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REVIEW ARTICLE

The Techniques of Blood Purification in the Treatment of Septic Shock

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ABSTRACT
In the last few decades, a number of techniques based on different principles of functioning have been developed to remove from the bloodstream of septic shock patients or suffering from other clinical conditions characterized by an exaggerated inflammatory response. Despite Yet, their use is based more on the personal experience than on the results of clinical trials that often-carried contrasting results.
In this review the rationale for the blood purification procedures, their technical features and the findings of clinical trials are exposed and discussed along with the possible rules of engagement.

1. Introduction.

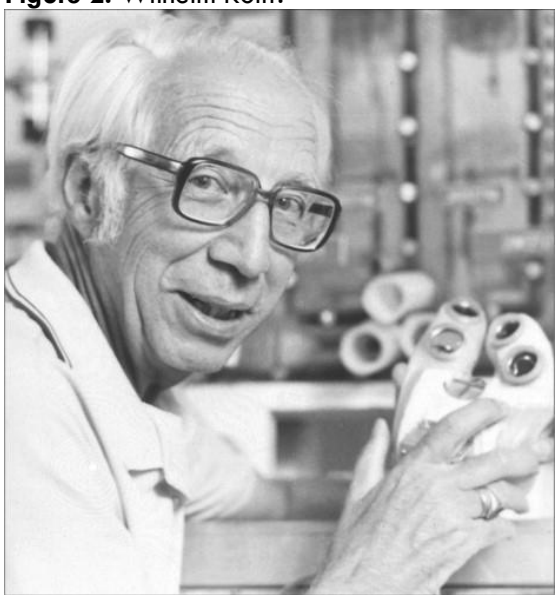
Since the very beginning of the history of western medicine it has been thought that many, if not all, diseases were caused by "evil spirits" deeply embedded into the human body; consequently, bloodletting was considered an appropriate treatment for (almost) all disorders affecting the mankind (Figure 1).

Figure 1: Ancient Greek painting in a vase, showing a physician bleeding a patient.

For centuries, besides some herbal medication, this was the only available therapeutic approach.

Yet, sometimes bloodlettings were carried on too enthusiastically and a number of patients, after repeated procedures, bled to death, including George Washington and King Louis the 14th. It is likely that, would these and many other patients have survived the hypovolemia, they succumbed to the procedure-related infections later on. Bloodletting remained into the practitioner's armamentarium up to the second half of the 19th century when it became clear that many disorders were caused by microorganisms and that their treatment did not take advantage from the withdrawal of blood. From then on, this practice is restricted to very few clinical circumstances, including hemochromatosis and polycythemia. In the 40s' of the 20th century the Dutch physician Wilhelm Kollf (1911-2009) (Figure 2) treated patients with acute kidney injury (AKI) by flowing their blood upon a synthetic membrane permeable to uremic toxin. Despite the elevated mortality (16 deceased patients out of 17 treated, 94% mortality!) of the first group treated with this device, the era of hemodialysis and derived Renal Replacement Treatments (RRT) was initiated and soon it spread all over the world [1].

Figure 2: Wilhelm Kollf.



A few decades later it was discovered that the organ damage(s) commonly observed in septic shock patients is determined by a wide number of o mediators released during the infecting germ-host interaction and two different strategies were developed. The first takes advantage from the administration of substances directed against these molecules or their cellular receptors and the second uses a number of devices to remove the mediators from the bloodstream using an extracorporeal device. The second stems from a study by Clowes et al [2] who demonstrated that the fluid removed from the bloodstream of septic and trauma patients using a commercially available hemofilter used for the treatment of AKI determined the same metabolic alterations observed in these subjects when it was injected in healthy mice; consequently, it was hypothesized that (a) the culprit molecule(s) were similar if not identical in both species; and, more importantly, (c) that this procedure could be used to abate the bulk of bloodborne mediators alleged for the occurrence of the multiple organ dysfunction syndrome in patients with septic shock and/or other conditions characterized by an excessive inflammatory reaction such as septic shock, hemophagocytic syndrome (HS), macrophage activation syndrome (MAS), etc. [3] The gradual passage from the RRT to the blood purification (BP) era was initiated.

