questionnaires and was confirmed by the Research Ethics Committee.

Patient and public involvement

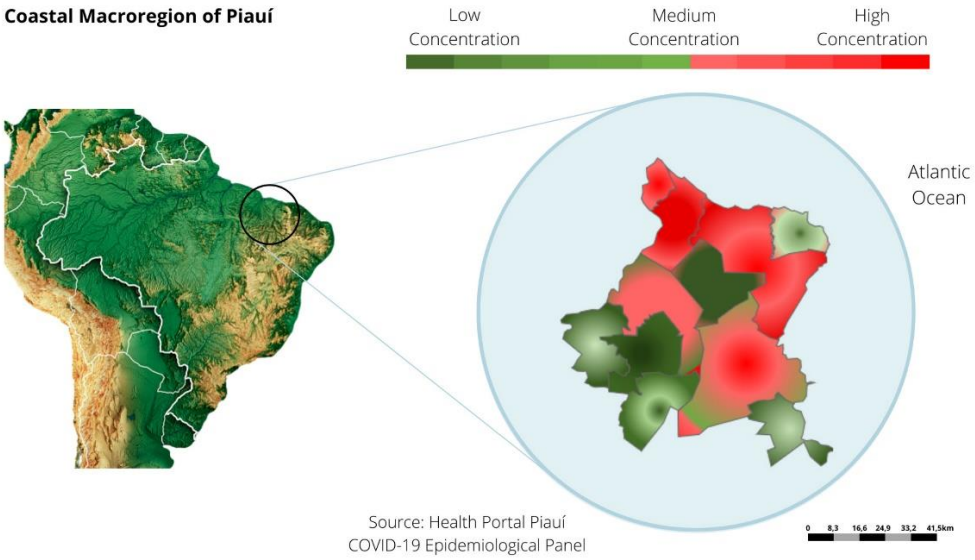
No patients were directly involved in designing the research question or in conducting the research. No patients were asked for advice on interpretation or writing up the results. The results of the present study will be made publicly available on the homepage of the Federal University of the Parnaíba Delta (https://www.ufpi.br/ufdpar).

RESULTS

Overall population analysis

This study involved patients residing in the coastal macroregion of Piauí (**Figure. 1**)

Figure 1- Map of the coastal macroregion of Piauí and location of the study.



Source: Adapted from ARRUDA *et al.*, 2021 and SOUZA, 2020.

The initial sample consisted of 302 patients, among which 178 patients were initially excluded due to they had chronic diseases or symptoms of the gastrointestinal tract (n=53), resided outside the study region (n=5), no contact after 3 attempts (n=19), unconfirmed diagnosis for COVID-19 (n=12), incorrect phone number in the database (n=44), asymptomatic patients for COVID-19 (n=9) and refusal to participate (n=36).

After applying the predetermined exclusion criteria and screening the data, 124 questionnaires were analysed and included in the research. The 124 patients included 53 men (42.7%) and 71 women (57.3%). Among patients who did not undergo pharmacological treatment for COVID-19, most had an income above three times the minimum wage (n = 18 [39.1%]). Meanwhile, among patients who underwent treatment, income tended to range between one and three times the minimum wage (n = 48 [61.5%]). The difference between family income was significantly ($p < 0.01$) related to the receipt of drug treatment for COVID-19 (**Table 1**).

Table 1- Characteristics of the socio-demographic characteristics of patients diagnosed with COVID-19.

