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REPLY TO: "PUTATIVE UNDERLYING MECHANISMS OF LIPID EMULSION TREATMENT FOR ALUMINUM PHOSPHIDE POISONING"

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To the Editor,

We thank the author of the recent Letter to the Editor regarding "Efficacy of intravenous lipid emulsion as an adjunctive therapy for acute aluminum phosphide poisoning: a randomized, open-label, pilot clinical trial" for their insightful comments[1]. We appreciate the opportunity to clarify important mechanistic and methodological aspects raised and correct the scientific record.

The author correctly points out that phosphine gas is hydrophilic, which challenges the traditional "lipid sink" hypothesis typically applied to lipophilic drugs like bupivacaine. Importantly, log P (octanol-water partition coefficient) is not strictly applicable to gases such as phosphine, as it is primarily defined for solutes partitioning between liquid phases. Phosphine toxicity is predominantly mediated *via* mitochondrial inhibition rather than membrane accumulation. While our discussion briefly acknowledged that intravenous lipid emulsion provides a concentrated source of free fatty acids as an energy substrate for the failing myocardium, we concur that these direct intracellular mechanisms likely play a far greater role than the indirect "lipid sink" effect[2]. Phosphine exerts toxicity primarily through inhibition of cytochrome c oxidase, generation of reactive oxygen species, and impairment of oxidative phosphorylation, ultimately leading to severe metabolic acidosis, myocardial depression, and refractory shock[3]. The provision of intravenous lipid emulsion likely bypasses this inhibition by supplying abundant fatty acids, restoring myocardial adenosine triphosphate (ATP) production, and attenuating mitochondrial dysfunction. The marked improvement in shock reversal and lactate clearance observed in our intervention group strongly supports this direct metabolic and inotropic rescue mechanism over simple intravascular sequestration.

We are also grateful to the author for identifying a statistical discrepancy in our primary outcome report. The raw observational data (patient counts for mortality and survival) presented in the primary outcome table of our trial are correct. However, due to an inadvertent software parameter assignment during our statistical analysis, the Relative Risk (RR) was calculated and reported for survival (Control *vs.* Intervention) rather than the standard clinical metric of mortality (Intervention *vs.* Control). In the original publication, the RR was incorrectly reported as 0.493 (95% CI: 0.335-

0.725). When properly analyzed to calculate the relative risk of mortality comparing the intravenous lipid emulsion group to the control group, the correct relative risk is 0.370 (95% CI: 0.211-0.649). The chi-square test statistic (χ^2 = 15.3, df = 1) and the statistical significance ($p < 0.001$) remain unchanged. Importantly, this correction does not alter the trial's fundamental findings. We sincerely apologize for this calculation oversight.

Finally, we welcome the author's post-hoc sample size estimation for future multicenter trials. Because ours was a pilot study designed to assess feasibility and preliminary efficacy, it was not formally powered. Our study was exploratory in nature, intended to generate preliminary clinical signals and inform future trial design. As rightly emphasized, adequately powered, multicenter randomized controlled trials are essential to validate these findings and establish clinical efficacy. We also agree with the suggested approach for future sample size estimation. Given the possibility of effect size overestimation in pilot trials, adopting conservative assumptions for planning definitive studies is methodologically sound. We hope that our pilot study serves as a foundation for future high-quality research in this critical and often fatal condition.

Conflict of Interest
The authors have no conflict of interest to declare.

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None.

Data Availability
Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Ethics Approval and Informed Consent
Not applicable.

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