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Early N-acetylcysteine for hospitalised patients with yellow fever

We read with interest the Article by Esper Kallas and colleagues[1] on the predictors of mortality in patients with severe forms of yellow fever. Among the 76 hospitalised patients in São Paulo, Brazil, who were included in the study, 27 (36%) died. High viral load was found to be a key determinant of fatal outcome, suggesting that an antiviral drug that is effective against the virus would help patient recovery.

In multivariate analysis, other factors associated with death included older age, neutrophil count, and higher baseline values of serum aspartate aminotransferase. The prognostic value of indirect bilirubin was found to be just above the two-tailed α level of 0·05 in the multivariate analysis—possibly because of the small sample size—but was highly significant in univariate analysis, as was the international normalised ratio, a key prognostic factor in acute liver diseases, which was not included in the multivariate analysis. Moreover, some patients developed hepatic encephalopathy. Taken together, these results strongly suggest that most (if not all) patients with yellow fever who died actually developed acute liver injury or liver failure, although the authors did not specify this diagnosis.[2]

Since symptomatic yellow fever is commonly heralded by persistent fever, it is reasonable to hypothesise that paracetamol is frequently ingested in the interval between onset of symptoms and hospital admission (and even during hospitalisation). Doses of paracetamol greater, and sometimes smaller, than 4 g daily have been associated with unintentional overdose with acute liver failure, especially in people who consume alcohol or during starvation.[2] Moderately increased bilirubin and high baseline concentrations of serum creatinine, two features of hospitalised patients with yellow fever,[1] are also common in paracetamol-associated acute liver failure,[2] thus suggesting that, apart from high viral load, severe paracetamol-induced liver injury could be an important cofactor of liver failure in patients with yellow fever and their 36% fatality rate.[1] Paracetamol was reported as a cofactor of acute liver failure due to hepatotropic viruses A, B, and E.

Accordingly, the following therapeutic recommendations could be proposed for improving the survival of symptomatic patients suspected to have yellow fever: cessation of paracetamol administration and early intravenous administration of N-acetylcysteine, the antidote to paracetamol hepatotoxicity, in patients with an international normalised ratio greater than 1·5, and also in patients in whom recent paracetamol ingestion is denied or absent.[2] Early administration of N-acetylcysteine was associated with a high survival rate in two independent, uncontrolled, short case series of patients with dengue fever—another arboviral infection—and early acute liver failure.[3,4]

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