Editorial

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Which Patient Phenotype Is the Ideal Candidate for Hemoadsorption in Acute and Chronic Kidney Disease?

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INTRODUCTION

Despite recent technological advances, current extracorporeal blood purification therapies (EBPT) present significant limitations both in chronic and acute renal failure.[1,2] This observation is supported by several lines of evidence demonstrating suboptimal performance and poor effectiveness in correcting metabolic and physiologic alterations induced by chronic uremia or acute kidney injury.[3,4] As such, new and more effective techniques are needed.[5] The development of new biomaterials and the utilization of new mechanisms of blood purification such as adsorption are new areas of intense research.[6] Studies on the application of hemoadsorption (HA) however, have produced controversial results or a level of evidence that is often considered insufficient to recommend the use of these techniques in routine medical practice.[7] In this editorial, we would like to underline the concept that HA can be an important additional treatment both in chronic and acute renal failure for specific patients characterized by peculiar phenotypes, as per the modern approach of precision medicine. We will discuss the case of chronic patients on maintenance hemodialysis (HDx), and the case of critically ill patients with sepsis-associated acute kidney injury (SA-AKI).

THE CASE OF CHRONIC HEMODIALYSIS

Although maintenance hemodialysis has lengthened survival in millions of end stage kidney disease (ESKD) patients over the last six decades,[8] the high incidence of complications, hospitalizations and mortality, highlight limitations and underline unsatisfactory results.[9] This has been, at least in part, ascribed to a solute retention syndrome, due to accumulation of metabolic waste products. These molecules are in the range of 10 to 50 kDa, and are generally defined as small, medium and large "middle molecules".[2] The unfolding story of middle molecules tells us today that the patients with residual renal function tend to have lower levels of uremia retention products and tend to present with fewer signs and symptoms of uremia. It has been demonstrated that accumulation of molecules such as Leptin may interfere with appetite;[10] beta-2 microglobulin (β2M) and Serum Amyloid-A correlate with the incidence of carpal tunnel syndrome;[11] high levels of parathyroid hormon (PTH) correlate with osteo-articular disorders and cardiovascular complications;[12] while retention of enzyme inhibitory proteins and light chains may cause inflammation, anemia and immunological dysfunction.[13] All these molecules are in the range of 10 to 50 kDa and are insufficiently cleared by classic dialysis techniques.[6] In some patients, symptom reduction and improved quality of life can be achieved using convective techniques such as hemodiafiltration (HDF)[14] or expanded HDx.[15] In fact, the use of high flux and medium cut-off membranes may contribute to a reduction of middle molecule accumulation due to a better sieving profile. In spite of these improvements, a variable proportion of patients on maintenance hemodialysis may still experience poor quality of life and symptoms such as pruritus, restless leg syndrome, sleep disorders, anemia despite the use of high-dose erythropoietic agents, skeletal pain and muscular weakness.[16] Such considerations have made the basis for the application of hemoadsorption combined with hemodialysis (HA-HDx) in ESKD patients with a peculiar clinical profile characterized by the presence of uremic symptoms and a background of subclinical inflammation.[17,18] The above-mentioned patients in fact represent the right phenotype for the application of HA-HDx.[19,20] In these circumstances, large clinical trials have demonstrated significant symptom reduction with improvement in quality of life in the group of patients treated with HA-HDx for at least one of the three sessions each week[21,22] and have led to the consideration that HA-HDx may represent a sustainable, cost-effective new frontier in chronic blood purification.[19–23] The logic and rationale behind the improvement is the high capacity of the sorbent to remove solutes in the medium–large molecular weight and even small protein-bound toxins responsible for the uremia retention syndrome.[7,24] We may therefore conclude that HA-HDx represents a viable option for chronic blood purification in those patients where classic dialysis techniques fail to achieve adequate correction of signs and symptoms and an acceptable quality of life. Such patients represent the right phenotype in which HA-HDx is indicated. This phenotype must be identified before proceeding to a

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prescription of hemoadsorption in addition to hemodialysis in order to maximize the benefits of this technique and strategy [Figure 1].

