Sepsis is defined as an organ dysfunction syndrome caused by the over-activation of inflammatory response (1,2). Kidney is one of the most commonly involved organs in sepsis, and there is a large body of evidence showing that even mild increase in serum creatinine contributes to significantly increased risk of death (3,4). Thus, strenuous efforts have been made to improve renal function during sepsis, including the avoidance of renal toxic agents, treatment with sodium bicarbonate to correct metabolic acidosis (5), and restriction of chloride-rich fluid and starch (3,6,7). However, the risk of acute kidney injury (AKI) is still high in the intensive care unit and a substantial number of patients requires renal replacement therapy to avoid life-threatening metabolic derangements.

In recent issue of JAMA, Pickkers and colleagues investigated the efficacy and safety of a new agent called human recombinant alkaline phosphatase in the treatment of sepsis-induced AKI (8). Although the primary end point did not reach statistical significance, there is a trend towards improved short-term renal function in the intervention group. Most probably, the beneficial effect of the drug is not as large as being presumed in calculating sample size. Thus, the statistical power of the study is not large enough to detect such a beneficial effect. Patients in intensive care unit (ICU) are usually having coexisting comorbidities and/or acute complications, which may compromise the potential effect of a single intervention. The median sequential organ failure assessment (SOFA) score in the present study is 10, indicating severe organ dysfunctions beyond the kidney. Other critical conditions such as hypoxemia, hypotension and overactivated inflammatory response contribute significantly to reduced endogenous creatinine clearance (ECC). These factors while distributed unevenly among the study population, also increased the heterogeneity of the study population, further compromising the statistical power of study. Thus, by expanding the sample size, some significantly positive results may be found to support the effectiveness of human recombinant alkaline phosphatase. One limitation of including heterogeneous population is that patients may respond differently to a treatment, and the final effect size is an average of the overall heterogeneous patient population. Case-mix or heterogeneity is the curse of critical care researches. Some sophisticated machine learning methods such as model-based recursive partitioning (9,10), latent class analysis with distal outcome can help to identify homogenous subpopulations (11-13). However, these methods require large sample size to have a stable estimate (i.e., the underlying structure of the latent class may be unstable if the sample size is small).

The primary end point of the present study is the area under the ECC curve (AUC) over 7 days after enrollment, which is calculated by the integral of the ECC function over time. There was a difference between treatment and control groups, but statistical significance was not
reached. The AUC in the treatment group was 55.1 mL/min [interquartile range (IQR), 15.0 to 93.9 mL/min] in the 1.6 mg/kg recombinant alkaline phosphatase group versus 45.6 mL/min (IQR, 17.7 to 112.4 mL/min) in the placebo group [absolute difference, 9.5 mL/min [bootstrap 95% confidence interval (CI), −23.9 to 25.5]; P=0.47]. In post hoc analysis, the authors found that there was significant difference between the two groups in 21 days [mean difference of 27.6 mL/min (95% CI, 8.7 to 46.6; P=0.004)]. Probably, the recombinant alkaline phosphatase may need time to take effect, which is evident in the Figure 2 of the original paper that the two ECC curves deviates more remarkably after day 7. Thus, there is probably a time-lag before the improvement of renal function can be observed. In such a situation, I propose that a model allowing time-varying effect can be helpful (14). For instance, the distributed lag non-linear model can simultaneously model non-linear exposure-response dependencies and delayed effects. This model has been successfully used in environmental exposure and outcome, in which the effect of an environmental factor does not immediate occurs in time after exposure (15). The recombinant alkaline phosphatase is given in the first 3 days, but the effect cannot be observed immediately and there is a time-lag for the drug to take effect. Thus, a model allowing time lag can be helpful in this clinical scenario. Another statistical model that can help to solve the time-varying effect is the incorporation of time-varying coefficient in Cox regression model (16). While it is a randomized controlled trial that the treated and untreated groups have balanced baseline characteristics (i.e., controlling for baseline covariates in multivariable model is not required), the use of such model with only the treatment variable but allowing its time-varying effect will help to disentangle the effect of recombinant alkaline phosphatase over time. However, all these sophisticated models are only to provide hypothesis-generating results. The final conclusion of the effectiveness of recombinant alkaline phosphatase can be drawn with further RCTs that extend the time window for the assessment of ECC. The sample size should be re-calculated to reach adequate statistical power.

The study is very important in the treatment of AKI because it represents a transition from bench to bedside. Human recombinant alkaline phosphatase has been extensively studied in animal studies that evidence is accumulating supporting its beneficial effect on sepsis-induced AKI (17,18). However, there is a long way to go from animal study to clinical application. The present study is the first well conducted randomized controlled trial aiming to investigate the efficacy and safety of the drug. The authors should be commended for their great effort to find novel agents for the treatment of sepsis-induced AKI.

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None.

**Footnote**

*Conflicts of Interest:* The author has no conflicts of interest to declare.

**References**


