PROPOSAL FOR A PROTOCOL FOR THE ETIOLOGICAL TREATMENT OF DENGUE.
Revisión de la Literatura y Reporte de Casos tratados

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SUMMARY

In several countries, a high number of patients diagnosed with Dengue have been reported and the recommended medical treatment is basically limited to the indication of the antipyretic Paracetamol or Acetaminophen.
As it is a viral infection that in a few days causes lymphopenia, eosinopenia, neutropenia and leukopenia, which frequently become severe, and can also cause a serious decrease in blood platelets, endothelial cell damage, plasma extravasation, bleeding profuse and multi-organ failure that can cause the death of the patient, it is justified to expand the therapeutic indications and include specific drugs directed against the viral and microbial load.
In this document we carry out a review of the medical literature, evidencing that several studies have been published on the use of drugs with antiviral effects in Dengue. Of these drugs, the one that has been published the most studies is ivermectin, of which there is extensive experience in its use.
Based on the various published evidence that we have reviewed and based on our experience in the treatment of coronavirus infections, a proposal for a Dengue Etiological Treatment Protocol has been prepared.
In the final part of the document, we make a report of the cases treated with the proposed Protocol, which we have been improving based on the experience with the cases already treated.

Keywords:

Dengue, Ivermectin, Amantadine, Nifuroxazide, Baking Soda.

BACKGROUND

Dengue is an infectious disease produced by the dengue virus, whose official acronym is DENV. It is an RNA virus belonging to the Flaviviridae family of which there are four serotypes. Infection with one serotype confers long-lasting immunity only against this serotype, but not against the others. Repeated or sequential infections increase the risk of contracting the severe form of Dengue. It is transmitted by mosquitoes called Aedes aegypti. This infectious disease has a higher prevalence or frequency in tropical and subtropical areas of the world.
In recent years, a high number of patients diagnosed with Dengue have been reported in several countries, so it is important to have an updated Treatment Protocol that includes specific drugs directed against the viral load [1].

FEVER IN DENGUE.

Fever is a very frequent symptom of Dengue, it has the characteristic of being high, ranging from 38 to 40 °C, and is usually accompanied by headache, retro-ocular pain and myalgia.
The treatment of fever in patients with Dengue has become the main concern of the doctor, largely due to the pressure exerted by the patient's relatives to reduce this symptom. But it must be understood that this has several beneficial effects. Our body produces a rise in temperature as a defense mechanism, because microorganisms are sensitive to heat, that is, a rise in temperature or hyperthermia will have an effect against the viral and microbial load, this must be explained to the patient. and their relatives, so that the main objective of the treatment against Dengue is not established to reduce fever using a symptomatic medicine that has no effect against the viral load and with which it will not obtain benefits against the infection itself.

ETIOLOGICAL TREATMENT OF THE INFECTION.

Dengue is a viral disease that rapidly generates immunosuppression (lymphopenia and leukopenia), and our proposal is that instead of applying a Treatment Protocol that is limited to the indication of an antipyretic such as Paracetamol or Acetaminophen, drugs against the viral load should be included. and microbial, that is, the therapeutic indications should be expanded, so that they include drugs directed against the etiology or cause of the disease, and not only indicate symptomatic, which also have against that they mask the real state of the infection, since they can give a false perception of temporary improvement.

PARACETAMOL OR ACETAMINOPHEN.

Due to the COVID epidemic, we observed that most of the Treatment Protocols included Paracetamol or Acetaminophen. Similarly, in the case of Dengue this antipyretic medication is almost always indicated.
In 2020 we published a review on the disadvantages of the indication of this antipyretic in COVID [2]. And something similar occurs in Dengue, since several studies and case reports have identified that the use of Paracetamol or Acetaminophen in Dengue, even in standard doses, causes an increase in the incidence of elevated liver transaminases [3, 4,5,6,7], that is, this medication affects the liver cells, generating a greater risk of compromise of this organ.
Due to these findings, we have published a document recommending that, if possible, this medication should not be used in Dengue [7].

STUDIES OF THE USE OF DRUGS AGAINST THE VIRAL LOAD IN DENGUE.

The search for an antiviral drug to treat dengue patients has been going on for decades [8]. From the review of the medical literature, it is evident that several studies have been published on the use of drugs with antiviral effects in Dengue. Of these drugs, the one that has published the most studies is ivermectin [IVM] [1,9-32], of which there is extensive experience in its use, but in a similar way to what has happened in the case of COVID, the doses that have used are low to treat a severe infection. Doses between 0.2 to 0.4 mg per kilo of weight have been used for many years for the treatment of scabies, pediculosis, myiasis, other parasitosis and as prevention. In the case of COVID and Dengue, these are significantly more severe infections and require higher doses than those required for scabies and infection prevention. Doses of between 0.4 to 0.6 mg per kilo of weight are indicated in mild cases and without warning signs, but in the most severe and serious cases, much higher doses are required, taking into account that the severity correlates with the level of the viral load.

In addition to IVM, studies have been published on the experience of using the antiviral Amantadine in Dengue [33,34], and taking into account that it is, like IVM, a drug with which there is already a lot of experience In its use in humans, we suggest considering its indication together with IVM in severe cases of Dengue that do not respond quickly to monotherapy with IVM. Other potential antivirals are Romantadine [35], antivirals against HIV and Hepatitis C [31,32,36], such as Rivavirin, Nelfinavir, Dasabivir and Oseltamivir (37) among others.

THE DEVELOPMENT OF A TREATMENT FOR DENGUE HAS BEEN IGNORED.

Despite the relevance and great burden that Dengue infection represents for global public health, in a publication of the so-called "Global Alliance against Dengue" carried out in 2023 in a prestigious medical journal [38], it is stated verbatim:

"Efforts focused on finding a treatment have been scarce, with some investigator-led clinical trials conducted, and a few performed by pharmaceutical companies. The importance of developing a treatment for dengue has largely been ignored".

Despite several studies having been carried out on the use of already approved, low-cost drugs and for which there is extensive experience in their use in humans, there is a continuous unnecessary postponement, on the part of the decision-making institutions, in authorizing formally the use of any of these drugs for Dengue [39].

BACKGROUND OF THE USE OF IVM AND THE WHO RECOMMENDATION OF ITS MASSIVE USE IN POPULATIONS WITH ENDEMIC INFECTIONS.

IVM is considered an essential drug by the WHO, it is approved by the US FDA. and has been widely used worldwide for almost 40 years. This medication continues to be administered massively to large populations including children for effective control of endemic infections [40,41,42,43], this with the support of the WHO [43,44] who have recently published that population treatment with ivermectin (also known as mass drug administration or MDA) is the main strategy to eliminate the transmission of onchocerciasis [44] and has been used by specialist doctors in prestigious hospitals, including in the US and UK even in its presentation of use veterinary [45,46,47,38,49,50,51,52].

Similar to what happens in the treatment against COVID, despite the fact that there are dozens of medical studies published on the use of IVM, there is a large group of media and other for-profit organizations and, institutions related and that receive economic contributions from them, which inform against its use and attack doctors and scientists

who investigate the benefits of this medicine, which, being low cost and without a patent, constitutes a very serious competition for new medicines with patents and much higher cost.

REVISED CLASSIFICATION OF DENGUE (WHO 2009).

The classification currently recommended by the World Health Organization (WHO) is the so-called revised classification of Dengue [53]. This was established in November 2009 and replaced the previous classification given in 1997. According to this, cases are classified into 3 diagnoses according to their severity [53,54,55].
It is then found that, from lesser to more seriousness of the disease, dengue cases are classified as:
A. DENGUE WITHOUT WARNING SIGNS.
B. DENGUE WITH WARNING SIGNS.
C. SEVERE DENGUE.

CLINICAL CHARACTERISTICS AND COMPLETE BLOOD COUNT (CBC) IN DENGUE.