Since then on, an ever-increasing number of substances with both pro-and anti-inflammatory properties produced in these clinical circumstances have been identified [4], and it was hypothesized that their neutralization could positively influence

the clinical course of sepsis and septic shock and/or of other clinical conditions characterized by an uncontrolled inflammatory reaction. With this aim, two different strategies have been developed. The first consists in the administration of inhibitors of a specific mediator or in the blockade of their cellular receptor; however, the results of many randomized controlled trials (RCT) were largely below the expectations derived from the experimental investigations and small Phase I human studies; yet some subgroup analysis indicated an increased survival of patients with elevated blood level of the mediator targeted by the study substance. The second is based on the mass separation process of either pathogen, germ-derived substances such as endotoxin and/or bloodborne mediators produced by the host via different mechanisms, including (a) their removal through an artificial membrane whose cutoff value is compatible with their molecular weight (MW); or (b) their adhesion on the surface of a substance able to scavenge them from the bloodstream.

This review aims to illustrate the more widely used techniques of BP, their properties and operating mechanisms and the results of some relevant clinical trials in order to identify their possible role in the treatment of septic shock and other conditions characterized by an excessive inflammatory reaction.

2. Rationale for Blood Purification.

The term blood purification is somewhat misleading as their final goal is to reduce their tissue concentration where their primarily exert their effects.

The reduction of the blood values of sepsis mediators represents a valuable therapeutic target because:

a. their abatement below a threshold level and/or the elimination of their peak values can reduce the associated organ damage [5];
b. it is possible to achieve of a gradient promoting the passage of mediators from the tissues to the blood and their subsequent extracorporeal clearance [6] promoting the leukocyte chemotaxis [7];
c. it determines the interaction between the membrane and the immune cells (8), as demonstrated by the modulation of surface molecules during different BP procedures;

Actually, it is likely the multiple mechanism (i.e. a + b), maybe in different time windows, cooperate to achieve the therapeutic effect of BP [9, 10].

In practical terms, the efficacy of all BP techniques is based on the interaction between the mediator(s) involved and the device used. As far as the former is concerned, their MW and hydrophilic or hydrophobic characteristics represent the limiting factor for the removal. Put in other words, a molecule exceeding the MW clearance capabilities of a certain material used cannot be eliminated and the use of another device with different characteristics, including the pore size for convective transport or the adsorptive surface for hemoadsorption (HA) is warranted (Table 1).

Table 1: relationship between the MW of the inflammatory mediators and the BP technique used.

Molecular Weight (kD)	Principle of Removal
Up to 50	Convective transport with conventional membranes Hemoadsorption
50-75	Convective transport with high permeability membranes Hemoadsorption
≥ 75 → >400	Convective transport with high-permeability membranes Plasma exchange

3. Taxonomy and principles of the BP techniques.

As stated above, different techniques are used as add-on treatments in septic shock or other clinical conditions characterized by elevated blood concentrations of inflammatory mediators, such as HS or MAS.

Basically, the BP can be subdivided in blood- and plasma- processing techniques (Table 2). The factors influencing the efficacy of the BP differ according to their principle of functioning. Consequently, for the hemofiltration (HF)-based techniques, that basically takes advantage from the same material used to treat AKI, the main determinant of their efficacy is the production of ultrafiltrate (UF), that, in turn, depends on (a) the blood flowing (Qb) inside the filter; (b) its permeability to the different molecules involved, that is mainly determined by the size of the pores the surface of the membrane; and (c) the surface of this latter. Instead, for the hemoadsorption- based techniques (HA), the Qb and the affinity for the substance(s) to be removed represent the main determinants of functioning.

Independently from these differences, both families share a number of characteristics, including (a) the time-dependent decay of the clearance capabilities; (b) the need of a dedicated vascular access using a large-bore catheter and (c) the anticoagulation of the extracorporeal circuit using heparin or citrate; moreover, many but not all, can be used in association with a Continuous Renal Replacement Therapy (CRRT) (Table 2) [11].

Table 2: Devices and clinically used and/or under evaluation.

