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Brief Report

Real-Life Practice of Kelleni's Protocol in Treatment and Post Exposure Prophylaxis of SARS CoV-2 Omicron HV.1 and JN.1 Subvariants

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Abstract: This brief report discusses the ongoing real-world practice using nitazxoanide, NSAIDs and/or azithromycin (Kelleni's protocol) to manage the evolving manifestations of SARS CoV-2 Omicron EG.5.1, its descendant HV.1 as well as BA.2.86 and its descendant JN.1 subvariants in Egypt. These subvariants are well-known for their highly evolved immune-evasive properties and the manifestations include some peculiar manifestations as persistent cough besides high fever in young children as well as persistent severe cough, high fever, change of voice and marked bone aches in high risk groups of adults. It's suggested that the ongoing SARS CoV-2 evolution is continuing to mostly affect the high risk groups of patients, to some of whom we've also successfully prescribed nitazoxanide and/or NSAIDs for post-exposure prophylaxis of all household contacts. We also continue to recommend starting the immune-modulatory antiviral Kelleni's protocol as soon as possible in the course of infection and adjusting it in a personalized manner to be more aggressive from the beginning for the high risk patients, at least until the currently encountered surge of infections subsides.

Keywords: SARS CoV-2; HV.1; BA.2.86; JN.1; post exposure prophylaxis; Kelleni's protocol; nitazoxanide; NSAIDs

Introduction

SARS CoV-2 evolution is ongoing together with the threat to return the world to square one. However, Africa has adopted early treatment approach and managed to avoid most of the burden of COVID-19 [1]. This brief report discusses the updated real-life practice of the Egyptian Kelleni's protocol in both treatment and post-exposure prophylaxis of SARS CoV-2 infection.

For almost four years we've been safely and perfectly practicing the immune-modulatory antiviral nitazxoanide, NSAIDs and/or azithromycin (the standard Kelleni's protocol) to early manage several respiratory viral infections including all SARS CoV-2 variants that have evolved and affected patients of all ages including pregnant ones and those suffering from various medical co-morbidities [2,3]. Notably, Egypt has officially acknowledged EG.5 subvariant only in August 2023 the SARS CoV-2, and in December 2023, Egypt has similarly acknowledged BA.2.86 and its descendant JN.1, which are currently the dominating global ones. Importantly, SARS CoV-2 variants of interests and concern are being closely monitored, due to their highly evolved immune-evasive properties which can lead to a potential reclassification of their global COVID-19 morbidity and mortality impact [4].

New Variants of Concern Are Detected Clinically before Being Named

We'd like to report that for over the past six months and ongoing, we've been experiencing a surge of unusually encountered more virulent respiratory infections which significantly affect the high risk groups of patients; especially young children and immune-compromised ones. Interestingly, the abrupt onset of persistent high fever reaching or occasionally exceeding 40 °C was

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a hallmark of those high risk patients, during the first two to three days of manifestations. For several times during the pandemic, new SARS CoV-2 variants of concern were highly suspected clinically before being officially named.

Adding Amoxicillin/Clavulanic to the Standard Kelleni's Protocol in Selected Cases

The high fever was efficently relieved by regular use of NSAIDs two to three times a day, along with cold packs and it's noteworthy that we've not encountered such intensity of fever in that frequency before and we've added amoxicillin/clavulanic acid to the standard Kelleni's protocol if the expected clinical improvement was not found at the end of the third day. Notably, this modification has adequately managed the debilitated high risk patients who might have experienced resistance to macrolides or a more severe secondary bacterial infection which is a known serious complication of COVID-19 [5].

Remarkably, though Mycoplasma pneumoniae infections, characterized by persistent dry cough and prolonged manifestations, were reported to surge especially in children in different countries after the lifting of COVID-19 restrictions, yet Egypt has had almost zero COVID-19 restrictions for over two years and these symptoms were reported in both high and low risk groups of patients of all ages. Moreover, though amoxicillin/calvulanic acid efficacy is lacking as regards to Mycoplasma pneumoniae which has no cell wall, yet enhanced antimicrobial activity of azithromycin against mycoplasma pneumoniae in the presence of amoxicillin/clavulanic acid could be suggested [6] as observed clinically in some treated pediatric patients during this surge.

