

# Evaluation of glucose-6-phosphate dehydrogenase (G6PD) status in US military and VA patients with COVID-19 infection

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A recent publication outlined several pieces of evidence suggesting that glucose-6-phosphate dehydrogenase (G6PD) deficiency may increase susceptibility to, and severity of illness with, COVID-19 infection.<sup>1</sup> These include an earlier study showing that G6PD-deficient cells are more susceptible to infection in vitro with another coronavirus (HCoV 229E); increased COVID-19 case fatality rates in Spain and Italy, where G6PD deficiency is more common and is typically caused by a variant with more severe manifestations; increased incidence of COVID-19 in Blacks and Asians in the UK and the USA compared with incidence in Caucasians, given that G6PD deficiency is also more common in people of African descent and Asians; similarity in complications of vascular endothelial dysfunction and coagulopathy in some patients with COVID-19 compared with G6PD-deficient individuals under oxidative stress conditions; and case reports of hemolysis in G6PD-deficient patients following initiation of hydroxychloroquine treatment for COVID-19 infection.

What is needed at this point are studies to either confirm or refute this apparent association between G6PD deficiency and COVID-19 infection. A genome-wide association study was conducted involving 1980 patients with severe COVID-19 in Spain and Italy.<sup>2</sup> The investigators detected genetic susceptibility associations with a 3p21.31 gene cluster and also with a 9q34.2 gene cluster associated with the ABO blood group locus. No apparent association with the Xq28 locus, where the gene coding for G6PD is located, was reported. However, this is the only study to date.

Since 1981, the United States Department of Defense has required that all Armed Forces personnel undergo G6PD

testing at the time of entry into service. This is to ensure that certain antimalarial agents, which are known to cause hemolysis in G6PD-deficient individuals, are not given to those service members who are thus affected. In 2004, the Army further mandated that soldiers undergo additional G6PD testing prior to deployment to malaria-endemic areas. As a result, the G6PD status is already known for all military members currently serving and a large number of Veterans. The information obtained from this screening test has formed the basis for reports on the prevalence of G6PD deficiency within the Armed Forces.<sup>3</sup>

A study to examine G6PD status in current military personnel and Veterans who have been diagnosed with COVID-19 infection may be beneficial. Patients should be stratified into groups based on severity of infection, from asymptomatic to moderate illness to severe illness requiring ventilator support. Comparing the prevalence of G6PD deficiency across these groups of COVID-19 patients with the known prevalence of G6PD deficiency in the Armed Forces population would provide further information as to whether there exists a correlation between G6PD deficiency and COVID-19 infection, and whether this correlation varies with severity of illness.

There are at least two limitations to such a study. First, the number of cases of COVID-19 among military personnel and Veterans may be too small to show a statistically significant relationship with G6PD status. This was a concern expressed by an official with the Defense Health Agency last summer during a discussion on the feasibility of such a study. However, the number of cases in both the military and Veteran population has climbed since then. Statistics reported by the Department of Defense on a daily basis show 58 081 cumulative cases of COVID-19 among military members as of 2 November 2020.<sup>4</sup> A similar daily report issued by the Department of Veterans

Affairs indicates there have been 77 395 patients with COVID-19 either tested or treated at VA facilities as of 3 November 2020. The vast majority of these were Veterans.<sup>5</sup>

Second, correlation does not beget causation. However, if there is a positive correlation, this would suggest a subset of patients who may be more susceptible to, or at greater risk for illness with, COVID-19 infection. Such knowledge may indicate a need for G6PD testing in certain civilian patients with COVID-19, as well as additional or alternative recommendations for treatment for patients with COVID-19 who have G6PD deficiency.

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