Characteristic of this viral infection is high fever accompanied by myalgia, general malaise, and frequently headache with retro-ocular pain and nausea and/or abdominal pain.
Regarding the blood count, in a few days there is a significant decrease in lymphocytes, which decrease to less than 1000 and even less than 500, which already indicates a degree of immunosuppression. It is also characteristic that in a few days the number of eosinophils decreases, in many cases being reported with 0%. In addition, some degree of neutropenia and leukopenia are frequently observed, and a severe decrease in blood platelet count may occur.
In cases of severe Dengue there is severe damage to the endothelial cells of the blood vessels, thrombocytopenia, increased vascular permeability, severe plasma extravasation ccausing shock or fluid accumulation with dyspnea or respiratory failure, profuse bleeding and multi-organ failure. that can lead to the death of the patient.
As it is a viral infection that has already been known for several decades, and due to the severity that the disease can reach, it is justified to expand the current therapeutic indications and include specific drugs directed against the viral and microbial load.

PROTOCOL FOR THE ETIOLOGICAL TREATMENT OF DENGUE.

Based on the various published evidences that we have reviewed, and based on our experience in the treatment of coronavirus infections, a Protocol for the Etiological Treatment of Dengue has been prepared, which is described in Table 1 and which we propose for the treatment in the initial and most acute stage of Dengue.

REPORT OF CASES TREATED.

Between the months of March and May 2023, there were 70 cases treated with the proposed Protocol, which we have been improving based on the experience with the cases already treated. The treatment and follow-up of the majority of cases was carried out by Dr. José Aníbal Córdova M., who treated them directly at their homes, and/or through teleconsultations. The places of residence of the treated patients are mainly towns in the north of the country (Peru), and of the 70 cases, 6 correspond to children under 12 years of age.
Regarding the classification of Dengue, there are the following numbers of cases:
A. DENGUE WITHOUT WARNING SIGNS: 52 cases.
B. DENGUE WITH WARNING SIGNS: 15 cases.
C. SEVERE DENGUE: 3 cases.
It is specified that this classification of the cases was carried out at the first moment of contact with the patient and/or their relatives. The classification of patients according to

TABLE 1

PROPOSAL FOR A PROTOCOL FOR THE ETIOLOGICAL TREATMENT OF DENGUE

A. DENGUE WITHOUT WARNING SIGNS (only: fever, headache, retro-ocular pain, abdominal pain, nausea, myalgia, rash):
- IVM: 1st dose of 0.6 mg per kilo body weight, then 0.4 mg per kilo body weight every 12 hours until completing 3 days.

B. DENGUE WITH WARNING SIGNS (+ intense abdominal pain, persistent vomiting, mucosal bleed, restlessness or lethargy):
1) IVM: between 1.0 to 1.2 mg per kilo body weight in a single daily dose (maximum dose: 120 mg, every 24 hours), for 3 days.
2) Nifuroxazide: 1 tablet of 400mg or 2 of 200mg every 12 hours for 5 days (dose for people over 12 years of age). If the patient weighs more than 80 kilos, 400 mg every 8 hours is indicated for 5 days. In children from 5 to 11 years old, 200 mg every 8 hours in a syrup bottle is indicated, from 1 to 4 years it would be every 12 hours for 4 days.
3) Others: Baking Soda, N-Acetylcysteine (NAC), Vit. D, Calcium, Colchicine can be added (see doses in the Severe Dengue table)

C. SEVERE DENGUE (+ shock, respiratory distress/failure, severe bleeding, severe multi-organ involvement/failure):
1) IVM: the 1st day: first dose of between 1.2 to 1.4 mg per kilo by body weight (maximum dose: 120 mg) and after 12 hours second dose of 0.6 mg/kilo (maximum dose: 60 mg, and no more than 180 mg per day).
From the 2nd day: between 1.2 to 1.4mg per kilo weight in a single daily dose for 3 more days (maximum dose: 120mg).
If no improvement is evident on the 2nd day, a 2nd antiviral can be added, such as Amantadine 100 mg 9 am and 9 pm.
If symptoms still persist on the 5th day, continue with daily doses of IVM of 0.6 mg/kg by body weight x 3 to 9 more days.
2) Nifuroxazide: 1 tablet of 400mg or 2 of 200mg every 8 hours. If the patient weighs + than 80 kilos, 400mg every 6 h. is indicated x 7 days. In children from 5 to 11 years old, 200 mg every 6 hours is indicated, from 1 to 4 years old it would be every 8 h.
3) Baking soda (or Sodium Bicarbonate): between 3 to 3.3 grams (1/2 teaspoon or, 1 1/2 envelopes of Andrews Salt in 1 glass of water) at 10am and 10pm for 3 days. If the weigh is greater than 95 kilos, a 3rd dose is added at 4 pm during the 3 days.
4) NAC: 600mg every 6 h. for 3 days. If the weight is between 80 to 95 kilos, 600mg every 4 h. or 1,200mg every 8 h. is indicated.
5) Vitamin D: 300,000 IU on the 1st and 3rd day or else, 60,000 IU for the first 3 days and then 30,000 IU per day for 7 more days.
6) Calcium: 600 mg at 8am, 3pm and 10pm for 3 days, and then twice a day, at 9am and 9pm, for 5 more days.
7) Colchicine: 0.5 or 0.6mg at 9am and 9pm x 6 days. If the weight is greater than 80kg, 1mg at 9am and 0.5mg at 9pm is indicated.
8) Zinc: 100 mg at 10am and 10pm for 15 days. 9) Tranexamic Acid: 1,000mg every 12 hours or 500mg every 8 hours.
10) Others: Vitamins A, B, C, E and K2, Statins such as Lovastatin, Rupatadine, Metformin, Mefenamic Acid, Doxycycline, others.

severity is used to determine the appropriate treatment to indicate.

GROUP A: DENGUE WITHOUT WARNING SIGNS:

In these cases, an initial dose of IVM of 0.6 mg per kilo of body weight was given, and then a dose of 0.4 mg per kilo of weight was continued every 12 hours until completing 3 days of treatment. In total in the 3 days there would be 6 shots. Some cases, feeling already cured at the beginning of the third day, no longer took the last 2 doses of IVM, that is, they only took 4 doses in 2 days.

GROUP B: DENGUE WITH WARNING SIGNS:

The protocol proposed in these cases is the following:
1) IVM: between 1.0 to 1.2 mg per kilo of weight in a single daily dose (every 24 hours) for 3 days. The maximum dose to be indicated is 120 mg.
2) Nifuroxazide: 1 tablet of 400 mg or 2 of 200 mg every 12 hours for 5 days, these doses are recommended for adults and children over 12 years of age. If the person weighs more than 75 kilos, a dose of 400 mg every 8 hours is indicated.
In children between 5 and 11 years of age, 200 mg every 8 hours of the syrup presentation is indicated, and in children between 1 and 4 years of age, a dose of 200 mg every 12 hours for 4 days is suggested.
3) Others: Baking soda or sodium bicarbonate, N-Acetylcysteine (NAC), Colchicine and Vitamin D can be additionally included. The doses of these are detailed in the following paragraphs on severe Dengue.

GROUP C: SEVERE DENGUE:

In these cases, the following protocol is proposed:
1) IVM: On the 1st day, a first dose is indicated (as an attack dose) of between 1.2 to 1.4 mg per kilo by body weight and after 12 hours a second dose of 0.6 mg per kg is indicated. The maximum dose to be indicated for the first dose is 120 mg, and 60 mg for the second dose, recommending not to exceed 180 mg between these 2 doses.
Starting on the 2nd day, doses of between 1.2 to 1.4 mg per kilo by body weight in a single daily dose (every 24 hours) for 3 more days are indicated.

If on the 2nd day there are no signs of improvement with monotherapy against the viral load with IVM, it is suggested to add a second antiviral, which may be Amantadine at a dose of 100 mg at 10am and 10pm. It should be taken into account that Amantidine cannot be taken in cases with a diagnosis of closed-angle glaucoma, digestive bleeding, severe renal failure, heart failure, myocarditis, arrhythmias or if you suffer from QT prolongation.

If symptoms still persist on the 5th day, continue with single daily doses of 0.6 mg per kilo by body weight after lunch for 3 to 9 more days.

2) Nifuroxazide: 1 tablet of 400 mg or 2 of 200 mg every 8 hours for 7 days.

If you weigh more than 80 kilos, 400 mg every 8 hours for 7 days is indicated.

In children from 5 to 11 years old, 200 mg every 8 hours in syrup is indicated, from 1 to 4 years old it would be every 12 hours for 5 days.