Denomination	**Principle/Targets**	**Mode**	**Producer**	**Recommended Duration** (hours* days)
Hemofiltration (at different Qf: see text)	Convective Removal of mediators	CRRT	Different	
Alteco®	Adsorption of LPS	Stand alone	Alteco Medical	2-6 * 2
oXiris®	Combined HA of LPS and convective removal of mediators	CRRT	Baxter	n.d.
Toraymixin®	HA of LPS on polymyxin B bound to polystyrene fibers	Stand alone	Toray	2 * 2
Matisse®	HA of LPS/DAMPS/PAMPS on albumin microbeads	CRRT	Fresenius	3-4
Seraph 100®	HA of pathogens/DAMPS/PAMPS of heparan sulphate microbeads	Stand alone	Extera Medical	4 (extension to 24 pending)
Hemopurifier®	HA of pathogens via PP and adsorption on synthetic agglutinin	Stand-alone / CRRT	Aethlon Medica	4
Garnet ®	HA of pathogens on mannose-binding lectin	Stand-alone / CRRT	BOA Biomedical	Not determined
Cytosorb®	HA of mediators on polystyrene microbeads	Stand-alone / CRRT	Cytosorbents	24
HA 330®	HA of mediators on resin macroporous column	Stand-alone / CRRT	Jafron	2*3 days
Plasma Exchange	Removal and substitution of 30-40 ml/kg of plasma volume	Stand-alone	Different	As needed

Legend: Qf: volume of ultrafiltrate/minute; CRRT: Continuous renal replacement treatment; HA: hemoadsorption; LPS: Lipopolysaccharide.; PP: plasmapheresis; DAMPS: damage-associated molecular patterns; PAMPS: pathogen-associated molecular patterns.

4. Blood processing techniques.

4.1 HEMOFILTRATION (HF).

Principles.

The basic mechanism of HF consists in the convective removal of H_2O and hydrophilic solutes, including mediators, from the bloodstream flowing on the surface of a synthetic membrane with a MW cutoff value of ~50 kD [9-11]. The UF removed has the same electrolyte composition of the plasma. Different strategies have been developed to improve the removal of mediators, including (a) the increase of the Qf, considered as a proxy of the intensity of treatment (Table 3); (b) the use of membranes with a higher cut-off (HCO) , but their use is associated with by high albumin losses [10]; to overcome this limitation, the HCO membranes can be used in the diffusive rather than the in convective mode or by slightly reducing the pore size and the surface [12]; and, finally, (c) the combination of two different hemofilters with different cut-off values: the first hemofilter, with a larger cut-off, produces an ultrafiltrate containing both large and small MW molecules and flows through another one with a smaller cut-off; then, only middle MW molecules will be cleared and those with lower MW are reinfused back to the patient as predilution fluid before the first hemofilter [13]; (d) the cascade-high-volume Hemofiltration (HVHF) which has been developed to remove middle molecules while retaining those with smaller MW, including vitamins and drugs [14].

Table 3: different intensities of HF.

Denomination	Qf (ml/kg/minute)
Standard volume CVVH	25-35
High-volume (HV) CVVH	35-60
Very HV CVVH	> 60
Pulse HV CVVH	85 * 6 hours, then 35 for 18 hours

Legend: CVVH: continuous veno-venous hemofiltration.

4.2 HEMOADSORPTION (HA).

Principles

Basically, the HA consists in the adhesion of circulating substances or pathogens on the surface of a material (sorbent) able to capture them. Long before being used in septic patients, HA has been employed to manage a number of intoxications [15]. The sorbents underwent a constant evolution: initially, inorganic aluminosylicated and charcoal were utilized, but more biocompatible materials, including organic polymer ion exchange resins and synthetic porous polymers [15] have subsequently replaced these materials. Independently from the material used, sorbents have a strong capacity to adsorb specific molecules via weak ionic bonds. Currently available sorbents are produced in different tri-dimensional arrays, including granules, microbeads, surfaces and fibers, with an area-to-surface ratio ranging from 300 to 1200 m^2/g and are packed in cartridges (Table 4). The Qb ranges from 150 to 400 ml/min, according to the patients' hemodynamic conditions.

Table 4: characteristics of available HA cartridges.

