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Letter to the Editor

Protecting Patients from Viral Respiratory Infections: Correspondence Regarding Klompas et al., NEJM June 14, 2023

Ed J van Hezik MD

WCC at SEA

Correspondence regarding Klompas et al, in NEJM June 14, 2023; titled "Strategic Masking to Protect Patients from All Respiratory Viral Infections", a plea for structured use of masks to protect against future CoV2 and other types of viral infections in a hospital setting. We do not disagree with this, but we think that instead of a passive mask barrier, another active way can also achieve this goal, but more broadly.

-The other respiratory viruses that Dr Klampos mentions are almost all of the 'single RNA enveloped' type. This is precisely the starting point of the proposed treatment method with an H_2S donor, this has already been described by Dr Casola's group in some top journals (references 5,6,7).

-In addition, NAC (very safe, known for a long time, cheap and available everywhere) has also been designated as an H_2S donor. This makes global application possible, especially in low-income countries. [ref 12-18]. NAC effervescent tablets are cheaper than a medically suitable mask. This also invites to include NAC as a comparator in future RC trials.

-This H_2S supplementation for the restoration of innate immunity can be applied at different scales (cohorts): e.g. community, hospital, wards, barracks, cruise ships, prison, etc. Then staff and Clients/Patients can be treated combined in such a cohort.

Dear Editor,

Klompas and colleagues aim to reduce the risk of hospital virus infections in vulnerable patients through masking protocols. [*NEJM June 14, 2023*][1].

As a first line of defense, the introduction of universal masking reduces the transmission of SARS-CoV-2 in healthcare facilities through source control and exposure protection. The

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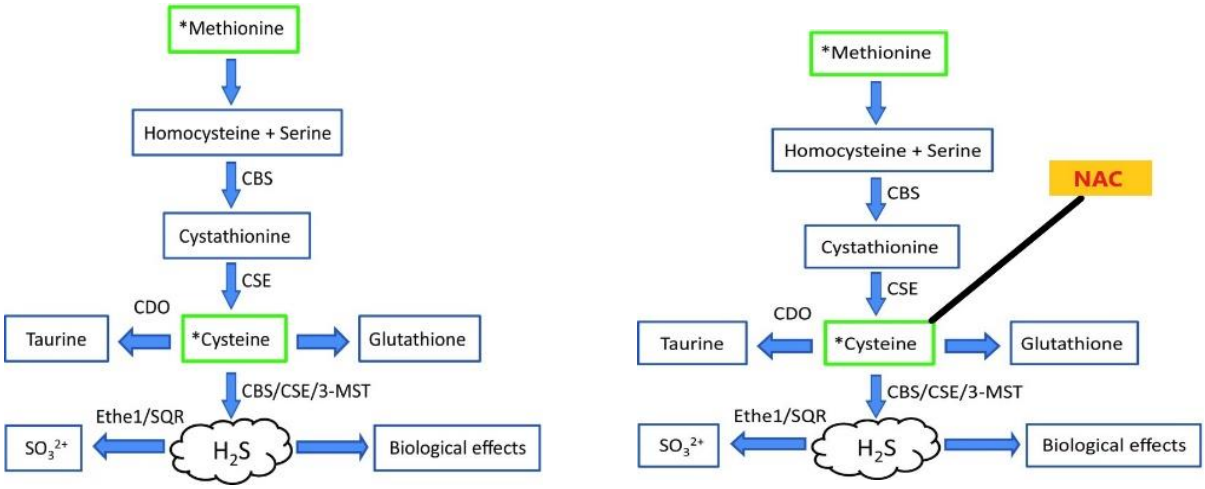
vaccines and boosters, then developed, will also strengthen immunity, provided that mutations of the virus do not intervene.But to optimally protect all vulnerable hospital patients against all viral respiratory infections, healthcare providers can also use targeted medication to try to reduce respiratory virus transmission in such a community /, the hospital /or "***any*** cohort " (*the size of which is to be determined depending on the virus pressure*). Studies have already been done with, for example, paxlovid and molnuparivir, given as early as possible; but cost and distribution, among others, formed some barrier.

