

Brief Report

Not peer-reviewed version

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Posted Date: 31 July 2023

doi: 10.20944/preprints202307.2079.v1

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Brief Report

Kelleni's Protocol Including Nitazoxanide and NSAIDs to Manage Dengue Virus Disease: A Novel Potential Game-Changer

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Abstract: The WHO has recently warned that this year, the global dengue fever cases could reach close to record highs. Peru has declared national emergency after a recent dengue virus disease outbreak has flared and the situation is rapidly evolving in other countries including some beyond the historical tropical and subtropical areas of transmission. In this brief report, the author discusses how a recent Egyptian dengue virus disease outbreak involving hundreds of patients of all ages was perfectly managed without a single mortality and how as he originally proved ibuprofen and NSAIDs safe and lifesaving to manage COVID-19, they could, together with the broad spectrum nitazoxanide as integral components of the Kelleni's immune-modulatory antiviral protocol, show similar effectiveness in early management of dengue virus disease.

Keywords: dengue virus disease; nitazoxanide; ibuprofen; NSAIDs; Kelleni's protocol

Dengue virus disease (DVD) that include dengue fever, dengue hemorrhagic fever and dengue shock syndrome, is caused by dengue virus; one of the Flaviviridae and it is considered by the WHO as the most rapid growing mosquito-borne infection and as one of the top ten global health threats. DVD has affected least 129 countries of which over 100 tropical and subtropical countries are considered endemic or hyper-endemic with an estimated global annual incidence up to 400 million annual infections of which only around 4.2 million infections were officially reported to the WHO in 2022 [1]. Furthermore, DVD is considered, probably due to climate change [2] and/or viral evolutionary mutations, as an evolving threat to the remaining countries [3] and confirmed cases of locally transmitted DVD were reported in France since 2010 and the numbers of domestic French DVD infections in 2022 were more than the sum of the reported infections in the previous ten years [4]. Alarmingly, in the first half of 2023, the number of DVD cases increased above the average reported in the past five years and it expanded out of the historical transmission areas. Moreover, the number of DVD cases reported until July 01, 2023 has surpassed the total numbers reported in the WHO region of Americas for the entire year of 2022 [5]. Importantly, half of the world population is currently considered to be at risk of contracting DVD and 400,000 cases of dengue hemorrhagic fever are reported annually with thousands of deaths especially in the high risk groups, including children and geriatric patients, due to serious complications as internal or external hemorrhage and shock [3], to be noted that no specific antiviral drug is available to manage DVD and only symptomatic treatment is provided [1,6,7].

Few days ago, on July 18, 2023 the Egyptian ministry of health has officially admitted DVD as the cause of an outbreak of high fever, headache, severe musculoskeletal pain, severe malaise, vomiting, diarrhea and/or some respiratory manifestations resembling SARS CoV-2 infection, that was noticed in some villages located in Qena governorate, Upper Egypt which, unlike other areas in Egypt, experienced DVD for the first time. However, this official announcement described that "some samples" only are positive for dengue virus and it came after an earlier denial/ reluctance that described this outbreak as a "strong flu". Moreover, to the best of my personal investigation, the characteristic dengue rash which is known to occur in almost half of the cases, whether in the acute

or the recovery phases was not frequently encountered. Meanwhile, an unusual rise in “atypical viral” pneumonia cases, though not in an alarming number as encountered in the Qena governorate outbreak, is being encountered elsewhere, to be noted that since the evolution of BA.2 “stealth” variant, the local rapid antigen tests are commonly showing negative results and they are, at least unofficially, required to show positive before an “official” diagnosis of COVID-19 is made, whether or not more advanced molecular investigations are later performed. Accordingly, I wish to inform that at least hundreds of patients of all ages, including some officially confirmed DVD patients, in the affected villages of Qena governorate were safely and effectively managed as COVID-19 using ibuprofen or other NSAIDs to manage their high grade fever and severe pain as well as parenteral crystalloids to manage those who were unable to receive adequate oral fluids; all patients recovered perfectly without any mortalities.

Notably, though SARS CoV-2 and dengue virus co-infection are well reported[8], yet ibuprofen and other NSAIDs are, basing on a conditional recommendation that based on a very low to low certainty, currently recommended against to be used with DVD [6,7] to avoid exacerbating the potential thrombocytopenic hemorrhagic or gastritis complications [6,8]. Interestingly, they were likewise falsely recommended against earlier to manage COVID-19 [9] before later proven safe and lifesaving [10–12]. Hence, I would like to clinically suggest that early administration of Kelleni’s immune-modulatory antiviral protocol using both nitazoxanide and ibuprofen/NSAIDs can abort the progression of the symptomatic DVD from the fever into the severe or critical hemorrhagic/shock phases in high risk groups of patients while interfering with the overlapping immune-inflammatory pathways similarly involved in other viral infections [10,13–15] and Kelleni’s protocol could probably be proven as best early management for SARS CoV-2 and dengue virus co-infection as well, relieving both the physicians as well as the health care authorities especially in the developing countries from the economic and logistic burdens to perform advanced microbiological and molecular investigations which are usually lacking[16]. Moreover, a call to a continued global survey for a potential genetic SARS CoV-2 jump should be also considered relevant and vigilant [16,17].

Notably, nitazoxanide and/or its active metabolite; tizoxanide were previously shown to in-vitro inhibit the replication of some flaviviridae including dengue virus serotype 2 [18,19]. However, until other reports or clinical trials can confirm my recommendation for the early use of ibuprofen/NSAIDs in the management of dengue fever, it is vigilant to prescribe NSAIDs basing on a personalized approach and to prescribe paracetamol together with nitazoxanide to those presenting relatively late while seeking the medical advice and/or lacking urgent medical intervention in their local areas as in the remote impoverished areas, regardless of the results of tourniquet test. Meanwhile, those patients presenting early in the course of infection or those presenting late yet living in rich-resourced countries with an ability to receive prompt medical care and showing negative tourniquet test, should receive ibuprofen/NSAIDs to manage their DVD.

Finally, I urgently recommend fellow physicians and colleagues especially in the Latin American countries as Peru, Brazil and Bolivia that are currently suffering from surge of DVD cases to immediately adopt nitazoxanide in its management; this safe and economic broad spectrum antimicrobial, as an integral part of Kelleni’s immune-modulatory antiviral protocol, has been highly effective and lifesaving in our African safe management of several RNA viral infections e.g. SARS CoV-2, RSV and Influenza in pediatric, geriatric and pregnant patients [11,20,21] and it is most likely, from my point of view, that dengue virus is going to join them.

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