3) Baking Soda (or Sodium bicarbonate): it is indicated to take between 3 to 3.3 grams (which is equivalent to 1/2 teaspoon of Baking soda or bicarbonate, or 1 1/2 envelopes of Andrews Salt, in 1 glass of water), take at 10am and 10pm for 3 days. In patients who weigh more than 95 kilos, they are instructed to add a third dose at 4pm on the first day. In patients who weigh more than 95 kilos, they are instructed to add a third dose at 4pm, that is, they would take 3 doses a day, at 10am, 4pm and 10pm, for the 3 days.

Baking soda is contraindicated in patients with hypocalcemia and hypochlorhydria.

4) N-Acetylcysteine [NAC]: 1 sachet/envelope or 1 tablet, of 600 mg every 6 hours (2,400 mg per day) for 3 days. In those who weigh between 80 to 96 kilos, 600 mg

every 4 hours or 1,200 mg every 8 hours (3,600 mg per day) is indicated. In patients who weigh more than 95 kilos, 1,200 mg every 6 hours (4,800 mg per day) is indicated.

If there is acute liver failure, an initial dose of 120 mg per kilo of body weight is recommended, followed by 60 mg/kg every 4 hours for 3 days [56,57.58,59,60,61,62]. The recommended doses vary according to the Estate of severity of the patient and their liver involvement.

If formulations in ampoules are available, NAC can be given intravenously [59,60,61].

5) Vitamin D: In case you can get drinkable ampoules of 600,000 IU (Raquiferol or another brand) or in syrup of 150,000 or 300,000 IU, we recommend taking doses of 300,000 on the 1st and 3rd day, or 200,000 IU a day for 3 days. If it is not possible to obtain the drinkable ampoules, it is indicated in capsules, in this case we recommend taking 60,000 IU for the first 3 days and then 30,000 IU per day for 7 more days.

6) Calcium: studies have been published in which a negative correlation between the serum calcium level and the severity of dengue infection has been evidenced [63,64,65]. A calcium dose of 600 mg 3 times a day (morning, afternoon and night: at 8 am, 3 pm and 10 pm) is recommended for 3 days, and then the dose is reduced to 2 times a day (9 am and 9 pm) for 5 more days.

7) Colchicine: we indicate it in practice for fever and inflammation. The suggested dose is 1 tablet of 0.5 or 0.6 mg at 9am and 9pm for 6 days, and may continue for 3 to 6 more days depending on the patient's evolution and the persistence of symptoms. In those who weigh more than 80 kilos, the Colchicine dose is increased to 2 tablets of 0.5 or 0.6 mg at 9am and the 9pm dose of 1 tablet is maintained. In case of analysis results indicating a severe inflammatory state, in addition to Colchicine, one or two doses of Dexamethasone could be indicated, it is suggested in 4 mg tablets or ampoules.

8) Zinc: the recommended dose is 100 mg at 9am and 9pm or 10am and 10pm, for 15 days. It is recommended to take it 1 hour away from food. When taking it, you should avoid consuming dairy products 2 hours before or after taking it, since calcium reduces its absorption. The form of Zinc as Picolinate is recommended, as it is a chelated Zinc, which improves its absorption by the body. Other forms of chelated Zinc such as Citrate and Gluconate can also be used, these have a better level of absorption than non-chelated

forms, but less than Picolinate. The drawback is that it is sometimes difficult to get these forms of Zinc.
9) Tranexamic acid: it has been indicated in cases with active bleeding. The initial dose is 1,000 every 12 hours or 500mg every 8 hours depending on the severity of the case. This dose is maintained until the patient is stable and then the dose is reduced [66].
10) Other Vitamins: Vitamins A, B, C, E and K2 can be additionally included. As it is the most acute stage of the infection, in which a greater quantity of these micronutrients is consumed, higher doses than usual are recommended.
11) Statins: such as Lovastatin. Studies have been published pointing out a potential antiviral effect of some statins, which is why it can be included in the Protocol [67,68,69,27,32,1]
12) Rupatadine: One study showed a trend toward a decreasing proportion of acute dengue patients developing dengue hemorrhagic fever [70] with the use of this H1 Antihistamine.
13) Metformin: several studies have been published pointing out an antiviral effect [71,72,1] and that it could be indicated together with ivermectin for Dengue [72], but it should be taken into account that it is not indicated in patients with renal failure.
14) Mefenamic Acid and COX-2 Inhibitors: there are studies that mention the use of Mefenamic Acid, which would even have an effect against the Dengue virus [67,68], so it should be considered as a alternative. There are also studies in which other NSAIDs [67,69] and COX-2 Inhibitors [70] are mentioned, of which one of the best known and most widely used is Celecoxib.
15) Others: there are published studies in which other medications are mentioned that show an effect against the dengue virus, among these are Doxycycline [69,1], Niclosamide [76] and Hydroxychloroquine [77], so their use could be considered. of any of these together with the IVM. To cover bacterial infections, broad-spectrum antibiotics, such as cephalosporins and metronidazole, may be indicated.

We have described the report of the 3 cases of severe Dengue in a previous publication [78] on the use of high doses of IVM. In these 3 cases, the maximum dose of 180 mg was given during the first day of treatment and they showed a significant clinical improvement after the third day of treatment and managed to recover within 6 to 9 days from the day they started taking ivermectin. They had continuous follow-up at home, with nursing staff and were not hospitalized.

INCLUSION OF NIFUROXAZIDE IN THE TREATMENT OF SEVERE DENGUE AND WITH WARNING SIGNS.

Regarding the indication for Nifuroxazide in cases of severe Dengue and Dengue with warning signs, this is based on our experience of its use together with IVM in moderate and severe cases with Acute COVID. In these patients, after starting the Nifuroxazide doses, within 24 hours we evidenced a general clinical improvement, of fever, chest pain and oxygen saturation [79,80]. Similarly, we are observing that in Dengue an improvement is obtained more quickly by including Nifuroxazide.
Nifuroxazide is an antimicrobial that has been used in humans for more than 50 years, it was patented in 1966. It is regularly used to treat intestinal infections and so-called traveler's diarrhea.
One explanation that we propose, regarding the improvement that patients present with the use of Nifuroxazide, is that this is partly due to the effect of reducing the load of pathogenic microorganisms of the intestinal flora, since in a disease that in very a few days after the onset of the disease generates significant lymphopenia and neutropenia (immunosuppression), an overgrowth of pathogenic organisms that were already present in the intestinal flora can occur. On the other hand, as we described in the publication that we carried out in 2021 [79], Nifuroxazide has many other favorable

effects, important antioxidant, anti-inflammatory and anticancer effects have been identified [81,82].

In this regard, it has been shown to attenuate acute pulmonary and myocardial lesions associated with disseminated infections such as sepsis [81]; this role would be explained by the interruption of the TLR4/ inflammasome NLRP3/ IL-1 signaling pathway. TLR means Toll-like Receptor, which are Toll-like receptors found in cell membranes and serve for the recognition of infectious agents by the organism and induce the production of proinflammatory cytokines and the expression of costimulatory molecules in mature cells that result in immunological warning signs.

It has also been shown to have a potent inhibitory effect on the Transcription Factor STAT3 (which stands for Signal Transducer and Activator of Transcription-3) [82-87] which is associated with various human cancers and usually indicates a poor prognosis. In addition, it has antitumor effects [88,89,90] and a hepatoprotective effect and improvement in the progression of Hepatic Encephalopathy have also been identified [91]. On the other hand, it has an effect of decreasing the cytokines TNF-α, IL-1β, and IL-6 [87,91].

INCLUSION OF BAKING SODA OR SODIUM BICARBONATE IN THE TREATMENT OF SEVERE DENGUE.

Baking soda or bicarbonate has been included in our protocols for Acute and Chronic COVID or Long COVID since 2020 [92,93]. In addition to mentioning that it would have antiviral effects, there are several reasons why it is recommended in cases of severe Dengue, we will mention the main reasons:

1) ALKALINIZER. It increases the pH of the organism, making it more alkaline, which is unfavorable for viruses in general.

3) ANTI-INFLAMMATORY. It activates the cholinergic anti-inflammatory pathway, in which the Spleen is an essential site for this process, since there is a circuit through the vagus nerve that requires the spleen for the anti-inflammatory effect to occur.

4) ERGOGENIC. improves exercise performance, can delay the onset of fatigue.