Sorbent	Brand Name	3D Arrangement	Surface (m^2)
Polystyrene divinylbenzene copolymer	Cytosorb®	Microbeads	45.000
Peptide with high affinity for LPS	Alteco®	Microdiscs	4
1. Mediators/DAMPS/PAMPS: Na^+ sulfonate molecules coating an AN 69 membrane 2. LPS: polycationic polyethylenimine (PEI)	oXiris®	Hollow fibers	1,5
Polymyxin-B	Toraymixin®	Hollow fibers	500
Immobilized human albumin	Matisse®	Microbeads	n.a.
neutral microporous resin and collodion coating	HA330	Microbeads	10.000
Ultra-high MW coated with end-pint attached heparin	Seraph 100®	Microbeads	40
Galanthus nivalis agglutinin	Hemopurifier®	Hollow fibers	n.a.
Fc-mannose-binding lectin	Garnet ®	Hollow fibers	n.a.

Legend: n.a.: not available. The technical features of the devices have been downloaded from the manufacturers 'site.

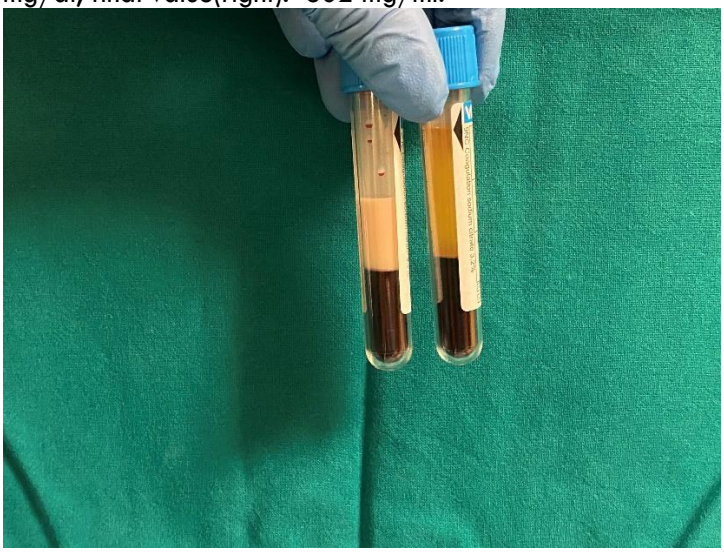
When the blood flows inside the cartridge, the adsorption occurs on the surface of the sorbent, and the maximal efficiency of the process occurs at the equilibrium phase, that is when the concentration of the marker solute at the inlet and at the outlet of the cartridge are very similar if not equal [15].

4.3 THERAPEUTIC APHERESIS (PEX).

Principles.

Therapeutic apheresis (TA) consists in the removal of plasma or blood cells including red and white blood cells and platelets from the bloodstream [16]. The TA-associated scavenging of bloodborne substances can be unspecific consisting in the removal of one of more volume of plasma and subsequent replacement with donors' plasma or albumin (plasma exchange-PEX) or selective, aiming to reduce the circulating bulk of specific high-MW substances exerting a noxious effect such as autoantibodies or toxic agents (plasmapheresis-PF) [16]. In the critical care setting, the PEX is suited to remove substance whose volume of distribution is limited to the intravascular space such as the lipoproteins.

Figure 3: reduction of triglycerides after PEX (3200 ml exchanged in 3 hours); initial value (left): 6600 mg/dl, final value(right): 602 mg/ml.



5. Clinical experiences.

Since the end of the 80' many clinical studies and RCT have been performed in order to establish the role, if any, of the different BP techniques in the treatment of septic shock patients. However, despite several thousands of patients enrolled, the results are controversial, with some investigations showing a beneficial effect on the outcome, other no effect and still other ones demonstrating a worse survival in the treatment group [17,18]. These contrasting results could be ascribed to different factors, including: (a) patient-related variables, such as the heterogeneity of the underlying conditions; (b) other therapies-related variables such as the appropriateness of the concomitant antibiotic, the nutrition etc.; (c) technique-related variables, including the timing of initiation, their intensity, the duration of the down-time etc.; and (d) outcome-related variables, such as the survival rate, the variation in the blood concentrations of mediators, the modulation of the vasopressor support etc. That said, it could be worthwhile to analyze separately each of the more commonly used BP techniques.

5.1: HEMOFILTRATION.