THE CASE OF THE CRITICALLY ILL PATIENT WITH SEPSIS OR SA-AKI

Several studies conducted in sepsis and SA-AKI have failed to demonstrate benefit from various interventions.[25] The main reasons for these often-expensive failures possibly lie in the inability to identify the right patients for enrollment and often the inappropriate choice of endpoints.[26] It is now evident that both sepsis and SA-AKI are a mixture of syndromes in which the cause and the response of the host play an important role in creating specific endotypes with peculiar characteristics and clinical pictures.[27–29] For this reason, it seems unlikely to foresee a positive response to a therapy of the overall studied population, especially in light of the different pathophysiological mechanisms involved.

In case of sepsis, for example, there are specific phenotypes characterized by severe hemodynamic instability, variations in temperature and leucocyte/platelet count, microthrombotic/microangiopathic profiles.[30] In recent years however, the possibility to measure endotoxin activity using a specific assay, endotoxin activity assay (EAA), has allowed clinicians to identify a specific patient endotype in which endotoxin is detectable in blood and may represent a target for extracorporeal removal. Polymyxin-B-coated polystyrene fibers have been included in a special adsorption cartridge (Toraymyxin, Toray, Japan) and are capable of removal of circulating endotoxin up to approximately 20 µg in a two-hour treatment.[31–33] The controversial results achieved so far in studies involving extracorporeal hemoadsorption with Toraymyxin[34,35] could be attributable to the remarkable heterogeneity of the treated populations in different studies.[30,36] Analyses have demonstrated that positive results are more likely in patients with significant organ failure and in patients with endotoxin activity between 0.6 and 0.9.[37] New studies should therefore be focused on this specific phenotype.[38] Different endotypes can be observed in septic patients and for these peculiar conditions different techniques can be indicated [Figure 2]. In case of presence of the microbial agent, removal of circulating bacteria or viral particles can be obtained by special affinity binder cartridges (Seraph 100).[39] This treatment has been used in combination with special adsorbing membranes such as modified AN69 (Oxiris, Baxter, Dirfield, USA) or adsorbing cartridges (CytoSorb, Cytosorbents, USA).[40] In case of presence of endotoxin in blood, detected by EAA, extracorporeal removal of endotoxin with polymyxin-B cartridge (Toraymixin, Toray, Japan) can be indicated alone or in conjunction with other adsorption or continuous renal replacement therapy (CRRT) techniques.[30] We should mention that different endotypes may be also a reflection of different conditions of the same patient in different time windows of the intensive care unit (ICU) stay. In these circumstances, the application of different adsorption and blood purification techniques can be time sensitive as suggested in a recent proposal of sequential application of extracorporeal techniques.[41]

On the other end of the spectrum from targeted removal of endotoxin, are broad-spectrum sorbents capable of removing a broad range of molecules including mediators and protein-bound solutes. Sepsis induces expression of a dozen of inflammatory mediators where no one molecule is responsible for the entire syndrome. In such circumstances, aspecific removal of the various mediators by hemoadsorption may represent the ideal condition to restore immune-homeostasis.[24,42–44] The cytokine release syndrome (CRS) is a systemic inflammatory response induced by bacteria, viruses, blood exposure to non-biocompatible materials, drugs, and antibody-based therapies or chimeric antigen receptor (CAR)-T cell therapy. Cytokines trigger a cascade with activation of innate immune cells (macrophages and endothelial cells) with further cytokine release. The presence of a CRS may be demonstrated by biochemical measurements in the presence of the typical clinical picture characterized by hypotension and organ dysfunction. Therefore, it makes no sense to apply a cytokine removal technique if there is no evidence of systemic inflammation or elevated biochemical levels of cytokines. On the other hand, there is a specific time window for this type of intervention which may prove beneficial in preventing the development of cytokine-mediated organ dysfunction or in protecting the kidney from disease and damage progression. Recently, special cartridges with microporous biocompatible resin have made recently available with high capacity of cytokine adsorption (Jafron HA330/HA380, Jafron, Zhuhai, China).[47] According to the peak concentration hypothesis[45,46] higher removal will occur for molecules with the highest concentration in blood and likely with the more impactful action on immune-dysregulation. In such condition, Patients with impending or overt cytokine storm induced by different causes represent the ideal population for extracorporeal cytokine removal by hemoadsorption [Figure 2].