5) PROTECTOR OF KIDNEY FUNCTION. It protects kidney function, suppresses inflammation, and improves cellular metabolism in patients with chronic kidney disease.

6) ANTI-CANCER. In cancer, the production of lactate or lactic acid increases, generating an acidic microenvironment at the intratumoral level, which in turn promotes cancer progression. Several studies have reported possible anticancer effects of sodium bicarbonate, especially when it is indicated via local infusion.

7) STOMACH ANTACID. It directly reduces acidity at the level of the stomach, which in turn reduces the risk of digestive bleeding due to the frequent use of NSAIDs.

8) FAVORABLE EFFECTS ON THE IMMUNE SYSTEM. generates a beneficial effect in autoimmune diseases.

9) ANTIHISTAMINIC. It has antihistamine properties, these would be associated with interactions with Calcium and the reduction of the acid medium.

In our previous publications we have described in more detail and with the corresponding references the multiple benefits of Baking soda or sodium bicarbonate [93,94]. This is sold as a powder in jars or in packets for use in the kitchen, it is also available in capsules. If it is taken in powder form, its taste is not pleasant. As alternatives, there are commercial presentations in effervescent sachets such as the so-called Andrews Salt, which contains 2.18 grams of Sodium Bicarbonate and 0.88 grams of Magnesium Sulfate in each sachet.

There are other trademarks with similar content, but it should be verified if it contains Aspirin or Acetylsalicylic Acid (ASA), in which case it should be avoided in Dengue.

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REFERENCES:

1.Palanichamy Kala M, St John AL, Rathore APS. Dengue: Update on Clinically Relevant Therapeutic Strategies and Vaccines. Curr Treat Options Infect Dis. 2023;15(2):27-52. Epub 2023 Apr 18. PMID: 37124673; PMCID: PMC10111087. DOI: https://doi.org/10.1007/s40506-023-00263-w

2. Aguirre-Chang, Gustavo. COVID 19: Paracetamol (Acetaminophen) should not be used in excess because it reduces glutathione and masking the clinical picture. ResearchGate. August 2020. https://www.researchgate.net/publication/344207944
DOI: http://dx.doi.org/10.13140/RG.2.2.14934.47680/2

3. Vasikasin V, Rojdumrongrattana T, Chuerboonchai W, Siriwiwattana T, Thongtaeparak W, Niyasom S, Lertliewtrakool N, Jitsiri S, Changpradub D. Effect of standard dose paracetamol versus placebo as antipyretic therapy on liver injury in adult dengue infection: a multicentre randomised controlled trial. Lancet Glob Health. 2019 May;7(5):e664-e670. PMID: 31000133.
DOI: https://doi.org/10.1016/S2214-109X(19)30032-4

4. Deen J, von Seidlein L. Paracetamol for dengue fever: no benefit and potential harm? Lancet Glob Health. 2019 May;7(5):e552-e553. PMID: 31000122.
DOI: https://doi.org/10.1016/S2214-109X(19)30157-3

5. Pandejpong D, Saengsuri P, Rattarittamrong R, Rujipattanakul T, Chouriyagune C. Is excessive acetaminophen intake associated with transaminitis in adult patients with dengue fever? Intern Med J. 2015 Jun;45(6):653-8. PMID: 25828253.\DOI: https://doi.org/10.1111/imj.12756

6. Syed AA, Aslam F, Hakeem H, Siddiqui F, Nasir N. Frequency of worsening liver function in severe dengue hepatitis patients receiving paracetamol: A retrospective analysis of hospital data. J Pak Med Assoc. 2017 Mar;67(3):400-404. PMID: 28303989.
https://jpma.org.pk/article-details/8117?article_id=8117

7. Aguirre-Chang G, Trujillo A., Córdova JA. Paracetamol (Acetaminophen) showed no effect on fever and pain in Dengue and on the contrary increases liver transaminases associated with its hepatotoxic effect. RG. June, 2023. https://www.researchgate.net/publication/371370377

8. Low JG, Ooi EE, Vasudevan SG. Current Status of Dengue Therapeutics Research and Development. J Infect Dis. 2017 Mar 1;215(suppl_2):S96-S102. PMID: 28403438; PMCID: PMC5388029. DOI: https://doi.org/10.1093/infdis/jiw423

9. Yamasmith E, Fadhil A-HS-A, Avirutnan P, Angkasekwinai N, Mairiang D, Wongsawat E, Tanrumluk S, Fongsri U, Suputtamongkol Y. Efficacy and Safety of Ivermectin against Dengue Infection: A Phase III, Randomized, Double-blind, Placebo-controlled Trial. The 34 th Annual Meeting The Royal College of Physicians of Thailand "Internal Medicine and One Health" 26 th-28 th. PEACH R Cliff Beach Resort. 2018; http://www.rcpt.org/abstractdb/media/abstract/CON2018/Best%20Resident27/BRA_77_Eakkawit.pdf

10. Avirutnan P et al. Pharmacokinetics and Pharmacodynamics of Ivermectin in Pediatric Dengue Patients (PKIDEN). Clinical Trial Phase II. 5th Asia Dengue Summit 2022. Singapore. Junio 2022. https://beta.clinicaltrials.gov/study/NCT03432442

11. Xu T-L, Han Y, Liu W, Pang X-Y, Zheng B, Zhang Y, Zhou XN. Antivirus effectiveness of ivermectin on dengue virus type 2 in Aedes albopictus. PLoS Neglected Tropical Diseases, 12(11): e0006934. 2018. PMID: 30452439; PMCID: PMC6277121.
DOI: https://doi.org/10.1371/journal.pntd.0006934

12.. Wagstaff KM, Sivakumaran H, Heaton SM, Harrich D, Jans DA. Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. Biochem J. 2012 May 1;443(3):851-6. PMID: 22417684; PMCID: PMC3327999.
DOI: https://doi.org/10.1042/BJ20120150

11. Xu TL, Han Y, Liu W, Pang XY, Zheng B, Zhang Y, Zhou XN. Efectividad antivirus de la ivermectina sobre el virus del dengue tipo 2 en Aedes albopictus . PLoS Enfermedades tropicales desatendidas , 12(11): e0006934. 2018.PMID: 30452439; PMCID: PMC6277121.
1. DOI: https://doi.org/10.1371/journal.pntd.0006934
12. Wagstaff KM, Sivakumaran H, Heaton SM, Harrich D, Jans DA. La ivermectina es un inhibidor específico de la importación nuclear mediada por importina α / β capaz de inhibir la replicación del VIH-1 y del virus del dengue. Biochem J. 1 de mayo de 2012; 443 (3): 851-6. PMID: 22417684; PMCID: PMC3327999.
DOI: https://doi.org/10.1042/BJ20120150

13. Mastrangelo E, Pezzullo M, De Burghgraeve T, Kaptein S, Pastorino B, Dallmeier K, de Lamballerie X, Neyts J, Hanson AM, Frick DN, Bolognesi M, Milani M. La ivermectina es un potente inhibidor de la replicación de flavivirus que se dirige específicamente a la helicasa NS3. Actividad: nuevas perspectivas para un fármaco antiguo. J Antimicrobios Quimioma . Agosto de 2012; 67 (8): 1884-94. Publicación electrónica del 25 de abril de 2012. PMID: 22535622; PMCID: PMC3888155.
DOI: https://doi.org/10.1093/jac/dks147

14. Tay MY, Fraser JE, Chan WK, Moreland NJ, Rathore AP, Wang C, Vasudevan SG, Jans DA. Localización nuclear del virus del dengue (DENV) 1-4 proteína no estructural 5; protección contra los 4 serotipos de DENV por el inhibidor Ivermectina. Res. antivirus. Septiembre de 2013;99(3):301-6. Publicación electrónica del 14 de junio de 2013. PMID: 23769930. DOI: https://doi.org/10.1016/j.antiviral.2013.06.002
115.0 Yang SNY, Atkinson SC, Wang C, Lee A, Bogoyevitch MA, Borg NA, Jans DA. El antiviral de amplio espectro ivermectina se dirige al transporte nuclear del huésped importina heterodímero α / β1 . Res. antivirus. 2020 mayo; 177: 104760 . Publicación electrónica del 3 de marzo de 2020. PMID: 32135219.
1. DOI: https://doi.org/10.1016/j.antiviral.2020.104760
15 . Yang SNY, Atkinson SC, Wang C, Lee A, Bogoyevitch MA, Borg NA, Jans DA. El antiviral de amplio espectro ivermectina se dirige al transporte nuclear del huésped importina heterodímero α / β1 . Res. antivirus. 2020 mayo; 177: 104760 . Publicación electrónica del 3 de marzo de 2020. PMID: 32135219.
DOI: https://doi.org/10.1016/j.antiviral.2020.104760