Variables		Total n=124		No treatment n=46		With treatment n=78		χ2	p-value
		N	%	N	%	N	%		
Sex	Feminine	71	57,3%	26	56,5%	45	57,7%	0,0162	0,5232
Color	White	38	30,6%	13	28,3%	25	32,1%	2,336	0,5057
	Brown	74	59,7%	30	65,2%	44	56,4%		
	Black	9	7,3%	3	6,5%	6	7,7%		
	Prefer not to declare.	3	2,4%	0	0%	3	3,8%		
Marital status	Single	61	49,2	25	54,3%	36	46,1%	0,6015	0,9628
	Divorcee	5	4%	1	2,2%	4	5,1%		
	Married	40	32,2%	14	30,4%	26	33,3%		
	Widowed	3	2,4%	1	2,2%	2	2,6%		
	Lives with a partner	15	12,1%	5	10,9%	10	12,8%		
Schooling								0,608	0,8945
	Literate	4	3,2%	1	2,2%	3	3,8%		
	Elementary school	7	5,6%	3	6,5%	4	5,1%		
	High school	53	42,7%	21	45,7%	32	41,0%		
	Higher education	60	48,4%	21	45,7%	39	50,0%		
Paid work	Yes	82	66,1%	30	65,2	52	66,7	0,0004	0,9849
Household income (in minimum wage)								17,153	0,0002*
	No income	36	29%	14	30,4%	22	28,2%		
	1 to 3	62	50%	14	30,4%	48	61,5%		
	Above 3	26	21%	18	39,1%	8	10,3%		
Housing location	Parnaíba	112	90,3%	40	86,9%	72	92,3%	4,2810	0,3693
	Luís Correia	9	7,3%	4	8,7%	5	6,4%		
	Ilha Grande	1	0,8%	1	2,2%	0	0%		
	Cocal dos Alves	1	0,8%	1	2,2%	0	0%		
	Murici dos portelas	1	0,8%	0	0%	1	1,3%		
Housing region	Urban area	82	66,1%	33	71,7%	49	62,8%	1,0276	0,3107
	Rural area	42	33,9%	13	28,3%	29	37,2%		

Regarding patients who received treatment, the findings revealed a higher frequency of the use of the combination of ivermectin and azithromycin (n = 35 [44.9%], Table II).

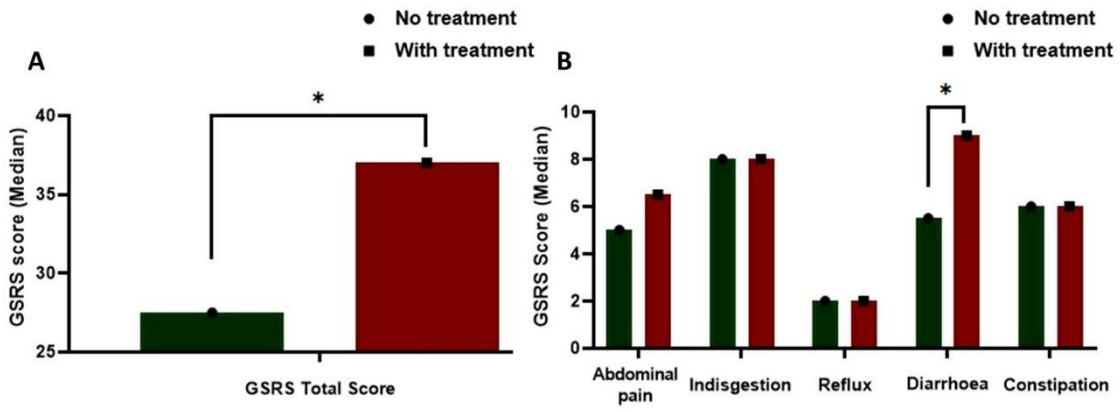
Table 2- Outcomes according to medicines used to treat severe acute respiratory syndrome virus 2 infection.

VARIABLES		Total n=78	
		N	%
Medicines used to treat COVID-19.	Azithromycin	14	17,9%
	Ivermectin	14	17,9%
	Hydroxychloroquine or Hydroxychloroquine + associations.	9	11,5%
	Azithromycin + Ivermectin	35	44,9%
	Others	6	7,7%
Medical prescription	Yes	63	80,8%
Adverse events (Need to stop)	Yes	6	7,7%

GSRS scores

The overall GSRS score significantly differed between treated and untreated patients (p = 0.022, **Figure. 2A**). In addition, a significant difference was observed between the two groups regarding the score for diarrhoea syndromes evaluated using the GSRS (p = 0.05). No significant differences were found for the other syndromes (**Table 3, Figure. 2B**).

Figure 2- Gastrointestinal side effects of the Brazilian COVID Kit. (A) Gastrointestinal Symptom Rating Scale (GSRS) - Total score and (B) Syndrome scores assessed by the GSRS. (*) p < 0.05.