We propose an alternative here, aimed at reactivating the innate immunity disrupted by the virus within such a cohort/hospital/community. Here it is also extremely important: in case of a positive test, a highly suspected virus contact or at the onset of flu symptoms, every adult in such a cohort/hospital/community starts as early as possible (within 4-5 days at the latest), with a 7-day course of an H_2S donor drug. (see below).

In 2021, two publications were published about the acute phase of COVID-19 with a somewhat different (*metabolic*) perspective: From cysteine degradation to H_2S synthesis (the so called transsulfuration pathway).[1,2] [figure 1a].

Figure 1.



a) Transsulfuration Pathway b) idem with suppletion: exogenous H_2S donor

On the one hand, metabolic cohort screening [3] showed a strongly accelerated degradation of cysteine (an H_2S precursor) occurring during the COVID virus infection; however, on the other hand, lower H_2S blood levels were found in critical ICU admission (clinically and individually).[4] Such a fast H_2S depletion may correspond to an acute failure to produce sufficient H_2S with cysteine as the required substrate. A low H_2S would then be a prognostic '"bad" parameter.[4]

Previous preclinical research [5] had already shown that infection with a "single RNA-enveloped virus" acutely reduced H_2S levels in the airway epithelium; resulting in an acute loss of innate immunity. However, immediate re-supplementation with (*exogenous*) H_2S

immediately restored this innate immunity, with not only strong antiviral but also anti-inflammatory effects [6,7]. This H_2S re-supplementation seems to act like an on/off switch.

It should be emphasized that every "single RNA-enveloped virus", not only Sars-CoV2, but also e.g., Influenza or RSV can cause this H_2S depletion [7], giving this integral H_2S repair mechanism a much greater and broader clinical and epidemiological impact.

Finally, very interesting: it is now also possible to measure the moment of the falling H_2S level precisely in the presymptomatic phase, while the first virus symptoms only appear 24 hours later.[8] This indicates the exact time window within which the antiviral treatment can be most effective. Based on these observations, COVID-19 can be characterized as "An Acute Virus-Induced H_2S Deficiency Syndrome". Its treatment means immediate H_2S replenishment of the virally induced acute deficiency, at the earliest possible stage, preferably even pre-symptomatic, but certainly at the first symptoms of a viral infection, analogous to the paxlovid and molnuparivir studies.

Here it is - as a leap of thought - useful to take a moment to consider the Aspirin History [9], where a substance unexpectedly turned out to have many more working principles over time.

This is also the case with N-acetylcysteine, as described earlier [1,2,10,11]. The required H_2S is obtained by manipulating the transsulfurylation pathway (bypass): via the exogenous addition of N-acetylcysteine (NAC) [figure 1b]. This supplements the endogenous cysteine and from this substrate the antiviral H_2S is formed in the transsulfurylation pathway, so exogenous NAC can be considered as a stable H_2S donor [1]. Especially in the acute/initial phase, this H_2S has an antiviral effect, and - separately from this - an anti-inflammatory effect [7]. The many and different reasons for using NAC or H_2S in COVID have been described in great detail [12-18]. Unfortunately, no well-designed RC trials of NAC have been set up for COVID-19.

NAC, a generic preparation without patent rights, is not a first choice. It has been argued several times to include NAC in the planning of future RC studies, possibly as a comparator.[24] The only RC study [19] started NAC too late and did not give steroids in the second phase of inflammation.

Nevertheless, two field studies in Spain and Italy are of interest as real-world material, retrospectively describing the effect in two very large cohorts treated with NAC [20,21] and two case control studies from Greece and Russia [22,23]. The former studies found less mortality ***versus*** the later studies better clinical parameters and shorter stay in hospital. The very critical short interval < 5 days between first symptoms and first taken dose of drug was not always secured in some studies. However, these studies deserve further attention and confirmation in an RC control setting.

In summary, a face mask policy related to respiratory virus transmission in society indeed can help to passively reduce (hospital) infections caused by frequent and underestimated respiratory viruses, including those other than SARS-CoV-2. , but an integrated antiviral policy **actively** aimed at H_2S control and timely H_2S re-supplementation -*"in any defined cohort or*

community"- deserves further attention and evaluation in RC studies.

Competing Interests

The author declares that he has no relevant or material financial interests that relate to the research described in this paper. Further, Dr. van HEZIK has nothing to disclose.

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