Brief Report

Kelleni's Protocol including NSAIDs and Nitazoxanide to Early Manage Dengue Virus Disease: A Novel Potential Broad Spectrum Antiviral Protocol.

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Posted Date: 30 August 2023

doi: 10.20944/preprints202307.2079.v2

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

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Kelleni's Protocol Including NSAIDs and Nitazoxanide to Early Manage Dengue Virus Disease: A Novel Potential Broad Spectrum Antiviral Protocol

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Abstract: The current recommendation to avoid non-steroidal anti-inflammatory drugs (NSAIDs) in management of dengue virus disease is, as it was adopted earlier in COVID-19, scientifically considered of very low to low certainty. In this perspective I argue, for the first time globally, basing on real-life practice that NSAIDs might be lifesaving in early management of dengue virus disease as I originally argued and proved rightful in COVID-19. Moreover, I also argue that the Egyptian immune-modulatory Kelleni's protocol, including nitazoxanide as an integral component, can be safely and effectively used to early manage COVID-19, human metapneumovirus, dengue virus disease, Zika virus separate or co-infections similar to what has already been experienced and published with separate or conjoined infections with SARS CoV-2, influenza, RSV and Norwalk viruses without the need of prior serological or molecular investigations to determine the causative agent.

Keywords: COVID-19; Human metapneumovirus; Dengue; Influenza; Kelleni's protocol; Norwalk virus; RSV; Zika virus

Introduction

Many researchers all over the world have tried to early distinguish COVID-19 from other viral infections as influenza, parainfluenza, RSV, human metapneumovirus, and dengue to administer the proper pharmacotherapy[1,2] and they have demonstrated how this important differentiation can be very challenging not only clinically but also as regards to radiological[3] or serological investigations due to possible cross reactivity between dengue virus and SARS CoV-2 antibodies leading to occasional false positive serology tests[4]. However, these and other insightful remarks[5] remained inadequate at numerous clinical situations, and co-infection with more than one viral infection is also another real-life medical challenge[2] with possible increased severity of the clinical condition[6] and more incidences of complications e.g. risk of ICU admission and mechanical ventilation[7]. Therefore, the search for a safe and effective broad-spectrum antiviral protocol that can be used to early manage multiple highly infectious viruses is continuing to be considered as a noble quest for a medical holy grail.

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 World Health Organization (WHO) as the most rapid growing mosquito-borne infection and dengue virus can be co-transmitted with other viruses such as Zika and Chikungunya viruses and human co-infections have been reported[8,9]. 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[10]. Furthermore, DVD is considered, probably due to climate change and/or viral evolutionary mutations, as an evolving threat to the remaining countries[11,12] and confirmed cases of locally transmitted DVD were reported in France since 2010 and the numbers of

 doi:10.20944/preprints202307.2079.v2

domestic French DVD infections in 2022 were more than the sum of the reported infections in the previous ten years[13]. 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[14]. 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[15]. 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. Notably, no specific antiviral drug is available to manage DVD and only symptomatic and supportive treatment is provided, and paracetamol (acetaminophen) is recommended to manage pain and fever instead of non-steroidal anti-inflammatory drugs (NSAIDs) which are currently recommended to be avoided in its management [9,16,17].

Dengue Outbreak in Qena, Egypt

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 that described the positivity of "some samples" for dengue virus with evidence of local transmission 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 early in 2022, 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. Notably, I suggest it's most likely that these described "atypical viral" pneumonia cases are due to SARS CoV-2 EG.5 variant of interest as later revealed and named globally to be noted that the first "officially" reported Egyptian EG.5 cases were announced on August 22, 2023; another late and unnecessary announcement as I suggest as for long we live in Egypt and Africa free from COVID-19 obsessions and mandates thanks to its early management using NSAIDs and Kelleni's protocol to be noted that the official statement described that it was the relatively scarce EG.5.2 that was detected, not EG.5.1 which is the one of current global interest due to its potential higher effective reproduction number, and when I asked for a clarification, I received a formal private confirmation that they committed no mistake, yet I wish if they could share publicly the detected genetic sequence.

Using NSAIDs and Kelleni's protocol to early manage Dengue Fever

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 together with broad spectrum antimicrobial drugs such as nitazoxanide and/or azithromycin (Kelleni's protocol)[18] 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[19], yet ibuprofen and other NSAIDs are, according to a conditional recommendation that based on a very low to low certainty, currently recommended against to be used with DVD [9,16], mainly to avoid development of the potential thrombocytopenic hemorrhagic or gastritis complications [16,19]. Interestingly, they were likewise falsely recommended against earlier to manage COVID-19 [20] before later proven safe and even lifesaving in SARS CoV-2, RSV, Influenza and Norwalk viral infections through earlier real-life practice and later clinical trials [1,21-23] as early treatment aborts the progression of these viral infection

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 30 August 2023 doi:10.20944/preprints202307.2079.v2

and abolishes the occurrence of the complications in the vast majority of cases, in not all of them[24]. Notably, nitazoxanide and/or its active metabolite; tizoxanide were previously shown to in-vitro inhibit the replication of some flavivirdae including dengue virus serotype 2 [25,26]. Moreover, nitazoxanide was also suggested to be effective against paramyxovirus infection including parainfluenza and humanmetapneumovirus[27].

