

## **COVID-19 reveals redox vulnerabilities in two minority groups**

**Adonis Sfera<sup>1</sup>, Afzaal Jafri<sup>1</sup>, Jason Thomas<sup>1</sup>, Carlos Manuel Zapata-Martín del Campo<sup>2</sup>,  
Daniel Gehlbach<sup>3</sup> and Carolina Osorio<sup>4</sup>**

<sup>1</sup>Patton State Hospital, San Bernardino, CA, United States

<sup>2</sup>National Institute of Cardiology “Ignacio Chavez”, Mexico City, Mexico

<sup>3</sup>University of California, Riverside, CA, United States

<sup>4</sup>Department of Psychiatry, Loma Linda University, Loma Linda, CA, United States

### **Abstract**

The COVID-19 pandemic spread rapidly throughout the world, but some populations were more affected than others. For example, compared to other groups, a higher morbidity and mortality was documented in African Americans and individuals of Mediterranean descent. These populations are marked by both increased prevalence of glucose-6-phosphate dehydrogenase (G6PD) deficiency, and lower utilization of angiotensin receptor blockers/angiotensin converting enzyme inhibitors in the treatment of hypertension. In this brief report, we suggest that G6PD status should be assessed in all COVID-19 positive individuals belonging to the two ethnic groups. If detected, N-acetylcysteine should be utilized to lower the oxidative burden and “sartans” should be prescribed as first-line therapy in hypertensive individuals.

**\*E-Mail:** [ADONIS.SFERA@dsh.ca.gov](mailto:ADONIS.SFERA@dsh.ca.gov)

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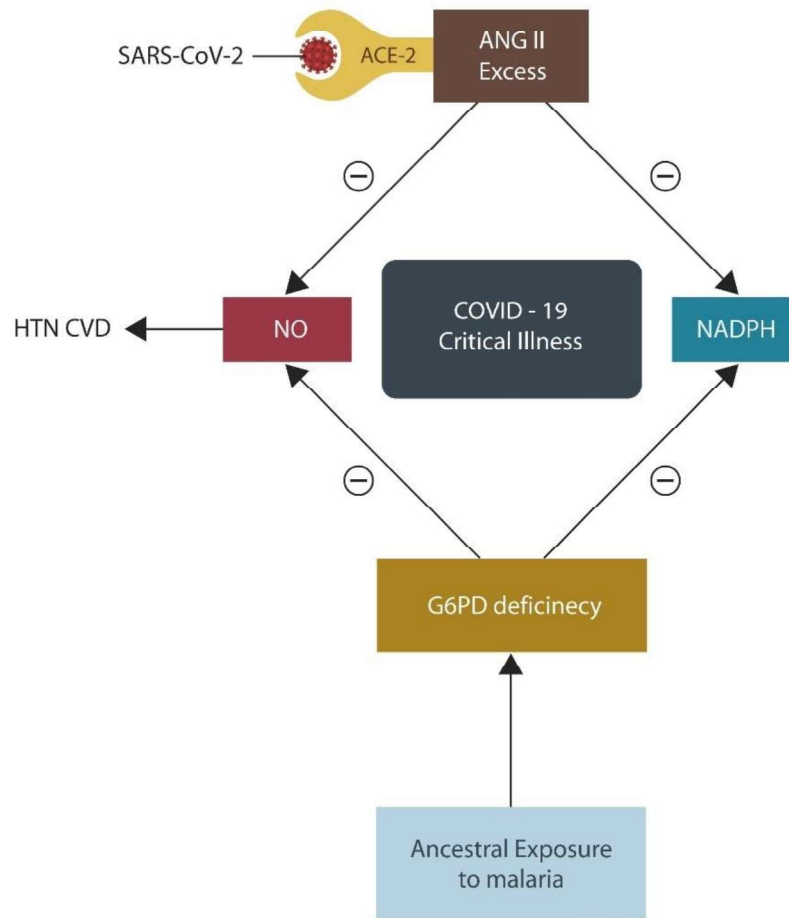
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## Visual Abstract



