

Letters to the Editor

Assessment of Inhaled Hydrogen Sulfide in Suppressing Deterioration in Patients With COVID-19

To the Editor: Novel coronavirus disease 2019 (COVID-19) is an emerging disease of public health concern, and the current pandemic is having a major global impact. While there is no specific recommended treatment for COVID-19, hydrogen sulfide has the potential to be of therapeutic value for managing acute respiratory illness in patients with COVID-19. However, inhaled hydrogen sulfide has not yet been formally evaluated. Given the extent of the COVID-19 pandemic and the large numbers of hospitalized patients requiring respiratory support, clinical use of inhaled hydrogen sulfide may become an alternate rescue therapy to Suppressing Deterioration in Patients with COVID-19 for the management of acute respiratory distress syndrome (ARDS) in patients with COVID-19.

Increasing attention is being focused on the development of therapeutic strategies against this disease. We read, with great interest, the article by Renieris et al. (1) “Serum hydrogen sulfide and outcome association in pneumonia by the SARS-CoV-2 corona virus” published in this journal. While there is no specific recommended antiviral treatment, and vaccines have yet to be approved, the authors provided a powerful evidence for the connection between hydrogen sulfide concentration in patients serum and outcome survivors of patients from SARS-CoV-2 illness; therefore, hydrogen sulfide (H₂S) inhalation therapy may be included in the strategy as a promising therapeutic candidate.

Although H₂S is considered a toxic substance at a high concentration, low concentrations are very useful and there are many studies showing its effect on the human body. Hydrogen sulfide is an important gaseous transmitter modulating several biological functions, ranging from lifespan extension to regulation of vascular tone, anti-oxidative and anti-inflammatory effects, nervous, cardiovascular, and immune system, in health and disease (2).

The role of H₂S is to assist the defense against coronavirus. This can be achieved by an antiviral property of H₂S through two lines, direct and indirect way, the direct way may be due to alterations of the viral membrane or through interfering with ACE2 and transmembrane serine protease 2 (3–6).

Currently, evidence shows that COVID-19 virus requires ACE2 to enter the host cell (7). Beside, the transmembrane serine protease (TMPRSS2) is the main host cell protease which cleaves the S protein of human coronaviruses on the cell membrane, allowing the virus to release fusion peptide for membrane fusion (8). Therefore, co-expression of ACE2 and TMPRSS2 is critical for the cell entry process of COVID-19 (9).

The other line through the contributions of H₂S to maintenance of elevated level of glutathione level (GSH), which can itself be another player with antiviral effect, very recently, GSH was also proposed as potentially useful agent against COVID-19 (10).

We advocate for a clinical trial exploring the use of inhaled H₂S for the management of COVID-19 ARDS to be conducted as a matter of urgency.

Mohammed A. M. Ali Qaba
Department of Chemistry, Collage of Science, University of Mosul, Mosul, Iraq
mamqupa@uomosul.edu.iq

Mhmood Khleel Saleem
Technical Instate/Mosul Northern Technical University, Mosul, Iraq

Nahla Kh. Ali Qaba
Training and Development Center Ninawa Health Directorate
Mosul, Iraq

Muataz A. Alani
Alkhansaa Teaching Hospital, Ninawa Health Directorate,
Mosul, Iraq

Muna Muneer Ahmed
Department of Family and Community Medicine, College of
Medicine, University of Mosul, Mosul, Iraq

Salih M. Sabry
Al-Shifa Hospital, Ninawa Health Directorate, Mosul, Iraq

The authors report no conflicts of interest.

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Abrupt Discontinuation Versus Down-Titration of Vasopressin in Patients Recovering from Septic Shock

To the Editor: We read with great interest the recently published article by Lam et al. (1) in *Shock*, where it was shown that there was not any difference in time to intensive care unit (ICU) discharge between abrupt arginine-vasopressin (AVP) discontinuation and down-titration in patients recovering from septic shock and that abrupt discontinuation of AVP appears to be safe and may lead to shortened AVP duration. We appreciate the important information presented in this article and we wish to comment on some associated issues.

Norepinephrine (NE) is used as the first-line catecholamine agent for increasing mean arterial pressure in septic shock patients due to its vasoconstrictive effects but, as many studies show that the vasodilation in septic shock is due to a deficiency of vasopressin, AVP is increasingly used as a secondary agent in the management of septic shock (2, 3). In your study the first catecholamine initiated was also norepinephrine in the vast majority of patients (91% and 89.2% in the abrupt and tapered discontinuation group respectively). Furthermore at AVP down-titration or abrupt discontinuation most patients in both groups continued to receive catecholamines (66.1% and 58.9% in the abrupt and tapered discontinuation group respectively, $P = 0.015$).

This is a first issue we wish to comment, as there was a statistically significant difference between the two groups. The abrupt AVP discontinuation could be better tolerated in patients receiving other vasopressors too. Our previous hypothesis is reinforced by the fact that more patients in the abrupt discontinuation group needed fluid bolus and catecholamine increase, although there were not statistically significant differences between the two groups. Furthermore more patients in the abrupt discontinuation group restarted AVP ($P < 0.001$), although the percentage of patients who restarted or needed increased AVP doses was small in both groups.

According to your results at AVP down-titration or abrupt discontinuation an important percentage of patients were not receiving other catecholamines. This is a second issue we wish to comment, as in our opinion an important question in septic shock patients is which vasopressor should be discontinued

first. A recent meta-analysis (4) showed that in septic shock patients treated with concomitant AVP and NE therapy, discontinuing AVP first may lead to a higher incidence of hypotension while this result was not associated with higher mortality or ICU length of stay.

An important, recently published trial (5) concluded that norepinephrine dysregulates the immune response in sepsis, compromises host defense, and may significantly contribute to sepsis-induced immunoparalysis, whereas vasopressin does not have similar immunologic effects. Previous *in vitro* and animal data indicate that norepinephrine treatment exerts immunosuppressive and bacterial growth-promoting effects, and may increase susceptibility toward infections in sepsis patients (6). Hence, the third comment we would like to make is that a reappraisal of the current vasopressor management in patients with sepsis would be appropriate. Although as a second-line therapy vasopressin analogues revealed no differences on mortality (7–9), a survival benefit was observed in a subgroup of vasopressin-treated patients (8) while it reduced the need for renal replacement therapy (7).

As personalized medicine is becoming a priority, future use of different vasopressors should perhaps be used in different subgroups of sepsis patients depending on their immunological profile.

Diamanto Aretha
Department of Anesthesiology and Intensive
Care Medicine
General University Hospital of Patras
School of Medicine
Rion, Patras, Greece
adaretha@yahoo.gr

Panagiotis Kiekkas
Western Greece University of Applied Sciences
Patras, Greece

Petros N. Karamanakis
Department of Neurosurgery, Olympion General Hospital
Patras, Greece

Eleftheria S. Panteli
Department of Anesthesiology and Intensive Care Medicine
General University Hospital of Patras, School of Medicine
Rion, Patras, Greece

The authors report no conflicts of interest.

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