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Can the Therapeutically-rational Exchange (T-REX) of Glucose-6-phosphate Dehydrogenase Deficient Red Blood Cells Reduce *Plasmodium falciparum* Malaria Morbidity and Mortality?

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Dear Editor,

Despite malaria's persistence as a global threat, progress in Nepal has been exemplary.¹ Nepal's success is due to aggressive interventions and vigilance.² Despite this success, *P. falciparum* malaria incidence is no longer declining in Nepal due to imported cases and multidrug resistance.¹ Because of *P. falciparum* multi-drug resistance, new therapeutic options are needed. Thus, we propose treating problematic cases of *P. falciparum* malaria with therapeutically-rational exchange (T-REX) of red blood cells (RBCs)^{3,4} in which glucose-6-phosphate dehydrogenase deficient (G6PDd) RBCs are infused instead of non-descript, "standard-issue" RBCs.

G6PDd-RBC T-REX may prove worthwhile since it involves removing the patient's parasitized RBCs which can be lethal due to their cytoadherence and replacing them with malaria-protective G6PDd RBCs which are thought to inhibit the parasites via oxidative stress. Fortunately, G6PDd-RBC units are prevalent in many blood banks; and many patients, with and without malaria, have already been transfused G6PDd RBCs (although randomly and unknowingly). Importantly, the World Health Organization (WHO) states that the low-dose of primaquine administered to patients with *P. falciparum* malaria is unlikely to cause toxicity in patients with G6PDd. Thus, infusing G6PDd RBCs into such patients is safe.

T-REX of G6PDd RBCs can be evaluated immediately because (1) prospective G6PDd blood donors usually qualify since they are generally healthy and not anemic, (2) prevalence of G6PDd in Nepal is substantial (> 10% in some regions⁵), and (3) many tests are available to identify units of G6PDd blood – as well as G6PDd donors. Of note, male blood donors are much more likely to be G6PDd because this condition is X-linked. Also, it is well-known

that the level of G6PD activity in the tubing segments of an RBC unit strongly correlates with the G6PD activity inside the blood bag. Thus, convenient tests such as the fluorescent spot test (FST) could be used to identify such units. If malaria patients are severely anemic, G6PDd RBCs can be transfused before initiating T-REX.

Surprisingly, although T-REX of valuable malaria protective RBC variants is feasible, T-REX using G6PDd RBCs (or any other malaria-resistant RBC variant) has never been evaluated for its potential to help *P. falciparum* patients.^{3,4} So, we urge clinicians to evaluate the benefits of G6PDd-RBC T-REX in patients who have – or are at high risk for developing – severe *P. falciparum* malaria in regions where G6PDd blood is available.

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