16. Suputtamongkol Y, Avirutnan P, Mairiang D, Angkasekwinai N, Niwattayakul K, Yamasmith E, Saleh- Arong FA, Songjaeng A, Prommool T, Tangthawornchaikul N, Puttikhunt C, Hunnangkul S, Komoltri C, Thammapalo S, Malasit P. La ivermectina acelera la circulación Aclaramiento de la proteína no estructural 1 (NS1) en pacientes adultos con dengue: un ensayo combinado de fase 2/3, aleatorizado, doble ciego y controlado con placebo. Clin Infect Dis. 2021 18 de mayo;72(10):e 586-e593. PMID: 33462580.
DOI: https://doi.org/10.1093/cid/ciaa1332

17. Arpornsuwan , M. y Arpornsuwan , M. Una propuesta de diagnóstico temprano y manejo temprano en la infección por dengue y posible COVID-19. Investigación exploratoria e hipótesis en medicina 2020;5(4):141-151. DOI: http://dx.doi.org/10.14218/ERHM.2020.00059
18. Martín AJ, Jans DA. Antivirales que se dirigen a la interfaz del virus IMP α / β 1 del huésped. bioquímica Trans social . 26 de febrero de 2021;49(1):281-295. PMID: 33439253; PMCID: PMC7925013.
DOI: https://doi.org/10.1042/BST20200568

19. Ooi EE. Repurposing Ivermectin as an Anti-dengue Drug. Clin Infect Dis. 2021 May 18;72(10):e594-e595. PMID: 33124646. OI: Oye EE. Reutilización de la ivermectina como fármaco contra el dengue. Clin Infect Dis. 2021 18 de mayo;72(10):e 594-e595. PMID: 33124646. OI: https://doi.org/10.1093/cid/ciaa1341
20. Varghese FS, Kaukinen P, Gläsker S, Bespalov M, Hanski L, Wennerberg K, Kümmerer BM, Ahola T. Discovery of berberine, abamectin and ivermectin as antivirals against chikungunya and other alphaviruses. Antiviral Res. 2016 Feb;126:117-24. Epub 2016 Jan 2. PMID: 26752081.
DOI: https://doi.org/10.1016/j.antiviral.2015.12.012
21. Palacios-Rápalo SN, Farfan-Morales CN, Cordero-Rivera CD, De Jesús-González LA, Reyes-Ruiz JM, Meraz-Ríos MA, Del Ángel RM. An ivermectin - atorvastatin combination impairs nuclear transport inhibiting dengue infection in vitro and in vivo. iScience. 2023 Oct 27;26(12):108294. 2023.108294. PMID: 38034354; PMCID: PMC10682259.
DOI: https://doi.org/10.1016/j.isci
22. Madhry D, Malvankar S, Phadnis S, Srivastava RK, Bhattacharyya S, Verma B. Synergistic correlation between host angiogenin and dengue virus replication. RNA Biol. 2023 Jan;20(1):805-816. Epub 2023 Oct 5. PMID: 37796112; PMCID: PMC10557563. Ivm
DOI: https://doi.org/10.1080/15476286.2023.2264003
23. Crump A. Ivermectin: enigmatic multifaceted 'wonder' drug continues to surprise and exceed expectations. J Antibiot (Tokyo). 2017 May;70(5):495-505. Epub 2017 Feb 15. PMID: 28196978.
DOI: https://doi.org/10.1038/ja.2017.11
24. Zhu Y, Liang M, Yu J, Zhang B, Zhu G, Huang Y, He Z, Yuan J. Repurposing of Doramectin as a New Anti-Zika Virus Agent. Viruses. 2023 Apr 27;15(5):1068. PMID: 37243154;
PMCID: PMC10221537. DOI: https://doi.org/10.3390/v15051068
25. Hirsch RR and Carvallo HE. Repurposed drugs for re emerging diseases: ivermectin in arboviruses. J. res. appl. med., Vol. 1, Nro 6, Art. 1. 2023.
https://researchandappliedmedicine.com/revistas/vol1/revista6/editorial-ingles.pdf
26. Denolly S, Guo H, Martens M, Płaszczyca A, Scaturro P, Prasad V, Kongmanas K, Punyadee N, Songjaeng A, Mairiang D, Pichlmair A, Avirutnan P, Bartenschlager R. Dengue virus NS1 secretion is regulated via importin-subunit β1 controlling expression of the chaperone GRp78 and targeted by the clinical drug ivermectin. mBio. 2023 Oct 31;14(5):e0144123. Epub 2023 Sep 13. PMID: 37702492; PMCID: PMC10653883. DOI: https://doi.org/10.1128/mbio.01441-23
27. Cruz, A. Evaluación de la actividad antiviral de los fármacos NDGA (Nordihydroguaiaretic acid, from the Larrea tridentata plant), Vitamina D, Lovastatina e Ivermectina ante infección con Dengue en células HuH7. Tesis para Maestría. Instituto Politécnico Nacional de México. Departamento de Infectómica y Patogénesis Molecular. 2017.
https://repositorio.cinvestav.mx/bitstream/handle/cinvestav/1056/SSIT0014968.pdf?sequence=1
https://repositorio.cinvestav.mx/handle/cinvestav/1056
28. Gobierno de México. Diseñan y prueban antivirales como estrategia para el control del Dengue. Octubre 2019.
https://conexion.cinvestav.mx/Publicaciones/dise241an-y-prueban-antivirales-como-estrategia-para-el-control-del-dengue
29. Niaz, A. Ivermectin is able to inhibit replication of HIV-1 and dengue virus by a specific inhibitor of importin α/β-mediated nuclear import mechanism. ResearchGate. December 2021.
http://www.eldiariodelarioja.com.ar/21888-comenz-el-estudio-para-dar-tratamiento-al-dengue
30. Low JG, Gatsinga R, Vasudevan SG, Sampath A. Dengue Antiviral Development: A Continuing Journey. Adv Exp Med Biol. 2018;1062:319-332. PMID: 29845542.
DOI: https://doi.org/10.1007/978-981-10-8727-1_22
31. Botta L, Rivara M, Zuliani V & Radi M. Drug repurposing approaches to fight Dengue virus infection and related diseases. Front Biosci (Landmark Ed), 2018, vol. 23, no 6, p. 997-1019.