The same approach can be utilized to identify the right population affected by AKI. As described in Figure 3, AKI is a multifactorial syndrome and only when presenting a specific endotype (Oliguria-based Stage 1 with sepsis or CRS-induced hypotension), there is a rationale for application of hemoadsorption, even in the absence of any RRT. In other stages, HA can be combined with CRRT if immune-modulation or cytokine removal is desired beyond the renal support.[29]

CONCLUSIONS

In conclusion, too many trials have failed for inappropriate enrollment of patients without a specific target or a well identified population. This has led to failures that do not necessarily mean that the intervention is useless. Applying the criteria of precision medicine, more and more peculiar endotypes should be selected to test the hypothesis of a beneficial effect of an intervention such as hemoadsorption in symptomatic maintenance hemodialysis patients, in septic patients with impending or overt cytokine storm, and in AKI patients where cytokines may represent the causative mechanism of renal dysfunction.

Once the right population has been identified, the end points of clinical trials should be clearly defined with a hierarchy of importance.[48] In particular, for extracorporeal therapies such as HA, a progression from biochemical end points (removal of molecules) to biological endpoints (cellular effects of molecule removal such as enzymatic reactions, cellular functions, immunological response), to pathophysiological endpoints (life parameters such as blood pressure, heart rate, PaO_2/FiO_2, diuresis, cardiac output, *etc.*), to clinical endpoints (clinical outcomes including organ function and disease severity, need

