Reviewer's report

Title: Therapeutic plasma exchange as rescue therapy in severe sepsis and septic shock: retrospective observational single-center study of 23 patients

Version: 3
Date: 4 November 2013
Reviewer: Tibor Fulop

Reviewer's report:

General Comments:
The paper is generally well written, with mostly very good English (some comments and potentials for improvement below). The paper examines a very exciting and interesting subject, which is the potential benefit of plasma exchange (PLEX) in septic patient. While it is a relatively simple, descriptive paper, nonetheless, it has its value due to the number of enrollees.

While currently it is almost impossible to deliver a controlled trial on a subject (not at least form a single center) the Authors did a fair job teasing out subcohort characteristics, where PLEX may offer benefit (high procalcitonine, certain type of sepsis). This is not surprising, as not all septic shocks are the same; in fact, what would be surprising if this technology would work uniformly for all patients. The clinical practice of the Authors, as described in their report, describes well the moving target for PLEX – used initially for massive septic DIC, then applied to lesser ill subjects with partial derangement of the coagulation cascade and septic shock (and the “lesser” is a very relative term here). It is interesting, that some Nephrologist, including myself, view the current technology of high-volume hemofiltration in in AKI/critically ill, septic patients as a virtual “size selective plasma exchange” - in disguise. However, the current prolonged use of hemofiltration may remove, especially with prolonged use, potentially useful substances (antibiotics, proteins). Such concern would not occur with 1-3 sessions of PLEX. It is interesting that TPE may have also a potential role in selected critically ill patient with excessive coagulation tendency, recovering from septic-inflammatory injury (e.g., the hypercoagubility interfering with renal replacement therapy) as noted in J Clin Apheresis 2011; 26(4):214: “Recurring Extracorporeal Circuit Clotting During Continuous Renal Replacement Therapy Resolved after Single-Session Therapeutic Plasma Exchange.”

While likely it will never be possible to offer this therapy to full-size adults on large scale, such experiences may provide impetus for new and emerging technologies for: 1.) better plasma substitutes; 2.) potentials for new and emerging technology to “clean” plasma of inflammatory mediators and at least partially recycling the endogenous proteins. One potential technology is e.g. the so called “CART” for recycling ascites proteins (see: “Single Center Experience of Cell-Free and Concentrated Ascites Reinfusion Therapy in Malignancy Related Ascites” Therapeutic Apheresis and Dialysis 2013; DOI: 10.1111/1744-9987.12049) [i.e., to recycle albumin and globulins]. Similar
technology may emerge for PLEX, if the benefits were proven in a proof-of-concept trial.

The authors have applied strong clinical criteria for identifying clinical sepsis (in real-life experience, close to 50% of the time cultures remain unhelpful) and used mostly membrane-based technology for PLEX. Such distinction is relevant, as centrifuge-based separators are x4-8 more expensive, depending on the center. Somewhat along the same theme, this writer acknowledges the relatively large cost of PLEX (even with plasma separator); however, at least in the US, 1 day of ICU stay would certainly cost much more than one plasma exchange.

I agree with the Authors that they have used platelet count as a surrogate for clinical endpoints... platelet count is known to be associated with sepsis and is an independent predictor of death. Also, appropriately, the authors paid attention to the fluid balance, which is an emerging risk factor associate with poor survival, especially in patients with Acute Kidney Injury (Fülöp et al. Volume-Related Weight Gain and Subsequent Mortality in Acute Renal Failure Patients Treated with Continuous Renal Replacement Therapy. ASAIO J 2010 (Jul-Aug); 56(4): 333-7.)

And finally, the authors acknowledged well the major limitations of their study, to which I have little to add. Nonetheless, I need to emphasize the relative value of this paper in the context of limited publications on the subject.

Bibliography. Appropriate and mostly up-to-date. Would suggest incorporating some additional references, see above.

Major comments:

My major concern is that the data is reported with median and 25-75% IQR by the authors. This may be a valid approach for markedly skewed data, however, most of the parameters (e.g. age, BMI, etc) is assumed to have a Gaussian ("normal" or bell-shaped) data distribution. Would suggest editing the paper by reporting on means +/- standard deviations, instead. This would make it easier to compare with existing paper, incorporate the results in future meta-analyses, etc. Use median & IQR only of the data distributions warrants it.

Somewhat along the same lines, most of the Results section can be better reported by creating 1-3 additional Tables (e.g.: Baseline Characteristics/Disease Severity; Survivor/Non-survivor Characteristics – with Inflammatory markers/SOFA scores... give p-value, if significant), and thus, "compacting" the paper better.

Would it be possible to show a time-series graph of the subject/year (i.e., the number of enrollees per year... unclear, whether there was temporal trend, reading the paper)

Minor comments:

ABSTARCT -

The first sentence of the Abstracts is probably not necessary.

Do not start sentence with “But,”... use, e.g.: “However,...” [this is a repeating
issue through the paper]

Patients & Methods:
Change to: “We performed a retrospective observational single-centre review on...”
Same thing, as above, to report on means (SD) rather than medians & IQR

BODY OF THE ARTICLE:
In materials and Methods:
“ii) data were anonymised” – use the word “de-identified”
Re: page 7-figure 2.: would be nice to have a p value (in the text)

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I have no competing interest to report