Sources: Authors (2024)

Table 3- Gastrointestinal symptoms and syndromes in patients with a positive diagnosis of COVID-19.

VARIABLES	No treatment n=46		With treatment n=78		
	Median	Min-Max	Median	Min-Max	p-value
GSRS score total	27,5	(15-78)	37,0	(15-81)	0,022*
Abdominal pain	1	(1-7)	1	(1-7)	0,039*
Heartburn	1	(1-7)	1	(1-7)	0,391
Acid reflux	1	(1-7)	1	(1-7)	0,225
Hunger pains	1	(1-7)	1	(1-7)	0,023*
Nausea	1	(1-7)	1,5	(1-7)	0,609
Abdominal noises (borborygme)	1	(1-7)	1	(1-7)	0,338
Abdominal distension	1	(1-7)	1	(1-7)	0,671
Eructation	2	(1-6)	1	(1-7)	0,802
Flatulence	1	(1-7)	1	(1-7)	0,581
Constipation	1	(1-7)	1	(1-7)	0,769
Diarrhoea	1	(1-7)	3	(1-7)	0,033*
Soft stools	1	(1-7)	3	(1-7)	0,201
Hard stools	1	(1-7)	1	(1-7)	0,372
Defecation urgency	1	(1-7)	2,5	(1-7)	0,030*
Rectal tenesmus	1	(1-7)	1	(1-7)	0,908
Abdominal pain syndrome	5	(3-18)	6,5	(3-21)	0,057
Indigestion syndrome	8	(4-22)	9	(4-24)	0,628
Reflux syndrome	2	(2-13)	2	(2-14)	0,127
Diarrhoea syndrome	5,5	(3-21)	9	(3-21)	0,05*
Constipation syndrome	6	(3-21)	6	(3-30)	0,240

Furthermore, when separately evaluating the 15 items of the GSRS, the scores for abdominal pain (p = 0.039), hunger pain (p = 0.023), diarrhoea (p = 0.033) and urgency of defecation (p = 0.030) were significantly different between treated and untreated patients. No significant differences were found between the groups regarding the scores for heartburn, reflux, nausea, abdominal noises, abdominal distension, eructation, flatulence, constipation, increased soft stools and hard stools or rectal tenesmus (Table 3).

DISCUSSION

Our epidemiological study of 124 patients with COVID-19 in a region of northeast Brazil is the first to demonstrate that the use of drugs from the Brazilian COVID Kit is associated with the development of gastrointestinal symptoms. In Brazil, the prescription and sale of hydroxychloroquine and ivermectin skyrocketed in 2020, even leading to shortages in the market (CFF, 2021). This act was encouraged by a protocol of the Ministry of Health guiding the use of hydroxychloroquine and azithromycin in the

treatment of non-hospitalised patients with COVID-19 that remained in force between May 2020 and May 2021 (BRASIL, 2020; CFM, 2020; FURLAN, CARAMELLI, 2021).

Our findings illustrated that 80.8% of patients treated for COVID-19 had a medical prescription, demonstrating that the use of drugs without scientific evidence for the treatment of COVID-19 was also supported by physicians in the region of study. In addition, our data highlighted a difference in family incomes between untreated and treated patients. Specifically, untreated patients had a higher rate of income exceeding three times the minimum age (39.1%), whereas treated patients had a higher rate of income between one and three times the minimum wage (61.5%). These data suggest that the family's financial situation may be an interfering factor in the decision to pursue treatment.

Our work is the first to address the use of ivermectin in conjunction with other drugs and their effects on the gastrointestinal tract. We demonstrated that the combination of azithromycin and ivermectin was most frequently used, being used by 44.9% of patients who received treatment for COVID-19. The transport and metabolic properties of ivermectin indicate that when it is co-administered with other drugs/chemicals that are potent inhibitors/inducers of CYP3A4 and MDR1 (P-gp), BCRP or MRP transporters or when polymorphisms of the drug transporters and CYP3A4 exist, drug or chemical interactions may result in suboptimal responses to therapy or toxic effects (RENDIC, 2021). In addition, gastrointestinal disturbances have been observed in hospitalised patients and outpatients after using ivermectin to prevent or treat COVID-19 (CDC, 2021). Furthermore, studies performed in rodents illustrated that ivermectin impairs the function and morphology of the gastrointestinal tract, especially at high doses (MENDONÇA *et al.*, 2019).