*The SARS-CoV-2 virus engagement of angiotensin-converting enzyme 2 (ACE-2) impairs angiotensin II (ANG II) processing, leading to its accumulation. Excessive ANG II inhibits endothelial nitric oxide (NO) and nicotinamide-adenine dinucleotide phosphate (NADPH), increasing oxidative stress. Lowered NO, exacerbates hypertension (HTN) and cardiovascular disease (CVD), increasing the susceptibility to COVID-19 complications. Populations with ancestral exposure to malaria, including African Americans and individuals of Mediterranean descent, present with high rates of glucose-6-phosphate dehydrogenase (G6PD) deficiency, a defect that also lowers NO and NADPH, increasing the vulnerability to COVID-19. Together, the SARS-CoV-2 infection and G6PD deficiency likely generate a catastrophic redox failure, engendering COVID-19 critical illness. “Sartans” inhibit ANG II, restoring redox homeostasis (not shown).*

## Introduction

On March 11, 2020 the World Health Organization declared COVID-19 a pandemic. At that time, the virus had been detected in 114 countries, and 4,291 people had lost their lives. Despite its rapid spread around the globe, individuals and populations have not been equally affected. For example, it is still unclear why older persons, African Americans and people from the Mediterranean basin have been more impacted compared to other groups. Indeed, a new study found that the SARS-CoV-2 fatality rate was 2.4 times higher in African Americans compared to Whites, Asians or Latinos, suggesting a probable racial vulnerability (1). This is further substantiated by the fact that other countries with a predominantly black population reported similar data (2). In addition, mortality rates comparable to those of African Americans have been documented in individuals from the Mediterranean basin, a region where G6PD deficiency is more common than in the rest of Europe (3).

Socioeconomic conditions likely play a major role in COVID-19 prognosis, however biological factors, including the management of hypertension and oxidative stress may be equally important. We surmise that, aside from healthcare inequalities, two modifiable risk factors may contribute to the higher COVID-19 morbidity and mortality in African Americans and Europeans of Mediterranean descent:

1) lower utilization of angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEi) in the treatment of hypertension, and

2) higher oxidative stress due to increased prevalence of glucose-6-phosphate dehydrogenase (G6PD) deficiency.

## Hypertension treatment practices

European hypertension studies have demonstrated that, compared to the Northern part of the continent, ARBs and ACEi are less often prescribed in the South (4). With the same token, in the US, African Americans are less likely to receive ARBs and ACEi as first line hypertension treatment (5). This prescription practice reflects the belief that the response to these drugs is hindered by the lower renin levels, demonstrated in this population. However, numerous clinical trials have found that ARBs and ACEi are equally efficacious in Black Americans and recommended that clinicians should use these agents as first line therapy (5-6). This data is significant as both ARBs and ACEi appear to lower the COVID-19 mortality rates. For example, a novel study found that patients treated with these drugs at the time of infection with the SARS-CoV-2 virus demonstrated a lower mortality rate of 30.4% compared to 41.2 % in individuals without prior exposure to ACEi or ARBs (7).

In our previous work, we found a positive correlation between COVID-19 critical illness and excessive angiotensin II (ANG II) and stated that “sartans” should be used early in the disease course (8-9). We based this assertion on the fact that ANG II upregulates oxidative stress, while ARBs and ACEi restore the redox homeostasis by lowering ANG II.

## The oxidative burden

Oxidative stress is an established hypertension risk factor and several antihypertensive drugs lower the blood pressure by acting as antioxidants (10). For example, ARBs and ACEi decrease reactive oxygen species (ROS) by upregulating both endothelial nitric oxide (NO) and the master antioxidant glutathione (GSH) (11-13). As a major product of the normal endothelium, NO acts as a vasodilator and regulator of oxygen supply by its action on the smooth muscle of blood vessels. African Americans synthesize 2 to 3 times less NO compared to the general population, placing this group at higher risk of redox dysfunction, hypertension and cardiovascular disease (14-17).

