Emerging evidence suggests that human leukocyte antigen (HLA) antibody-mediated rejection (AMR) through donor-specific antibodies (DSAs) contributes to lower graft and patient survival in liver transplant patients. Therapeutic plasma exchange (TPE) is currently a category I indication for AMR in ABO-compatible renal transplant patients and a category III indication for AMR in lung allograft rejection. Current guidelines do not include AMR in liver allografts as an indication for TPE; however, criteria for chronic antibody-mediated rejection in liver allograft patients, including the presence of DSA, were recently proposed. Over the past 2 years, the transfusion medicine service at Houston Methodist Hospital has been consulted for TPE in 8 liver transplant patients with potential AMR and positive DSAs. Herein, we describe our relevant observations from these patients, which included five women and three men, ranging in age from 32-71 years. All had received an orthotopic liver transplant ranging from ~1 month to 2 years prior to TPE. All patients had DSAs. All but one patient had class II DSAs, including six patients with antibodies directed against the DQ antigens. Four patients had class I DSAs. The number of DSAs ranged from one to eight, with two patients having eight DSAs prior to TPE. For certain DSAs, TPE led to rapid reduction in DSA mean fluorescence intensity to undetectable levels, as determined by the single antigen bead assay. Class I antibodies and antibodies with lower mean fluorescence intensity were more likely to decrease or disappear after two to three sessions of TPE performed approximately every other day. Despite this, some DSAs, especially Class II DSAs directed against DQ antigens with high pre-TPE mean fluorescence intensity, persisted after repeated, regular TPE sessions. In two patients, TPE led to complete reduction in DSAs to undetectable levels. Patients tolerated TPE with 5% albumin as a replacement fluid without major bleeding or thrombotic complications. No adverse events occurred during the TPE procedures; however, one patient experienced major hematoma/hemothorax during central line placement for TPE. Fresh frozen plasma was used as a replacement fluid in only rare circumstances to replace fibrinogen or prior to an invasive procedure. The overall data suggest that liver transplant patients tolerate TPE without major complications. However, TPE appears effective for removal of DSAs as assessed by the single antigen bead assay for only certain antibodies. TPE practitioners should become familiar with the potential risks and benefits of TPE in liver transplant patients being treated for AMR as the definition of AMR and the role of DSAs becomes more established.