On the basis of previous investigations, it was hypothesized that a higher volume of UF produced per unit of time (Qf) could be associated with an improved survival of septic shock patients and a kind of dose-effect relationship between the Qf and the outcome was then hypothesized; however, despite some studies demonstrated encouraging results [19-21], a large RCT using HVHF comparing elevated (70ml/kg/hour) with normal (35ml/kg/hour) Qf failed to confirm these findings [22] and this approach has been substantially abandoned; by the way, in patients treated with higher Qf a significant loss of antibiotic was demonstrated [23]. Moreover, despite the result of an experimental study showing a reduction of the catecholamine request in a porcine model of sepsis, a recent study of cascade HVHF in septic shock patients failed to demonstrate any beneficial effect when compared with standard care [14]. The use of HCO membranes has been associated with the reduction of several septic mediators in some studies but other investigation did not confirm these findings [24,25].

5.2: HEMOADSORPTION

5.2.1: Hemoadsorption on Polystyrene – Bound Polymyxin.

Whereas this approach is commonly used in Japan, in Western countries different RCTs using a Polymixin-Based Hemoperfusion (Toraymixin®) cartridge carried conflicting results. In the Early Use of Polymyxin-B Hemoperfusion in Abdominal Septic Shock (EUPHAS) study [26], the patients treated with this technique demonstrated hemodynamic and respiratory improvements associated with a trend toward a better outcome; however, a subsequent study performed in patients with septic shock due to peritonitis, the ABDOMIX Trial [27], demonstrated a trend increased mortality in the treatment group as compared with controls. Finally, the Evaluating the Use of Polymyxin B Hemoperfusion in the Randomized Controlled of Adults Treated for Endotoxemia and Septic Shock Trial (EUPHRATES) performed in septic shock patients with elevated blood endotoxin levels measured with the Endotoxin Activity Assay (EAA) demonstrated a beneficial effect on different variables, including survival, only in patients with high EAA [28]. Taken together, it appeared that this approach could be effective when the expected mortality ranges from 30 to 40 % and/or with elevated EAA.

Table 5: some relevant RCTs with Toraymixin.

Study/Author	Treatment group N.	Control group N.	Results
Euphas	30	34	Improved hemodynamics and survival in the treatment group
Abdomix	119	113	non-significant increase in mortality and no improvement in organ failure in the treatment group.
Euphrates	84	78	No difference in mortality at 28 days in the treatment group

On the basis of these and similar other results, a non-recent MA [17] demonstrated that the use of PBH was not associated with a better survival as compared with standard treatment; instead, a more recent MA showed that septic shock patients treated with PBH had a better survival than those in the control group (18).

5.2.2 Hemoadsorption on Polystyrene Divinylbenzene Copolymer-Based Microbeaads.

Although some experimental and clinical investigations demonstrated that the use this sorbent (Cytosorb®) is associated both with the reduction of blood levels of many inflammatory cytokines, the reduction of the vasopressors and the improved survival of patients with septic shock [29-33], other studies failed to confirm these findings [34-36]. Also the efficacy of this sorbent in terms of removal of mediators is matter of debate: whereas in a recent MA Heymann et al [36] failed to demonstrate a significant reduction of Interleukin 6+ and TNF, Jansen et al. [37] demonstrated their marked reduction in a group of endotoxin-challenged healthy volunteers treated with Cytosorb® as compared with the controls.

Recently, Hawchar et al [38] demonstrated in 1434 patients with different clinical conditions treated with Cytosorb® (including 936 cases of septic shock) that the of hospital mortality it was lower than expected according to the APACHE II score (59% vs 66%, respectively). Then, although it is difficult to draw definite conclusions, is possible that different variables can account for these contrasting results, including the heterogeneity of patients treated, the intensity of the treatment and the timeframe of initiation with the clinical course [39]. Actually, Berlot et al. [40] demonstrated in a group of septic shock patients that in survivors either the amount of blood processed was higher and the interval of time elapsing from the onset of shock and the start of Cytosorb® were shorter than in nonsurvivors. In hyperinflammatory conditions other than sepsis, Bottari et al. [41] demonstrated that its use was able to blunt the hyperinflammatory conditions and advocated a shorter turnover of the cartridge in order to take the maximal advantage from the adsorptive capabilities of the resin,.