Aside from decreased NO, African Americans (even after adjustment for most variables) display lower GSH plasma levels compared to other groups (18). Indeed, decreased GSH in this population was also associated with a higher incidence of prostate cancer, suggesting that ARBs and ACEi may be protective as they lower oxidative stress (19-20) (11-13).

Taken together, the SARS-CoV-2 virus alters the body redox systems by inhibiting ANG II hydrolysis, increasing oxidative stress. This may prove catastrophic in individuals or populations with preexistent redox defects, such as those described in malaria-exposed groups (see the next section). In addition, underutilization of ARBs and ACEi as antihypertensive treatments in this population, further disrupts the redox homeostasis, increasing COVID-19 morbidity and mortality.

## Ancestral malaria and oxidative stress

Malaria is an old enemy of mankind that throughout many centuries exacted a heavy mortality toll on the population of Africa and the surrounding regions, including the Mediterranean basin. In response, the residents of these areas gradually developed plasmodium-resistant red blood cell phenotypes, including glucose-6-phosphate dehydrogenase (G6PD) deficiency,  $\alpha$ -thalassemia, and hemoglobin C (21). Although protective against malaria, these genetic variants increased oxidative stress, contributing to other pathologies, such as cancer, cardiovascular disease and neuropsychiatric disorders (22-26). Novel data links G6PD deficiency to COVID-19 complications, suggesting that populations with ancestral malaria exposure are at increased risk of critical illness. Indeed, the US Army statistics estimate that 12.2% of African American males and 4.1% of females present with G6PD deficiency, connecting the oxidative stress in this group to unfavorable COVID-19 prognosis (27).

G6PD is the rate-limiting enzyme that catalyzes the conversion of NADP to NADPH, preventing GSH depletion (28). Therefore, deficient G6PD contributes to ROS accumulation, a pathology described in severely ill COVID-19 patients (29-30). In addition, G6PD deficiency is also associated with chronically depleted NO, predisposing to hypertension, cardiovascular disease and coagulopathies, conditions prevalent in many African Americans (31). For this reason, G6PD status should be assessed in all COVID-19 positive individuals, especially those belonging to the two ethnic groups.

Moreover, as N-acetylcysteine (NAC) is an FDA approved drug and an established GSH enhancer, it should be routinely utilized in African Americans and southern Europeans with COVID-19 (32). Indeed, NAC is currently in clinical trials for COVID-19, emphasizing further the importance of redox dysfunctions in this viral infection (NCT04792021).

### Future directions

Older individuals are more susceptible to COVID-19 complications and respond less well to vaccines, therefore the development of new treatments for SARS-CoV-2 critical illness should never be abandoned (34).

Further studies are needed to determine whether COVID-19 morbidity and mortality can be lowered by the routine assessment of G6PD status and utilization of ARBs and ACEi as first line therapy for hypertension in susceptible populations.

### Conclusion

African Americans and people of Mediterranean descent present with a higher prevalence of hypertension and cardiovascular disease, along with an increased risk of COVID-19 critical illness.

Aside from the healthcare disparities, biological factors likely predispose these populations to oxidative stress and SARS-CoV-2 complications. Indeed, increased prevalence of G6PD deficiency and the less frequent use of ARBs and ACEi in the treatment of hypertension can explain the higher mortality rates demonstrated in

African Americans and southern Europeans. As these are modifiable risk factors, screening for G6PD deficiency and adjusting hypertension treatments could save lives.

Clinicians should also be mindful that individuals with G6PD deficiency may be more prone to COVID-19-related thromboembolic events and that several commonly used therapeutics, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), quinolones, nitrofurantoin and hydroxychloroquine can exacerbate this pathology (33). For this reason, the above drugs should probably be avoided in G6PD deficient patients with COVID-19.

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