As per my clinical experience, it's become increasingly not uncommon for those high-risk patients to require an extended course of Kelleni's antiviral protocol including a 5-day-course of double antibiotics; azithromycin and amoxicillin/clavulanic acid in addition to the standard nitazoxanide and NSAIDs [3].

Managing Persistent Cough and Some Interesting Cases

Persistent cough was quite evident and prevalent in this current surge of SARS CoV-2 infections. It was managed by both natural antitussives and loratadine[1], but a personalized administration of cloperastine suspension or pholcodine containing syrup was required in selected severe cases. Furthermore, change of voice was occasionally the main presentation in young healthy adults who have been re-infected during this current surge, along with mild to moderate diarrhea, headache, fatigue, malaise and some patients experienced marked retro-orbital pain or persistent severe cough. These symptoms, other than cough, were effectively managed by NSAIDs with or without nitazoxanide.

Notably, immune-compromised patients, and an adult receiving immunotherapy with nivolumab to manage his slowly regressive hepatocellular carcinoma, experienced more frequent persistent troublesome cough, marked bone aches and fatigue. However, when these patients were early managed, the standard Kelleni's protocol was sufficient.

Remarkably, a young female child presented with several bouts of hematochezia without respiratory symptoms or abdominal colic. She was perfectly managed using nitazoxanide and azithromycin, without NSAIDs to avoid exacerbating bleeding attacks. we advised the parents to use acetaminophen if the child developed subsequent fever, although it was not ultimately required. Noteworthy, hematochezia associated with COVID-19 has been previously described as more common in geriatric COVID-19 male patients suffering from other co-morbidities [7], yet pediatric and female patients have also been reported [8,9].

Practicing Kelleni's Protocol for Post-Exposure SARS CoV-2 Prophylaxis

Furthermore, we've repeatedly used NSAIDs and/or nitazoxanide for post-exposure prophylaxis of high risk house-hold contacts and this approach has clinically proven to be safe and effective. It has sometimes prevented but mostly significantly alleviated the inevitable infection. Unfortunately, a pioneering clinical trial (NCT04435314) to assess the efficacy of nitazoxanide in

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SARS CoV-2 post exposure prophylaxis was aborted due to "sponsor's strategic decision". Moreover, we suggest that nitazoxanie is not pharmacologically fit to be tested as a drug used chronically for "prevention" as some authors did [10] and in any performed clinical trial that assess post exposure prophylaxis the intensity of symptoms as well as the duration of illness should be carefully assessed.

Remarkably, during the describe surge of infections, we've also prescribed nitazoxanide, without NSAIDs, to a pregnant patient in her late second trimester and most of the symptoms were alleviated within two days except for prolonged severe cough that was only relieved after adding loratadine to the herbal antitussives. Moreover, when nitazoxanide was used as an immediate post-exposure prophylaxis to this pregnant patient when re-infected in her third trimester, the clinical outcome was better and the severe cough was not even encountered. However, the recently acquired previous immunity though couldn't prevent the re-infection; it could probably have played at least a partial role in this favorable response.

Conclusions

Finally, in addition to recommending starting the personalized Kelleni's protocol as early as possible for the management of all current respiratory tract viral infections, especially in high risk groups of patients, we recommend adding amoxicillin/clavulanic acid for children younger than 5 years from the onset of manifestations, at least until this surge is over.

Fortunately, all cases encountered thus far have fully recovered within one week without any post COVID complaints. However, it's quite evident from a clinical standpoint that SARS CoV-2 evolution is ongoing and this could reignite panic particularly in countries that have not yet adopted early immune-modulation in the pharmacological management of COVID-19.

Ethics Statement

Not applicable as it's an update to an already published safe and lifesaving protocol that has been practiced throughout the pandemic and adheres to all the ethical principles in the Declaration of Helsinki. No specific personal patients' information is disclosed.

Funding

None.

Conflict of Interests

None.

Data Availability

Not applicable.

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