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Management of severe malaria: Enthusiasm for fluid resuscitation dampened by lung water

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Despite treatment with effective parasite-killing drugs, many adults die from severe malaria each year. Among the common complications of *Plasmodium falciparum* infection, metabolic acidosis and renal failure portend the worst outcome. In a multi-center study of severe malaria in Southeast Asian adults, metabolic acidosis was present in 49% of patients and they had a mortality of 32%. Twenty-one percent of patients presented with renal failure and their mortality was 45% [1]. The goal of the study by Hanson et al. was to determine whether fluid resuscitation might improve acidosis and renal function [2]. This question is non-trivial because although the elevated lactate implies shock at a cellular level, it is unclear to what extent hypovolemia contributes to acidosis and renal failure. Blood pressure at admission was adequate (100/60 mm Hg [IQR 90–115 / 60–70]) in most patients from the multicenter study [1]. Radioisotope dilution studies showed that blood volume was normal to elevated (75–90 mL/kg) in adults with malaria [3], and that plasma volume expands to replace the volume of destroyed red blood cells [4]. In a hemodynamic study of adults with acidosis, central venous pressure and pulmonary artery occlusion pressure were low (approximately 3 and 8 cm H₂O) while systemic vascular resistance index was in the upper range of normal (approximately 1600 dyne•s/cm⁵/m²) with a high cardiac index (4.0 L/min/m²) consistent with compensated hypovolemia [5].

In the current study, twenty-six adults with severe malaria underwent fluid resuscitation guided by estimates of cardiac index (goal > 3.0 L/min/m²), global end diastolic volume index (goal > 700 mL/m² [note that GEDVI integrates multiple stroke volumes over a measurement period]) and extravascular lung water (stop fluids if EVLW exceeds 10 mL/kg). Fluid administration was driven primarily by a GEDVI that was persistently below the goal of 700 mL/m² (mean GEDVI increased from 473 to 585 mL/m² over 6 hours). CVP rose from 4.5 cm H₂O on admission to 10 cm H₂O at 6 hours, and the increase was proportional to the amount of fluid given. The effect on acid-base status and renal function was mixed: lactate improved from 3.2 to 1.7, but the pH and base deficit worsened as chloride levels rose. The significant correlation between the amount of fluid given and the change in acid-base parameters implied that fluid resuscitation worsened pH and base deficit. Although plasma creatinine and blood urea nitrogen decreased over 24 hours of fluid resuscitation, fluids failed to reverse anuria in all eight patients with this complication. Overall, fluid administration triggered by hourly estimates of GEDVI had no meaningful benefit on acid base status at 6 hours or renal function at 24 hours. What was the impact of fluid administration on pulmonary edema?

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Extravascular lung water (EVLW) was estimated by trans-thoracic thermodilution, which measures the temperature in the distal aorta after an injection of cold saline into the inferior vena cava [6]. Estimated EVLW increased from 8 to 10 mL/kg, the threshold to stop fluid administration that was recommended by the instrument manufacturer. Eight of twenty-four patients developed pulmonary edema, and five of those died despite respiratory support.

Liberal fluid resuscitation triggered by estimates of GEDVI and stopped by estimates of EVLW failed to prevent pulmonary edema from developing. Were there any hints at admission as to who would progress to pulmonary edema and who wouldn't? At admission, patients who would go on to develop pulmonary edema tended to have a higher CVP (7 vs. 3 cm H₂O, $p = 0.15$), a greater GEDVI (594 vs. 466, mL/m², $p = 0.08$), a higher lactate (6.3 vs. 2.7 mmol/L, $p = 0.04$), and were more likely to be anuric (4/8 vs. 2/16, $p = 0.13$). Although these measures lack predictive value, they suggest that baseline characteristics such as lactatemia and renal failure, initially considered to be indications for fluid administration, may in fact be contraindications. The 2006 WHO guidelines for the treatment of severe malaria recommended limiting fluid administration to the replacement of insensible losses in oliguric patients with elevated blood urea nitrogen and creatinine. Whether fluid administration hastened the demise of these patients or simply failed to reverse progression to death cannot be determined since there was no comparison group that received maintenance fluid only. This study illustrates that the same caution used to administer fluids to malaria patients in resource-limited settings may need to be applied in high-level intensive care units with modern hemodynamic monitoring.

Why did fluid administration fail to reverse the metabolic acidosis and renal failure caused by *Plasmodium falciparum* infection? Unlike sepsis, where shock is driven by severe hypovolemia and systemic vasodilation, in severe malaria impaired perfusion is more likely caused by microcirculatory obstruction [7] [8]. Parasites express adhesion molecules on the surface of infected red blood cells that bind to endothelial receptors like ICAM-1 and CD36 [9]. They bind to endothelium to avoid being removed from circulation by the spleen. Adhesion not only causes physical obstruction to flow, as revealed by imaging of rectal mucosa in this study, but also triggers endothelial activation with subsequent thrombosis [10], inflammation [11] and impaired nitric oxide-dependent vasoregulation [12].

In the future, fluid resuscitation will have a limited role in the treatment of shock caused by infection with *P falciparum* [13]. Drugs that block adherence of parasitized red blood cells to vascular endothelium are more attractive [14]. Reversing adhesion would enhance parasite clearance, limit endothelial injury, and restore microcirculatory function. Although an individual parasite can express one of a hundred different adhesion molecules, it was recently discovered that only a small subset of parasite adhesion molecules are found in patients with severe disease [15]. This raises the possibility of designing small molecule inhibitors to displace parasites bound to endothelium via a limited repertoire of highly virulent adhesion molecules. Such an intervention might restore perfusion to vital tissues and hopefully improve survival from severe malaria.

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