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Timing and phenotype in refining the role of plasma exchange in amatoxin-induced acute liver failure

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Letter to the Editor,

We read with great interest the study by Stahl et al. [1], which provides the most comprehensive real-world evaluation to date of therapeutic plasma exchange (PEX) in acute liver failure due to amatoxin intoxication (AT-ALF). In a field characterized by limited evidence and heterogeneous practice, the authors' finding that adjunctive PEX is associated with improved 28-day transplant-free survival—specifically in patients with hepatic encephalopathy (HE) grade ≥ 2—offers an important and clinically actionable insight.

A major strength of the Amanita-PEX study lies in its etiological precision. Unlike prior studies that pooled ALF of diverse causes with distinct disease kinetics and inflammatory profiles, this cohort focuses exclusively on AT-ALF, a prototypical hyperacute and toxin-mediated injury. This approach substantially reduces biological heterogeneity and allows a clearer interpretation of the therapeutic signal. Importantly, the observed benefit of PEX was confined to patients with advanced encephalopathy, the subgroup in whom systemic inflammation and toxin burden are most pronounced. This phenotype-specific association strongly supports the concept that the effectiveness of PEX is determined not by the intervention alone, but by patient selection and timing.

Indeed, previous conflicting results regarding PEX in ALF may be better explained by differences in disease stage at initiation rather than by true inefficacy of the therapy. In contrast to early high-volume PEX in the trial by Larsen et al. [2], and later intervention in patients with advanced multiorgan failure in the study by Burke et al. [3], the Amanita-PEX cohort largely reflects real-world "rescue" use after progression to HE grade ≥ 2. The consistency of benefit within this clearly defined, high-risk phenotype suggests that PEX should be viewed as a targeted intervention for the right patient at the right time, rather than as a universally applicable therapy.

Beyond patient selection, the findings of Stahl et al. carry important implications in regions where access to liver transplantation is limited. Amatoxin-induced toxicity represents a growing public health challenge, as evidenced by data from Türkiye, where more than 30,000 cases were reported between 2018 and 2023, with a mortality rate of 6.6% and liver transplantation performed in only 1.3% of hospitalized patients [4]. Climate-related changes in rainfall patterns have been associated with a marked increase in amatoxin-related exposures, further amplifying this burden. Although emergency transplantation remains the curative treatment for AT-ALF, rapid clinical deterioration and logistical constraints often preclude timely access [5]. In this context, PEX emerges not as a competitor to transplantation, but as a necessary therapeutic option—either as a bridge to recovery or as a means of stabilization while transplant candidacy is evaluated.

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Taken together, these data support a pragmatic clinical framework in which PEX is prioritized for patients with AT-ALF who demonstrate early neurological deterioration. Structured referral pathways and timely initiation of adjunctive PEX in patients with HE grade ≥ 2 may help align therapeutic decisions with disease biology, particularly in settings where transplantation is not readily accessible. We commend the authors for addressing an important evidence gap that is unlikely to be filled by randomized trials given the rarity of AT-ALF. Future studies should focus on dynamic risk stratification models incorporating encephalopathy kinetics and biomarkers of systemic inflammation, to better target this important supportive therapy to patients most likely to derive meaningful benefit.

Abbreviations

ALF	Acute Liver Failure
AT-ALF	Amatoxin-associated Acute Liver Failure
HE	Hepatic Encephalopathy
PEX	Therapeutic Plasma Exchange

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