5.2.3 Hemoperfusion on Modified AN 69 Membrane.

Experimentally, this technique that is available under the brand name of oXiris® was demonstrated to have the same endotoxin-removing capabilities of Toraymixin® and was similar to Cytosorb® as far as the clearance of mediators is concerned [42]; as far as the former is concerned, the main difference consists in the feasibility of a CRRT using the same cartridge. Presently, the clinical experience is based on small case series of patients with septic shock and/or Covid-19 in whom the improvement of the hemodynamic conditions, the decrease of the blood concentrations of endotoxin and septic mediators, and the decrease of the expected mortality was observed [43 – 45]); however, as recently stated by Li et al. [46] by reviewing a number of studies concerning the use of this technique in septic shock patients, not dissimilarly from what has been stated above for other BP techniques, the heterogeneity of the patients and the different underlying conditions create a background noise and prevent to establish the real role of this procedure.

5.2.4 Hemoadsorption on Heparan Sulphate Microbeads.

The procedure is based on a single-use cartridge (Seraph 100®) containing a ultra-high molecular weight polyethylene microbeads coated with heparin mimicking the pathogen-linking heparan sulphate receptors located on the cell surface; similarly to these latter, the microbeads are able to bind a wide array of bacterial and viral strains and some substances released by the damaged tissues such as Histones, ATP, High Mobility Group Box 1, RNA etc. [47, 48] that contribute to amplify and perpetuate the inflammatory reaction triggered by the infecting agents. Recently, Eden et al [49] demonstrated that this technique was associated with either the increase of time-to-positivity or negativity of the blood cultures in 11/15 of chronically dialyzed patients with bloodstream infections caused by different gram + and - bacterial strains, and Votrico et al [47] observed a dramatic reduction of the blood pathogen load in a small group of chronic critically ill patients (CCIP) suffering from viral reactivation.

5.2.5 Plasma Exchange.

If the role the different techniques of HA is not well yet clear, even less definite is that of PEX. Besides the time-honored indications in critically ill patients including thrombogenic thrombocytopenic purpura and hemolytic-uremic syndrome, [16], its use in septic shock patients appears somewhat overshadowed by HA. This notwithstanding, a recent RCT involving 40 patients [50] demonstrated a trend for a better survival and the improvement of multiple organ failure in patients treated with a single PEX with an exchange volume of > 3000 ml of plasma associated with standard treatment ST as compared with the control group which received the ST only; as expectable, the decrease of biomarkers of sepsis as well as the replenishment of factors supplied with the plasma, including Protein C, Protein S, ADAMTS 13 was observed in the PEX but not in the control group; moreover, patients in PEX group were weaned faster from the vasopressors and had a more pronounced decrease of blood lactate levels; similar results have been demonstrated also by David et al [51] who observed a decrease of the vasopressor needs in group of septic shock patients.

6. Rules of engagement and areas if uncertainness.

Before discussing the possible rules of engagement (ROE) for the BP techniques it could be worthwhile to recall the rise and decline of the couple plasma filtration and adsorption (CPFA) as it represents a typical example of the wide grey areas existing in this field.

Briefly stated, the CPFA was a 3-step process consisting in (a)) the partial extraction of plasma from the blood via a plasma filter; (b) its processing within a cartridge where a number of septic mediators were absorbed by a synthetic resin arranged in microtubules; and (c) the reinfusion of the purified plasma upstream a second filter used for continuous veno-venous hemodiafiltration. To assess the potential role of CPFA in septic shock patient, RCT (Compact 2) using a threshold value (≥ 0.20 L/kg/session) of plasma processed that in a precedent study was associated with a better outcome was launched; however, it was prematurely stopped when an intermediate analysis on 115 patients demonstrated an increased mortality in the treatment group [52]. Similar results have been reported also by Gimenez-Esparta in another RCT (ROMPA) in 49 septic shock patients treated with CPFA [53]. Overall, these results caused the virtual disappearance of the CPFA from the therapeutic armamentarium. Indeed, the puzzling is question is: why the CRTs about the use of the CPFA as well as of other BP techniques failed to demonstrate any beneficial effect whereas, conversely, in single center studies the outcome was positively influenced by them [54]? Besides the multiple variables can influence the outcome on a single-patient basis, it is hypothesizable that patients treated in a single ICU could take the maximal advantage from the expertise of the local ICU staff, while the results of CRT can be influenced by the co-existence of ICU of different volumes of procedures performed.