This study revealed that the GSRS scores for abdominal pain, hunger pain, diarrhoea and bowel movement urgency were significantly higher in treated patients than in untreated patients. In addition, when divided into syndromes, the GSRS subscale score for diarrhoea syndromes was significantly higher in treated patients, whereas the scores did not differ between the groups for abdominal pain, indigestion and reflux syndrome. In view of this, it is suggested that gastrointestinal symptoms are correlated with the receipt of experimental treatment for COVID-19.

One of the possible causes of the development of diarrhoea syndromes is changes in the intestinal microbiota caused by the use of drugs. Among them, antibiotics such as

azithromycin influence the pathogenesis of diarrhoea by altering the composition and metabolic function of the intestinal microbiota (SILVERMAN, KONNIKOVA, GERBER, 2017). This is in line with studies suggesting that changes in the gastrointestinal microbiome in patients with COVID-19 were driven by antibiotic use rather than the severity of SARS-CoV-2 infection (YEOH *et al.*, 2021). In our study, we demonstrated that azithromycin was among the main drugs used to treat COVID-19 in the population studied. Specifically, the drug was used by 17.9% of the research participants who received treatment, and it also used in combination with ivermectin and hydroxychloroquine. The use of azithromycin has already been associated with the development of side effects such as nausea, diarrhoea abdominal pains and decreased appetite, in line with our data (DE BENEDETTI, VAIANO, 2019).

In addition, we observed that hydroxychloroquine was used by 11.5% of treated patients, making it the least commonly used drug in the COVID Kit. Among patients with pre-existing diseases, cardiovascular disease was prevalent (data not shown). The wide discussion around the risks of QT interval prolongation and arrhythmia associated with hydroxychloroquine (MERCURO *et al.*, 2020; YETKIN, YALTA, WALTENBERGER, 2020) could be one reason for the less frequent prescription and use of this drug by these patients. Concerning the gastrointestinal tract, hydroxychloroquine is associated with symptoms such as dyspepsia, abdominal pain and dysgeusia (SRINIVASA, TOSOUNIDOU, GORDON, 2017). In patients with COVID-19, its use is correlated with stomach pain, nausea, diarrhoea and vomiting (LOFGREN *et al.*, 2020), which are similar to the symptoms found in our study. When hydroxychloroquine is used in combination with other drugs such as azithromycin in patients with COVID-19, diarrhoea is the most frequent adverse effect (OLDENBURG *et al.*, 2021; MILLION *et al.*, 2020).

In addition, we found that 26.9% of patients used corticosteroids (data not shown) together with azithromycin, ivermectin and/or hydroxychloroquine even though 97.4% of patients had only mild disease not requiring hospitalisation and the use of corticosteroids has only proven beneficial in preventing disease in patients with moderate-to-severe COVID-19 (FADEL *et al.*, 2020). In addition, the use of corticosteroids in patients with severe SARS-CoV-2 infection is controversial (LIU *et al.*, 2020).

Our findings demonstrated that gastrointestinal symptoms in patients with COVID-19 are not only associated with SARS-CoV-2 infection because we observed

increases in gastrointestinal symptom scores in patients treated with Brazilian COVID Kit drugs versus patients who did not receive any treatment. However, this study had some limitations. First, the study included a small number of patients with a positive diagnosis for COVID-19 who did not receive treatment, and the study only assessed medicines disseminated locally in a Brazilian territory. However, this is in line with expectations given the incentive for early treatment without scientific evidence in Brazil (BRASIL, 2020; CFM, 2020). Second, some patients refused to participate in the research because of the current political environment in Brazil. Third, this was an uncontrolled study with mostly mild cases. Fourth, because of the small number of participants, it was not possible to stratify the treatment group and assess the correlations with the observed effects. Considering that antimicrobials can alter the microbiota and lead to diarrheal symptoms (SILVERMAN, KONNIKOVA, GERBER, 2017), future work to elucidate the effect of each drug in the COVID Kit on gastrointestinal alterations may complement our findings.