https://article.imrpress.com/journal/FBL/23/6/10.2741/4630/Landmark4630.pdf
32. Troost B, Smit JM. Recent advances in antiviral drug development towards dengue virus. Curr Opin Virol. 2020 Aug;43:9-21. Epub 2020 Aug 11. PMID: 32795907. HIV, Hep C, lovastatin
DOI: https://doi.org/10.1016/j.coviro.2020.07.009
33. Lin CC, Chen WC. Treatment Effectiveness of Amantadine Against Dengue Virus Infection. Am J Case Rep. 2016 Dec 5;17:921-924. PMID: 27920420; PMCID: PMC5158130.
DOI: https://doi.org/10.12659/AJCR.901014
34. Koff WC, Elm JL Jr, Halstead SB. Inhibition of dengue virus replication by amantadine hydrochloride. Antimicrob Agents Chemother. 1980 Jul;18(1):125-9. PMID: 7416739; PMCID: PMC283951.
DOI: https://doi.org/10.1128/AAC.18.1.125
35. Koff WC, Elm JL Jr, Halstead SB. Suppression of dengue virus replication in vitro by rimantadine hydrochloride. Am J Trop Med Hyg. 1981 Jan;30(1):184-9. PMID: 7212165.
DOI: https://doi.org/10.4269/ajtmh.1981.30.184
36. Rashmi SH, Disha KS, Sudheesh N, Karunakaran J, Joseph A, Jagadesh A, Mudgal PP. Repurposing of approved antivirals against dengue virus serotypes: an in silico and in vitro mechanistic study. Mol Divers. 2023 Aug 26. Epub ahead of print. Erratum in: Mol Divers. 2023 Nov PMID: 37632595. DOI: https://doi.org/10.1007/s11030-023-10716-5
37. Riswari SF, Tunjungputri RN, Kullaya V, Garishah FM, Utari GSR, Farhanah N, Overheul GJ, Alisjahbana B, Gasem MH, Urbanus RT, de Groot PG, Lefeber DJ, van Rij RP, van der Ven A, de Mast Q. Desialylation of platelets induced by Von Willebrand Factor is a novel mechanism of platelet clearance in dengue. PLoS Pathog. 2019 Mar 8;15(3):e1007500. PMID: 30849118; PMCID: PMC6426266. DOI: https://doi.org/10.1371/journal.ppat.1007500
38. Dengue Alliance. Treatments for dengue: a Global Dengue Alliance to address unmet needs. Lancet Glob Health. 2023 Nov;11(11):e1680-e1681. Epub 2023 Aug 31. PMID: 37660714.
DOI: https://doi.org/10.1016/S2214-109X(23)00362-5
39. Niranjan R, Saxena N, & Das A. Dengue control, if not by vaccination and vector strategies, then possibly by therapeutics. The Lancet Infectious Diseases. Correspondence. Jan, 2024.
DOI: https://doi.org/10.1016/S1473-3099(23)00782-X
40. Foy BD, Some A, Magalhaes T, Gray L, Rao S, Sougue E, Jackson CL, Kittelson J, Slater HC, Bousema T, Da O, Coulidiaty AGV, Colt M, Wade M, Richards K, Some AF, Dabire RK, Parikh S. Repeat Ivermectin Mass Drug Administrations for Malaria Control II: Protocol for a Double-blind, Cluster-Randomized, Placebo-Controlled Trial for the Integrated Control of Malaria. JMIR Res Protoc. 2023 Mar 20;12:e41197. PMID: 36939832; PMCID: PMC10132043.
DOI: https://doi.org/10.2196/41197
41. Dabira ED, Soumare HM, Lindsay SW, Conteh B, Ceesay F, Bradley J, Kositz C, Broekhuizen H, Kandeh B, Fehr AE, Nieto-Sanchez C, Ribera JM, Peeters Grietens K, Smit MR, Drakeley C, Bousema T, Achan J, D'Alessandro U. Mass Drug Administration With High-Dose Ivermectin and Dihydroartemisinin-Piperaquine for Malaria Elimination in an Area of Low Transmission With High Coverage of Malaria Control Interventions: Protocol for the MASSIV Cluster Randomized Clinical Trial. JMIR Res Protoc. 2020 Nov 19;9(11):e20904. PMID: 33211022; PMCID: PMC7714640.
DOI: https://doi.org/10.2196/20904
42. Heukelbach J, Winter B, Wilcke T, Muehlen M, Albrecht S, de Oliveira FA, Kerr-Pontes LR, Liesenfeld O, Feldmeier H. Selective mass treatment with ivermectin to control intestinal helminthiases and parasitic skin diseases in a severely affected population. Bull World Health Organ. 2004 Aug;82(8):563-71. Epub 2004 Sep 13. PMID: 15375445; PMCID: PMC2622929.
Full text: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2622929/pdf/15375445.pdf
43. Jittamala P, Monteiro W, Smit MR, Pedrique B, Specht S, Chaccour CJ, Dard C, Del Giudice P, Khieu V, Maruani A, Failoc-Rojas VE, Sáez-de-Ocariz M, Soriano-Arandes A, Piquero-Casals J,

Faisant A, Brenier-Pinchart MP, Wimmersberger D, Coulibaly JT, Keiser J, Boralevi F, Sokana O, Marks M, Engelman D, Romani L, Steer AC, von Seidlein L, White NJ, Harriss E, Stepniewska K, Humphreys GS, Kennon K, Guerin PJ, Kobylinski KC. A systematic review and an individual patient data meta-analysis of ivermectin use in children weighing less than fifteen kilograms: Is it time to reconsider the current contraindication? PLoS Negl Trop Dis. 2021 Mar 17;15(3):e0009144. Erratum in: PLoS Negl Trop Dis. 2023 Jan 6;17(1):e0011053. PMID: 33730099; PMCID: PMC7968658.
DOI: https://doi.org/10.1371/journal.pntd.0009144
44. OMS. Oncocercosis. https://www.who.int/es/news-room/fact-sheets/detail/onchocerciasis
45. Marty FM, Lowry CM, Rodriguez M, Milner DA, Pieciak WS, Sinha A, Fleckenstein L, Baden LR. Treatment of human disseminated strongyloidiasis with a parenteral veterinary formulation of ivermectin. Clin Infect Dis. 2005 Jul 1;41(1):e5-8. Epub 2005 May 11. PMID: 15937753.
DOI: https://doi.org/10.1086/430827
46. Vazquez Guillamet LJ, Saul Z, Miljkovich G, Vilchez GA, Mendonca N, Gourineni V, Lillo N, Pinto M, Baig A, Gangcuangco LM. Strongyloides Stercoralis Infection Among Human Immunodeficiency Virus (HIV)-Infected Patients in the United States of America: A Case Report and Review of Literature. Am J Case Rep. 2017 Apr 3;18:339-346. PMID: 28366929; PMCID: PMC5386446.
DOI: https://doi.org/10.12659/ajcr.902626
47. Zeitler K, Jariwala R, Restrepo-Jaramillo R, Kapadia S, Casanas B, Alrabaa S, Sriaroon C. Successful use of subcutaneous ivermectin for the treatment of Strongyloides stercoralis hyperinfection in the setting of small bowel obstruction and paralytic ileus in the immunocompromised population. BMJ Case Rep. 2018 Jun 4;2018:bcr2017223138. PMID: 29866667; PMCID: PMC5990086.
DOI: https://doi.org/10.1136/bcr-2017-223138
48. Barrett J, Broderick C, Soulsby H, Wade P, Newsholme W. Subcutaneous ivermectin use in the treatment of severe Strongyloides stercoralis infection: two case reports and a discussion of the literature. J Antimicrob Chemother. 2016 Jan;71(1):220-5. Epub 2015 Oct 12. PMID: 26462990. DOI: https://doi.org/10.1093/jac/dkv315
49. Lichtenberger P, Rosa-Cunha I, Morris M, Nishida S, Akpinar E, Gaitan J, Tzakis A, Doblecki-Lewis S. Hyperinfection strongyloidiasis in a liver transplant recipient treated with parenteral ivermectin. Transpl Infect Dis. 2009 Apr;11(2):137-42. Epub 2008 Dec 17. PMID: 19144097.
DOI: https://doi.org/10.1111/j.1399-3062.2008.00358.x
50. Hennessey DC, Ballesteros ÓA, Merchán DJ, Guevara FO, Severiche DF. Subcutaneous ivermectin for the treatment of the hyperinfection syndrome by Strongyloides stercoralis. Biomedica. 2020 Jun 15;40(2):228-232. English, Spanish. PMID: 32673452; PMCID: PMC7505505.
DOI: https://doi.org/10.7705/biomedica.5140
51. Grossi PA, Lombardi D, Petrolo A, Rovelli C, Di Rosa Z, Perriccioli G, Rossi A, Minoja G, Scaglione F, Dalla Gasperina D. Strongyloides stercoralis Hyperinfection in an HIV-Infected Patient Successfully Treated with Subcutaneous Ivermectin. Trop Med Infect Dis. 2018 Apr 27;3(2):46. PMID: 30274442; PMCID: PMC6073990.
DOI: https://doi.org/10.3390/tropicalmed3020046
52. Turner SA, Maclean JD, Fleckenstein L, Greenaway C. Parenteral administration of ivermectin in a patient with disseminated strongyloidiasis. Am J Trop Med Hyg. 2005 Nov;73(5):911-4. PMID: 16282302. https://pubmed.ncbi.nlm.nih.gov/16282302/
53. World Health Organization (WHO) and TDR (Special Programme for Research and Training in Tropical Diseases). Dengue guidelines for diagnosis, treatment, prevention and control: New edition 2009.
https://iris.paho.org/bitstream/handle/10665.2/31071/9789995479213-spa.pdf?sequence=1&isAllowed=y

