Methemoglobin and nitric oxide therapy in Ugandan children hospitalized for febrile illness: results from a prospective cohort study and randomized double-blind placebo-controlled trial.

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BACKGROUND: Exposure of red blood cells to oxidants increases production of methemoglobin (MHb) resulting in impaired oxygen delivery to tissues. There are no reliable estimates of methemoglobinemia in low resource clinical settings. Our objectives were to: i) evaluate risk factors for methemoglobinemia in Ugandan children hospitalized with fever (study 1); and ii) investigate MHb responses in critically ill Ugandan children with severe malaria treated with inhaled nitric oxide (iNO), an oxidant that induces MHb in a dose-dependent manner (study 2).

METHODS: Two prospective studies were conducted at Jinja Regional Referral Hospital in Uganda between 2011 and 2013. Study 1, a prospective cohort study of children admitted to hospital with fever (fever cohort, n = 2089 children 2 months to 5 years). Study 2, a randomized double-blind placebo-controlled parallel arm trial of room air placebo vs. 80 ppm iNO as an adjunctive therapy for children with severe malaria (RCT, n = 180 children 1-10 years receiving intravenous artesunate and 72 h of study gas). The primary outcomes were: i) masimo pulse co-oximetry elevated MHb levels at admission (>2 %, fever cohort); ii) four hourly MHb levels in the RCT.

RESULTS: In the fever cohort, 34 % of children admitted with fever had elevated MHb at admission. Children with a history of vomiting, delayed capillary refill, elevated lactate, severe anemia, malaria, or hemoglobinopathies had increased odds of methemoglobinemia ($p < 0.05$ in a multivariate model). MHb levels at admission were higher in children who died (n = 89) compared to those who survived (n = 1964), $p = 0.008$. Among children enrolled in the iNO RCT, MHb levels typically plateaued within 12-24 h of starting study gas. MHb levels were higher in children receiving iNO compared to placebo, and MHb > 10 % occurred in 5.7 % of children receiving iNO. There were no differences in rates of study gas discontinuation between trial arms.

CONCLUSIONS: Hospitalized children with evidence of impaired oxygen delivery, metabolic acidosis, anemia, or malaria were at risk of methemoglobinemia. However, we demonstrated high-dose iNO could be safely administered to critically ill children with severe malaria with appropriate MHb monitoring.