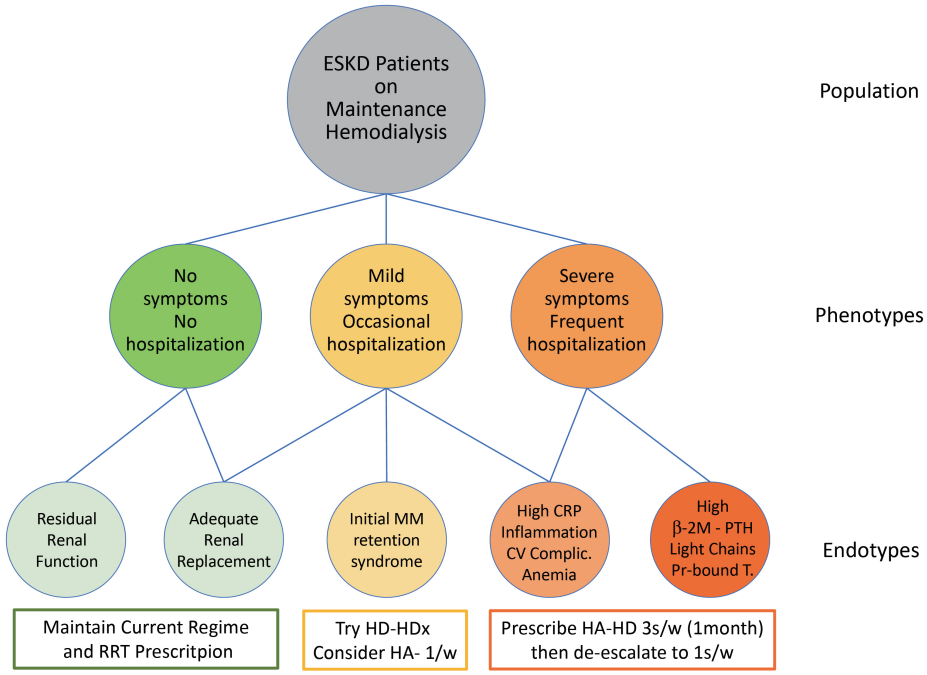

Figure 1. Among patients with ESKD undergoing chronic hemodialysis, different phenotypes (observable traits) can be present. Within each single phenotype, further distinction can be made into specific endotypes (underlying mechanisms responsible for the observable trait) that may require different therapeutic management. In particular HA-HDx is indicated in those patients with intractable uremic symptoms and frequent complications related to uremia retention molecules and inflammation. In these patients an initial phase may require 3 sessions per week while in the maintenance phase (after one month) one session per week of HA-HDx and 2 sessions per week of HD can be safely prescribed. ESKD, end stage kidney disease; MM, middle molecules; CRP, C-reactive protein; CV, cardiovascular; β-2M, beta-2 macroglobulin; Pr-Bound T, protein bound toxins; RRT, renal replacement therapy; HA-HDx, hemoadsorption combined with hemodialysis; HDF, hemodiafiltration, HDx, expanded hemodialysis; PTH, parathyroid hormone; s/w, sessions per week.

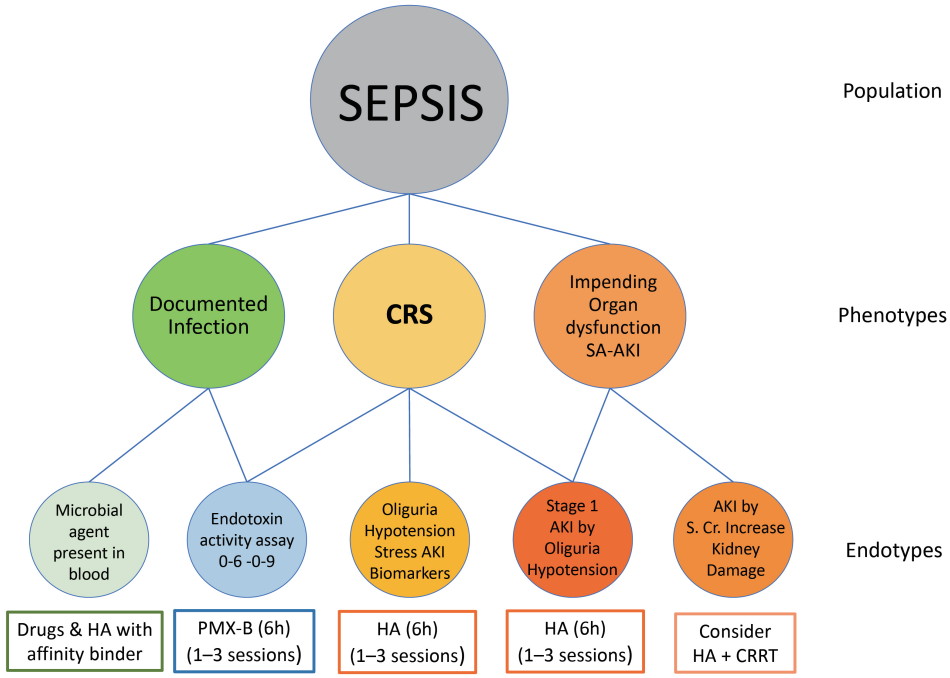

Figure 2. Among patients with sepsis, different phenotypes (observable traits) can be present. Within each single phenotype, further distinction can be made into specific endotypes (underlying mechanisms responsible for the observable trait) that may require different therapeutic management. In particular, if the causative microbiological agent is present in blood, besides pharmacological antibiotic or antiviral therapy, hemoadsorption with affinity binder can be considered. If Endotoxin Activity Assay indicates presence of LPS in blood and the concentration is between 0.6 and 0.9 EAU. HA with Polymixin-B cartridge is indicated. If a CRS is clinically suspected or biologically documented, extracorporeal cytokine removal sessions are indicated with hemoadsorption cartridges. If impending or overt organ dysfunction and stage 3 AKI are present, HA can be combined with CRRT. AKI, acute kidney injury; HA, hemoadsorption; LPS, lipopolysaccharide; CRS, cytokine release syndrome; CRRT, continuous renal replacement therapy; EAU; endotoxin activity units; PMX-B, polymixin-B.