54. . Jayarajah U, Dissanayake U, Abeysuriya V, De Silva PK, Jayawardena P, Kulatunga A, Fernando H, Madarasinghe M, Hapugoda D, Perera L, Kannangara V, Udayangani C, Peiris R, Faizer S, Yasawardene P, De Mel S, De Zoysa I, Seneviratne SL. Comparing the 2009 and 1997 World Health Organization dengue case classifications in a large cohort of South Asian patients. J Infect Dev Ctries. 2020 Jul 31;14(7):781-787. PMID: 32794470.
DOI: https://doi.org/10.3855/jidc.12468
55. Tsai CY, Lee IK, Lee CH, Yang KD, Liu JW. Comparisons of dengue illness classified based on the 1997 and 2009 World Health Organization dengue classification schemes. J Microbiol Immunol Infect. 2013 Aug;46(4):271-81. Epub 2012 Sep 28. PMID: 23022142.
DOI: https://doi.org/10.1016/j.jmii.2012.07.005
56. Sharieff S, Idrees A, Rafai W, Bukhari SUS. Use of Oral N-Acetylcysteine (NAC) in Non-Acetaminophen-Induced Acute Hepatic Failure. Cureus. 2023 Mar 7;15(3):e35852. PMID: 37033589; PMCID: PMC10077496. DOI: https://doi.org/10.7759/cureus.35852
57. Tafere GG, Wondafrash DZ, Demoz FB. Repurposing of N-Acetylcysteine for the Treatment of Dengue Virus-Induced Acute Liver Failure. Hepat Med. 2020 Nov 3;12:173-178. PMID: 33177895; PMCID: PMC7650016. DOI: https://doi.org/10.2147/HMER.S263840
58. Sriphongphankul H, Liabsuetrakul T, Osatakul S. Clinical Outcomes of Children Diagnosed Dengue-Associated Acute Liver Failure with or without N-Acetylcysteine Treatment: A Retrospective Cohort Study. J Trop Pediatr. 2021 May 17;67(2):fmab039. PMID: 34100091.
DOI: https://doi.org/10.1093/tropej/fmab039
59. Kanter MZ. Comparison of oral and i.v. acetylcysteine in the treatment of acetaminophen poisoning. Am J Health Syst Pharm. 2006 Oct 1;63(19):1821-7. PMID: 16990628.
DOI: https://doi.org/10.2146/ajhp060050
60. Dissanayake DMDIB, Gunaratne WMSN, Kumarihamy KWMPP, Kularatne SAM, Kumarasiri PVR. Use of intravenous N-acetylcysteine in acute severe hepatitis due to severe dengue infection: a case series. BMC Infect Dis. 2021 Sep 20;21(1):978. PMID: 34544380; PMCID: PMC8454086.
DOI: https://doi.org/10.1186/s12879-021-06681-9
61. Gupta M, Gupta S, Sood D, Gupta A, Jesrani G. Role of N-acetylcysteine in liver injury due to dengue fever. Trop Doct. 2023 Oct;53(4):475-480. Epub 2023 Jun 13. PMID: 37312532.
DOI: https://doi.org/10.1177/00494755231176317
62. Amjad W, Thuluvath P, Mansoor M, Dutta A, Ali F, Qureshi W. N-acetylcysteine in non-acetaminophen-induced acute liver failure: a systematic review and meta-analysis of prospective studies. Prz Gastroenterol. 2022;17(1):9-16. Epub 2021 Jul 14. PMID: 35371352; PMCID: PMC8942009.
DOI: https://doi.org/10.5114/pg.2021.107797
63. Kumar G, Saini RP, Rani A. Study of Correlation of Serum Calcium Level with Disease Severity in Dengue Patients. J Assoc Physicians India. 2022 Apr;70(4):11-12. PMID: 35443506. https://pubmed.ncbi.nlm.nih.gov/35443506/
64. Constantine GR, Rajapakse S, Ranasinghe P, Parththipan B, Wijewickrama A, Jayawardana P. Hypocalcemia is associated with disease severity in patients with dengue. J Infect Dev Ctries. 2014 Sep 12;8(9):1205-9. PMID: 25212087.
DOI: https://doi.org/10.3855/jidc.4974
65. Shivanthan MC, Rajapakse S. Dengue and calcium. Int J Crit Illn Inj Sci. 2014 Oct-Dec;4(4):314-6. PMID: 25625064; PMCID: PMC4296335.
DOI: https://doi.org/10.4103/2229-5151.147538
66. Kularatne, S.A.M., Ralapanawa, U., Dalugama, C. et al. Series of 10 dengue fever cases with unusual presentations and complications in Sri Lanka: a single centre experience in 2016. BMC Infect Dis 18, 674 (2018). DOI: https://doi.org/10.1186/s12879-018-3596-5

67. Osuna-Ramos JF, Farfan-Morales CN, Cordero-Rivera CD, De Jesús-González LA, Reyes-Ruiz JM, Hurtado-Monzón AM, Palacios-Rápalo SN, Jiménez-Camacho R, Meraz-Ríos MA, Del Ángel RM. Cholesterol-Lowering Drugs as Potential Antivirals: A Repurposing Approach against Flavivirus Infections. Viruses. 2023 Jun 28;15(7):1465. PMID: 37515153; PMCID: PMC10383882. DOI: https://doi.org/10.3390/v15071465

68. Bryan-Marrugo OL, Arellanos-Soto D, Rojas-Martinez A, Barrera-Saldaña H, Ramos-Jimenez J, Vidaltamayo R, Rivas-Estilla AM. The anti dengue virus properties of statins may be associated with alterations in the cellular antiviral profile expression. Mol Med Rep. 2016 Sep;14(3):2155-63. Epub 2016 Jul 13. PMID: 27431377. DOI: https://doi.org/10.3892/mmr.2016.5519

69. Niranjan R, Murugasamy V, Sunilkumar A, Manoj H, Ganesh K, Vidhyapriya P, Sankari T, Muthukumaravel S, Kumar A. Atorvastatin attenuates NS1 (Non-structural protein-1) of dengue type-2 serotype-induced expressions of matrix metalloproteinases in HL-60 cells, differentiated to neutrophils: Implications for the immunopathogenesis of dengue viral disease. Int Immunopharmacol. 2022 Nov;112:109082. Epub 2022 Sep 12. PMID: 36108401.
DOI: https://doi.org/10.1016/j.intimp.2022.109082

70. Malavige GN, Jeewandara C, Wijewickrama A, Gunasinghe D, Mahapatuna SD, Gangani C, Vimalachandran V, Jayarathna G, Perera Y, Wanigatunga C, Dissanayake H, Prathapan S, Narangoda E, Idampitiya D, Gomes L, Wickramanayake S, Sahabandu P, Ogg GS. Efficacy of rupatadine in reducing the incidence of dengue haemorrhagic fever in patients with acute dengue: A randomised, double blind, placebo-controlled trial. PLoS Negl Trop Dis. 2022 Jun 1;16(6):e0010123. PMID: 35648794; PMCID: PMC9191706.
DOI: https://doi.org/10.1371/journal.pntd.0010123

71. Farfan-Morales CN, Cordero-Rivera CD, Osuna-Ramos JF, Monroy-Muñoz IE, De Jesús-González LA, Muñoz-Medina JE, Hurtado-Monzón AM, Reyes-Ruiz JM, Del Ángel RM. The antiviral effect of metformin on zika and dengue virus infection. Sci Rep. 2021 Apr 22;11(1):8743. PMID: 33888740; PMCID: PMC8062493. DOI: https://doi.org/10.1038/s41598-021-87707-9

72. Kellstein D, Fernandes L. Symptomatic treatment of dengue: should the NSAID contraindication be reconsidered? Postgrad Med. 2019 Mar;131(2):109-116. Epub 2019 Jan 16. PMID: 30575425.
DOI: https://doi.org/10.1080/00325481.2019.1561916

73. Rothan HA, Bahrani H, Abdulrahman AY, Mohamed Z, Teoh TC, Othman S, Rashid NN, Rahman NA, Yusof R. Mefenamic acid in combination with ribavirin shows significant effects in reducing chikungunya virus infection in vitro and in vivo. Antiviral Res. 2016 Mar;127:50-6. Epub 2016 Jan 18. PMID: 26794398. DOI: https://doi.org/10.1016/j.antiviral.2016.01.006