FINAL CONSIDERATIONS

This is the first report on the gastrointestinal effects of drugs in the Brazilian COVID Kit. We demonstrated that use of the COVID Kit is associated with increased risks of gastrointestinal symptoms and diarrhoea syndromes in patients with a positive diagnosis of COVID-19. Specifically, the treatment was associated with diarrhoea, urgency of defecation, hunger pain and abdominal pain.

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REFERENCES

ANDREANI, J. *et al.* In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect. **Microbial pathogenesis**, v. 145, p. 104228, 2020.

ARRUDA, E. A. G. *et al.* Clinical Features, Pathobiology, Efficacy, and Toxicity of Tenofovir Disoproxil Fumarate and Emtricitabine for Mild to Moderate SARS COV 2 Infections. **European Journal of Respiratory Medicine**, v. 3, n. 3, p. 238-248, 2021.

ASAI, S. *et al*. Influence of methotrexate on gastrointestinal symptoms in patients with rheumatoid arthritis. **International Journal of Rheumatic Diseases**, v. 22, n. 2, p. 207-213, 2019.

BRASIL. Ministério da Saúde. **Nota Informativa Nº 17/2020- SE/GAB/SE/MS**. Orientações do Ministério da Saúde para Manuseio Medicamentoso Precoce de Pacientes com Diagnóstico da COVID-19. Ministério da Saúde, Brasília, DF, 11 ago. 2020. Disponível em: https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/estudos-e-notas-informativas/2020/old-file-removed-covid-05mar2021-11h37.pdf/view. Acesso em: 25 ago. 2020.

CDC.Centers for Disease Control and Prevention. Rapid increase in ivermectin prescriptions and reports of severe illness associated with use of products containing ivermectin to prevent or treat COVID-19. **CDC Health Alert Network no. CDCHAN-00449**, v. 8, p. 26, 2021.

CFF. Conselho Federal de Farmácia. **Notícia:** Venda de Remédios sem eficácia comprovada. 2021. Disponível em: https://cff.org.br/noticia.php?id=6197&titulo=Venda+de+remédios+sem+eficácia+comprovada+contra+a+Covid+dispara. CFF, 2020. Acesso em: 23 de nov. 2022

CFM. Conselho Federal de Medicina. **Parecer nº 4/2020:** Tratamento de pacientes portadores de COVID-19 com cloroquina e hidroxicloroquina. Disponível em: https://sistemas.cfm.org.br/normas/visualizar/pareceres/BR/2020/4. Acesso em: 07 jun 2021.

CHOWDHURY, A. T. M. M. *et al*. A Randomized Trial of Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin therapy on COVID19 patients. **Research Square**. p. 1-19, 2020.

CIOTTI, M. *et al*. The COVID-19 pandemic. **Critical reviews in clinical laboratory sciences**, v. 57, n. 6, p. 365-388, 2020.

DE BENEDETTI, G.; VAIANO, A. S. Oral azithromycin and oral doxycycline for the treatment of Meibomian gland dysfunction: A 9-month comparative case series. **Indian Journal of Ophthalmology**, v. 67, n. 4, p. 464-471, 2019.

ELFAKHARANY, Y. M. *et al*. Possible Hepatotoxic Effects In Adult Male Albino Rats On Combination Of Ivermectin And Paracetamol Drugs Used In COVID-19 Infection Management Protocol. **Egyptian Society of Clinical Toxicology Journal**, v. 9, n. 2, p. 13-28, 2021.

FADEL, R. *et al*. Early short-course corticosteroids in hospitalized patients with COVID-19. **Clinical Infectious Diseases**, v. 71, n. 16, p. 2114-2120, 2020.

FONSECA, S. N. S. *et al*. Risk of hospitalization for Covid-19 outpatients treated with various drug regimens in Brazil: comparative analysis. **Travel medicine and infectious disease**, v. 38, p. 101906, 2020.

FURLAN, L.; CARAMELLI, B. The regrettable story of the “Covid Kit” and the “Early Treatment of Covid-19” in Brazil. **The Lancet Regional Health–Americas**, v. 4, 2021.