Independently from these results, a pragmatic ROE for the initiation of a determined BP technique must take into consideration three main variables, including (a) the underlying conditions, as these procedures and other advanced approaches (i.e. extracorporeal membrane oxygenation and other life-supporting procedures) are futile in moribund patients or with reduced life expectancy: (b) the aggressive search and treatment of the septic sources, as PB represents an add-on to antibiotics and surgery and not the therapy of the infection; and (c) the timing, because, as demonstrated by Berlot et al [40], it appears that the early initiation of BP is associated with a better outcome. Even in the absence of specific studies, it is reasonable that the same consideration applies in hyperinflammatory conditions other than septic shock.

7. Areas of uncertainty and Controversial Points.

In the lack of RCT fulfilling the criteria of the Evidence Based Medicine, the current guidelines of the Surviving Sepsis Campaign [55] do not encourage or discourage the use of any specific BP technique, leaving to the intensivist the choice. Moreover, independently from the BP technique used, all clinical investigations have been performed in patients in the acute phase of septic shock that is characterized by elevated blood levels of inflammatory mediators but there no data deriving from CCIP in whom the ant-inflammatory mediators with the subsequent immunoparalysis prevail; actually, this population is expected to increase due to the advanced age and comorbidities surviving the acute injury causing the ICU admission.

Currently, the uncertainties concerning the BP can be summarized as follows:

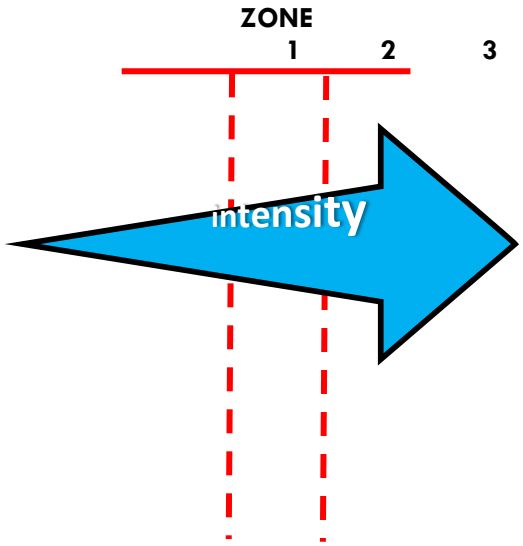
A. The monitoring of efficacy: Since the outcome of patients with septic shock and/or with hyperinflammatory conditions can be influenced by factors other than the BP used, including the appropriateness of the antibiotic treatment, the drainage of septic foci, the underlying conditions and frailties etc., the survival by itself could not represent a reliable

marker of efficacy of BP; consequently, other biological and clinical variables, such as the variation of the blood lactate levels and the request of catecholamines should be used as proxies of efficacy [56].

B. The undesired effects: Besides the iatrogenic risks associated with the use of indwelling large-bore catheters and the need for anticoagulation, all the BP procedures can induce an undesired hypothermia and makes the patients prone to bloodstream infections.

C. The intensity of the procedure. It is hypothesizable that an optimal area of intensity exists which is preceded and followed by areas of either under- and over-dosage of treatment that are associated with potentially harmful side effects (Figure 4). Actually, the risk of elimination of drugs and nutrients cannot be overlooked especially with elevated Qb or Qf. The risk of elimination of antibiotics could be particularly relevant in the initial phase of treatment when the adsorptive capabilities of the resin are maximal but the therapeutic blood levels of antibiotics must be achieved as soon as possible [57].

Figure 4: effects of BP at different intensities of BP.



Zone 1: under dose: the culprit substance/s is/are poorly removed; Zone 2: appropriate dose: the substances are removed in the desired amount. Zone 3: excessive dose: drugs (antibiotics etc.), vitamins, hormones (catecholamines etc.) and nutrients are removed leading to an insufficient blood concentration.

8. Conclusions.

In the last 30 years several different techniques of BP have been developed to blunt the exaggerated inflammatory response observed both in septic shock and in other clinical conditions not determined by an underlying infection. Yet, despite thousands of patients enrolled in clinical studies, both their precise role the best technique to use remain uncertain, because the results of RCTs carried conflicting results or are biased by a number of factors including the different goals of the treatment (variations of the blood concentration of mediators vs. decrease of the vasopressor need vs. outcome), the heterogeneity of the patients and of their underlying conditions, the modalities and intensities of the treatment etc.

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