74. Rothan HA, Buckle MJ, Ammar YA, Mohammadjavad P, Shatrah O, Noorsaadah AR, Rohana Y. Study the antiviral activity of some derivatives of tetracycline and non-steroid anti inflammatory drugs towards dengue virus. Trop Biomed. 2013 Dec;30(4):681-90. PMID: 24522138. Texto completo en: https://www.msptm.org/files/681_-_690_Rothan_HA.pdf

75. Lin CK, Tseng CK, Wu YH, Liaw CC, Lin CY, Huang CH, Chen YH, Lee JC. Cyclooxygenase-2 facilitates dengue virus replication and serves as a potential target for developing antiviral agents. Sci Rep. 2017 Mar 20;7:44701. PMID: 28317866; PMCID: PMC5357798.
DOI: https://doi.org/10.1038/srep44701

76. Kao J-C, HuangFu W-C, Tsai T-T, Ho M-R, Jhan M-K, Shen T-J, et al. (2018) The antiparasitic drug Niclosamide inhibits dengue virus infection by interfering with endosomal acidification independent of mTOR. PLoS Negl Trop Dis 12(8): e0006715.
DOI: https://doi.org/10.1371/journal.pntd.0006715

77. Wang LF, Lin YS, Huang NC, Yu CY, Tsai WL, Chen JJ, Kubota T, Matsuoka M, Chen SR, Yang CS, Lu RW, Lin YL, Chang TH. Hydroxychloroquine-inhibited dengue virus is associated with host defense machinery. J Interferon Cytokine Res. 2015 Mar;35(3):143-56. Epub 2014 Oct 16.

PMID: 25321315; PMCID: PMC4350140. DOI: https://doi.org/10.1089/jir.2014.0038
78. Aguirre-Chang, Gustavo, Córdova M., José Aníbal and Trujillo F., Aurora. Side Effects by dose of 180 mg of Ivermectin. Report of 4 Cases: 1 with COVID and 3 with severe Dengue. ResearchGate. May 2023. https://www.researchgate.net/publication/371165631
79. Aguirre-Chang, Gustavo, Córdova M., José Aníbal and Trujillo F., Aurora. COVID by variants of SARS CoV-2: Inclusion of Nifuroxazide in the First Line of Therapeutic Action. ResearchGate. February 2021. https://www.researchgate.net/publication/349089526
80. Aguirre-Chang G, Córdova M. JA, Trujillo F. A. COVID by variants of SARS CoV-2: Inclusion of Nifuroxazide and Atapulgite. ResearchGate. January 18, 2021.
DOI: http://dx.doi.org/10.13140/RG.2.2.25174.68166/2
https://www.researchgate.net/publication/348590133
81. Khodir A., Samra Y., Said E. A novel role of nifuroxazide in attenuation of sepsis-associated acute lung and myocardial injuries; role of TLR4/NLPR3/IL-1β signaling interruption. Life Sciences, Vol. 256, September 2020. DOI: https://doi.org/10.1016/j.lfs.2020.117907
82. Althagafy HS, El-Aziz MKA, Ibrahim IM, Abd-Alhameed EK, Hassanein EHM. Pharmacological updates of nifuroxazide: Promising preclinical effects and the underlying molecular mechanisms. Eur J Pharmacol. 2023 Jul. Epub 2023 May 14. PMID: 37192715.
DOI: https://doi.org/10.1016/j.ejphar.2023.175776
83. Nelson EA, Hideshima T, Gashin LB, et al. Nifuroxazide Inhibits STAT3 Function and Shows Potent Anti-Tumor Activity Against Multiple Myeloma. Blood (2006) 108 (11): 3450.
DOI: https://doi.org/10.1182/blood.V108.11.3450.3450
84. Nelson EA, Walker SR, Kepich A, Gashin LB, Hideshima T, Ikeda H, Chauhan D, Anderson KC, Frank DA. Nifuroxazide inhibits survival of multiple myeloma cells by directly inhibiting STAT3. Blood. 2008 Dec 15;112(13):5095-102. Epub 2008 Sep 29.
DOI: http://dx.doi.org/10.1182/blood-2007-12-129718
85. Song L, Cao X, Ji W, Zhao L, Yang W, Lu M, Yang J. Inhibition of STAT3 enhances UCP1 expression and mitochondrial function in brown adipocytes. Eur J Pharmacol. 2022 Jul 5;926:175040. Epub 2022 May 19. PMID: 35598846.
DOI: http://dx.doi.org/10.1016/j.ejphar.2022.175040
86. Jia H, Cui J, Jia X, et al. Therapeutic effects of STAT3 inhibition by nifuroxazide on murine acute graft graft-vs.-host disease: Old drug, new use. Molecular Medicine Reports. 2017 Dec;16(6):9480-9486. DOI: http://dx.doi.org/10.3892/mmr.2017.7825
87. Said E, Zaitone S, Eldosoky M, Elsherbiny N. (2017). Nifuroxazide, a STAT3 inhibitor, mitigates inflammatory burden and protects against diabetes-induced nephropathy in rats. Chemico-Biological Interactions. 281. DOI: http://dx.doi.org/10.1016/j.cbi.2017.12.030
88. Bailly C. Toward a repositioning of the antibacterial drug nifuroxazide for cancer treatment. Drug Discovery Today. 2019 Sep;24(9):1930-1936.
DOI: http://dx.doi.org/10.1016/j.drudis.2019.06.017
89. Yang F, Hu M, Lei Q, et al. Nifuroxazide induces apoptosis and impairs pulmonary metastasis in breast cancer model. Cell Death & Disease. 2015 Mar;6:e1701.
DOI: http://dx.doi.org/10.1038/cddis.2015.63
90. Luo, Y., Zeng, A., Fang, A. et al. Nifuroxazide induces apoptosis, inhibits cell migration and invasion in osteosarcoma. Invest New Drugs 37, Oct;37(5):1006-1013. Epub 2019 Jan 25. PMID: 30680584.
DOI: https://doi.org/10.1007/s10637-019-00724-4

91. Khodir A, Said E. Nifuroxazide attenuates experimentally-induced hepatic encephalopathy and the associated hyperammonemia and cJNK/caspase-8/TRAIL activation in rats, Life Sciences, Vol. 252, 2020. DOI: https://doi.org/10.1016/j.lfs.2020.117610
92. Aguirre-Chang Gustavo. and Trujillo Aurora. COVID-19: "Therapeutic Test" for patients with Persistent Symptoms or Post-Acute. For Long COVID, Sub-Acute and Chronic COVID, Long hauler, Post-COVID Syndrome, Post-acute Sequelae or Persistent COVID. Research Gate. September 2020. https://www.researchgate.net/publication/344325326
93. Aguirre-Chang G. and Trujillo A. Sub-Acute and Chronic COVID: "Therapeutic Test" for patients with Post Acute COVID Persistent Symptoms for the diagnosis of Persistent Viral Infection. ResearchGate. April 2021. https://www.researchgate.net/publication/351051024
94. Aguirre-Chang Gustavo and Trujillo F, Aurora. First Protocol and Therapeutic Test with Emtricitabine/Tenofovir disoproxil (Truvada or generic) to assist the diagnosis of viral persistence in Post-Acute COVID Syndrome (PACS) or Long COVID and in ME/CFS. ResearchGate. December 2022. https://www.researchgate.net/publication/366412536
95. Other publications available at: https://www.researchgate.net/profile/Gustavo-Aguirre-Chang

93. Aguirre-Chang G. y Trujillo A. COVID Sub-Agudo y Crónico: "Prueba Terapéutica" para pacientes con Síntomas Persistentes de COVID Post-Agudo para el diagnóstico de Infección Viral Persistente. Puerta de la investigación. Abril de 2021. https://www.researchgate.net/publication/351051024
94. Aguirre-Chang Gustavo y Trujillo F, Aurora. Primer Protocolo y Prueba Terapéutica con Emtricitabina/Tenofovir disoproxilo (Truvada o genérico) para ayudar al diagnóstico de persistencia viral en Síndrome de COVID Post-Agudo (PACS) o COVID Largo y en EM/SFC. Puerta de la investigación . Diciembre de 2022. https://www.researchgate.net/publication/366412536
95. Otras publicaciones disponibles en: https://www.researchgate.net/profile/Gustavo-Aguirre-Chang