GÉRARD, A. *et al*. “Off-label” use of hydroxychloroquine, azithromycin, lopinavir-ritonavir and chloroquine in COVID-19: a survey of cardiac adverse drug reactions by the French Network of Pharmacovigilance Centers. **Therapies**, v. 75, n. 4, p. 371-379, 2020.

KING, C. R. *et al*. Inhibition of human adenovirus replication by the importin α/β1 nuclear import inhibitor ivermectin. **Journal of Virology**, v. 94, n. 18, p. 10.1128/jvi. 00710-20, 2020.

LIU, J. *et al*. Corticosteroid treatment in severe COVID-19 patients with acute respiratory distress syndrome. **The Journal of clinical investigation**, v. 130, n. 12, p. 6417-6428, 2020.

LOFGREN, S. M.M. *et al*. Safety of Hydroxychloroquine among Outpatient Clinical Trial Participants for COVID-19. **medRxiv**, 2020.

MAHMOUDI, J. *et al*. Nephrotoxicity of chloroquine and hydroxychloroquine in COVID-19 Patients. **Advanced Pharmaceutical Bulletin**, v. 11, n. 1, p. 6-7, 2020.

MENDONÇA, J. C. *et al*. Gastrointestinal effects of ivermectin treatment in rats infected with Strongyloides venezuelensis. **Acta tropica**, v. 194, p. 69-77, 2019.

MERCURO, N. J. *et al*. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). **JAMA cardiology**, v. 5, n. 9, p. 1036-1041, 2020.

MILLION, M. *et al*. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: a retrospective analysis of 1061 cases in Marseille, France. **Travel medicine and infectious disease**, v. 35, p. 101738, 2020.

OLDENBURG, C. E. *et al*. Effect of oral azithromycin vs placebo on COVID-19 symptoms in outpatients with SARS-CoV-2 infection: a randomized clinical trial. **Jama**, v. 326, n. 6, p. 490-498, 2021.
RENDIC, S. P. Metabolism and interactions of Ivermectin with human cytochrome P450 enzymes and drug transporters, possible adverse and toxic effects. **Archives of Toxicology**, v. 95, n. 5, p. 1535-1546, 2021.

SILVERMAN, M. A.; KONNIKOVA, L.; GERBER, J. S. Impact of antibiotics on necrotizing enterocolitis and antibiotic-associated diarrhea. **Gastroenterology Clinics**, v. 46, n. 1, p. 61-76, 2017.

SOUZA, A. Mapas em representação tridimensional. **Confins. Revue franco-brésilienne de géographie/Revista franco-brasilera de geografia**, n. 47, 2020.

SOUZA, G. S. *et al*. Translation and validation of the Brazilian Portuguese version of the gastrointestinal symptom rating scale (Gsrs) Questionnaire. **Arquivos de Gastroenterologia**, v. 53, n. 3, p. 146-151, 2016.

SRINIVASA, A.; TOSOUNIDOU, S.; GORDON, C. Increased incidence of gastrointestinal side effects in patients taking hydroxychloroquine: a brand-related issue?. **The Journal of rheumatology**, v. 44, n. 3, p. 398-398, 2017.

VELAVAN, T.; MEYE, C. The COVID-19 epidemic. **Trop Med Int Health**. v. 25, n. 3, p. 278-80, 2020.

OMS. Organização Mundial de Saúde. Coronavirus disease 2019 (COVID-19) situation report-97 [Internet]. World Health Organization, [report 97; 2020 April 26]. [cited 2021 Jun 07]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200426-sitrep-97-covid-19.pdf.

WONG, A. O. *et al*. Adverse effects of hydroxychloroquine and azithromycin on contractility and arrhythmogenicity revealed by human engineered cardiac tissues. **Journal of Molecular and Cellular Cardiology**, v. 153, p. 106-110, 2021.

WU, F. *et al*. A new coronavirus associated with human respiratory disease in China. **Nature**, v. 579, n. 7798, p. 265-269, 2020.

YEOH, Y. K. *et al*. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. **Gut**, v. 70, n. 4, p. 698-706, 2021.

YETKIN, E.; YALTA, K.; WALTENBERGER, J. An antiarrhythmic approach to hydroxychloroquine-induced QT prolongation. **Netherlands Heart Journal**, v. 28, n. 7, p. 437-438, 2020.