ANTIMONIAL-RESISTANT *LEISHMANIA DONOVANI*: INCREASING THE CLINICAL PREDICTIVE VALUE OF THE CURRENT *IN VITRO* SUSCEPTIBILITY TEST

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Antimonials have been the first-line treatment against visceral leishmaniasis (VL) worldwide for decennia. During the past 10 years however, the efficacy of sodium stibogluconate (SSG) was shown to decrease, particularly in the Indian sub-continent, an observation associated with the emergence of SSG-resistant parasites. We studied the relation between clinical SSG treatment outcome in Nepalese VL and drug susceptibility of the infecting parasites, as characterised *in vitro* using intracellular amastigotes. Our data confirm the relation between clinical treatment failure and parasite SSGresistance, but indicate that *in vitro* resistant parasite isolates are also found in 65% of the patients attaining definite cure. These findings question the predictive value of the current *Leishmania in vitro* SSG susceptibility assay for clinical treatment outcome. The drug SSG was shown to act as an inducer of oxygen/nitrogen radicals (ROS/RNS) in both macrophages and parasites. This oxidative stress challenge contributes greatly to parasite death. We hypothesise that the current *in vitro* SSG test system fails to attain the same level of ROS/RNS induction upon SSG exposure as occurs in vivo, and therefore fails to identify SSG-resistant isolates uniquely related to clinical treatment failure. We will discuss how to modify the current *in vitro* SSG test model in order to increase the clinical predictive value. Results of suggested test systems applied to Nepalese clinical isolates, which include direct ROS/RNS exposure, will be presented and compared to results of the current standard SSG-only susceptibility system. Our findings will be situated in the context of a possible upgrade of the current SSG susceptibility assays.

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