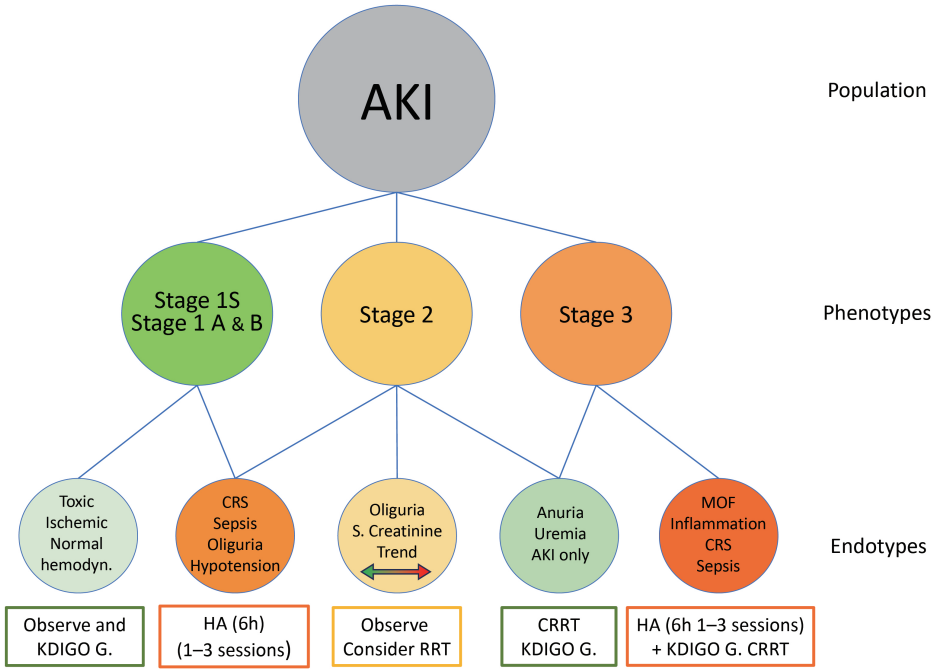

Figure 3. Among patients at risk for AKI or with established AKI, different phenotypes (observable traits) can be present. Within each single phenotype, further distinction can be made into specific endotypes (underlying mechanisms responsible for the observable trait) that may require different therapeutic management. In particular, HA seems to be indicated in patients with SA-AKI when stage 1S or Stage 1 by oliguria only is present. In these conditions an evident damage is not present and the oliguric state may be due to cytokine-mediated hypotension and endothelial dysfunction. HA associated with CRRT may be indicated when persistent AKI is present with a typical trait of immuno-dysregulation or hyper-inflammation. AKI, acute kidney injury; CRS, cytokine release syndrome; HA, hemoadsorption; CRRT, continuous renal replacement therapy; MOF, multiple organ failure; KDIGO, Kidney Disease: Improving Global Outcomes.

for dialysis, hospital free days, mechanical ventilation free days, survival). These represent of course the ultimate endpoints, but before getting sufficient evidence for them, it is important to avoid dismissing a treatment as "non effective", just because the solid hard endpoint such as survival is not affected. Evidence is a wall and every small brick represent an addition to current knowledge. In order to optimize this advancement in the acquisition of new evidence, it is important to share consensus on a structured research agenda[29,49] and proceed with collaborative effort to well designed studies, registries and biga data collection.

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Authors contribution

Ronco C and Kellum JA equally contributed to the preparation and the content of the manuscript.

Ethics approval and consent to participate

Not applicable.

Conflicts of interest

Claudio Ronco has been advisor or member of the speaker bureau or received honoraria for presentations in the last 3 years from the following companies: Asahi medical, Aferetica, Baxter, Biomerieux, B. Braun, Cytosorbents, Fresenius medical care, Medtronic, Jafron Medical, ESTOR, Nipro, Medica, GE. John Kellum J.A. Kellum discloses grant support and consulting fees from Astute Medical/BioMerieux and Baxter and currently is a full-time employee of Spectral Medical.

Data availability statement

No additional data.

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