Real-life insightful medical practice is the most important lantern amid pandemics

Real-life insightful medical practice, not the potentially catastrophic theories[20] nor the theoretical potentially biased meta-analysis studies[18], has been a cornerstone in our battle against COVID-19, and it's most likely to play the same role in the times of current and future pandemics when no specific chemotherapy or treatment approach is available. Recently, DVD cases are soaring in many countries all over the world and I urgently recommend fellow physicians and colleagues especially in the heavily affected Latin American countries as Peru, Brazil and Bolivia 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, Influenza and Norwalk in pediatric, geriatric and pregnant patients [1,18,28] and it is most likely, from my scientific and clinical point of view, that dengue virus and Zika virus infection could be similarly managed. Moreover, Kelleni's protocol could be considered ideal to manage DVD and COVID-19 co-morbidity and it continues to clinically manage pediatric, geriatric and pregnant patients suffering from several other RNA viruses as Influenza, RSV and Norwalk viruses without prior requirements to perform expensive serological and/or molecular investigations and this approach is considered very valuable economically [1,28]. However, until other reports or clinical trials can confirm my recommendation for the early use of ibuprofen/NSAIDs in the management of dengue fever, as happened with COVID-19, it is vigilant to prescribe NSAIDs basing on a personalized approach and to prescribe paracetamol together with nitazoxanide and azithromycin (modified Kelleni's protocol) 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 (Figure 1). Meanwhile, those patients who are presenting early in the course of infection or those presenting late yet showing negative tourniquet test and 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. Moreover, urgent well designed clinical trials should be considered to assess the full safety of NSAIDs in early management of DVD as described in this perspective and to assess the efficacy of nitazoxanide with or without NSAIDs in its management.

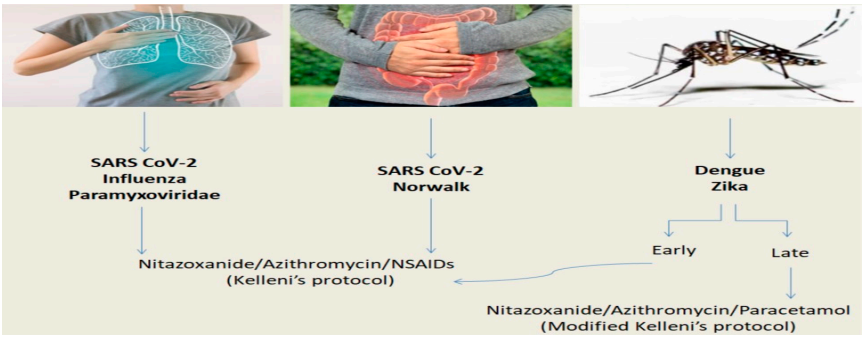

Figure 1. Real-life clinical practice using Kelleni's protocol to early manage several RNA viruses without the need to determine the causative agent.

Conclusion

Taken together, I would like to suggest that early administration of Kelleni's immune-modulatory antiviral protocol using both nitazoxanide and ibuprofen/NSAIDs, whether or not combined with the broad spectrum antimicrobial azithromycin according the personalized medical

assessment, 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 [21,24,29,30] and hence Kelleni's protocol using NSAIDs, nitazoxanide with or without azithromycin according to the clinical personalized evaluation, could probably be proven as best first line early management for SARS CoV-2 and dengue virus and/or other described an yet to be explored respiratory and GIT viral (co)infections, saving precious lives especially in the developed countries that were and are the most affected countries as regards to COVID-19 mortality and relieving the health care professionals as well as the health care authorities globally and especially in the developing countries from the burden to perform advanced serological, radiological, and/or molecular investigations which are considered unnecessary to start antiviral pharmacotherapy using the broad spectrum Kelleni's protocol[18,28,31].

Patient and public involvement

This perspective describes a real-life medical practice that occurred amid a mysterious unprecedented outbreak that was later officially announced to be due to dengue virus and it followed all the ethical principles in the Declaration of Helsinki. No written consents were required as the clinical management was spontaneous when no official confirmation was present to confirm dengue virus disease.

Conflict of interests: None.

Funding: This paper was not funded.

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