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Artificial Organ Treatment for Multiple Organ Failure, Acute Renal Failure, and Sepsis: Recent New Trends

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Abstract: Sepsis remains the major cause of mortality worldwide, claiming millions of lives each year. The past decade has seen major advances in the understanding of the biological mechanisms involved in this complex process. Unfortunately, no definitive therapy yet exists that can successfully treat sepsis and its complications. At variance with targeting single mediators, therapeutic intervention aimed at the nonselective removal of pro- and anti-inflammatory mediators seems a rational concept and a possible key to successful extracorporeal therapies. A further advantage may lie in the continuous nature of such therapy. With such continuous therapy, sequentially appearing peaks of systemic mediator overflow may be attenuated and persistently high plasma levels reduced. This theoretical framework is proposed as the underlying biological rationale for a series of innovative modalities in sepsis. In this editorial, we will review recent animal and human trials that lend support to this concept. We will also review the importance of treatment dose during continuous renal replacement therapy as a major factor affecting survival in critically ill patients with acute renal failure. Additionally, we will review novel information related to other blood purification techniques using large pore membranes or plasma filtration with adsorbent perfusion. Although these approaches are still in the early stages of clinical testing, they are conceptually promising and might represent an important advance. **Key Words:** Sepsis—Cytokines—Acute renal failure—CRRT—Dialysis.

Sepsis continues to provide a major challenge to clinicians. Despite vast advancements achieved in the understanding of its pathways and mechanisms, the incidence of sepsis is increasing and the mortality and morbidity rates remain high, generating a considerable burden to health budgets worldwide (1). Severe sepsis and septic shock are the most common causes of multiple organ failure (MOF) (2). MOF remains the most frequent cause of death in patients admitted to the intensive care unit, with a mortality rate exceeding 50% (3,4). Once acute renal failure develops, the mortality might exceed 70% (5). Only recently, activated protein C (APC)(drotrecogin alfa [activated]) has been the first biologic agent approved in the United States for the treatment of severe sepsis. In contrast to antithrombin III or tissue factor pathway inhibitor (6,7), activated protein C improved survival in the treatment group ($p = 0.005$), but also led to a remarkably greater risk of serious bleeding (3.5 percent vs. 2.0 percent, $p = 0.06$) (8). However, for reasons inherent to the study itself and to restrictions placed on its prescription by the Food and Drug Administration (9), continuing controversy exists with regard to its role. Accordingly, a very large study of APC in more than 11,000 patients is due to start in March 2003.

In this editorial, we will briefly review the present state of our knowledge of sepsis, development of multiple organ failure, and the biological basis for the effect of innovative extracorporeal approaches. As technology offers devices to implement traditional or new modalities, the application of a rigorous analysis derived from basic and clinical sciences in sepsis might lead to major advances provided that randomized, controlled studies are performed. As the sepsis story continues to unravel with the ongoing discovery of more malignant inflammatory mediators, the development and use of blood purification therapies seems a logical, feasible, and exciting challenge.

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Sepsis

The terms sepsis, systemic inflammatory response syndrome (SIRS), sepsis syndrome, and septic shock are often used interchangeably and this continues to create confusion in clinical practice and literature (10).

Sepsis encompasses a complex mosaic of interconnected events that generate SIRS (Fig. 1). Molecules such as bacterial lipopolysaccharides (LPS), microbial lipopeptides, microbial DNA, peptidoglycan, and lipoteichoic acid interact with the Toll-like receptors (TLR 4) and related molecules (MD-2, MyD88), the principal sensors of the innate immune response (11–13). Stimulus-receptor coupling activates different signal transduction pathways, leading to exacerbated generation of pro- and anti-inflammatory cytokines and their relative positive or negative modulatory proteins: soluble surface receptors, the specific receptor antagonist for interleukin-1(IL-1), and phospholipase A2-dependent, arachidonic acid-derived platelet-activating factor, leukotrienes, and thromboxanes. At the plasma level, activation of the complement (C3a, C5a, and their desarginated products) and coagulation pathways interact with the process as products generated in the fluid phase may in turn trigger and sustain cell activation. Other agents play a role in the pathophysiology of sepsis, such as surface-expressed and soluble adhesion molecules, kinins, thrombin, myocardial depressant substance(s), endorphin, and heat shock proteins.

In physiological conditions, the biological activity of sepsis-associated mediators is under the control of specific inhibitors that may act at different levels. In sepsis, the homeostatic balance is altered and a profound disturbance of relative production of different mediators may be observed (as reviewed in ref. 14). In particular, the spillover into the circulation of mediators intended to have autocrine or paracrine effects generates systemic effects including endothelial damage (15), procoagulant, fibrinolytic, and complement activities, hemodynamic shock, and vaso-paralysis (16–22).

The pathogenesis of sepsis was initially described as an overproduction of pro-inflammatory factors in the host. The concept was established on the basis of several studies. The injection of LPS into experimental animals and healthy human subjects reproduces the initial phase of bacterial infection. In human subjects, LPS alters capillary integrity and affects the cardiovascular system (23), leads to the production of cytokines (24–27), and activates the plasminogen activator inhibitor, which inhibits the fibrinolytic pathway (28). Peak concentrations of interleukin-1 (IL-1), tumor necrosis factor–alpha (TNF), IL-6, and IL-8 occur within 2 to 3 hours of LPS infusion (24,25). Recent studies on knockout mice have shown that ICAM-1 mutant mice are resistant to the lethal outcome of endotoxin-induced pneumonitis (29). At the same time, other researchers began to acknowledge the contribution of anti-inflammatory mediators to the pathogenesis of sepsis/SIRS (30,31). Bone coined the acronym CARS for the "compensated anti-inflammatory response syndrome" to describe the excessive anti-inflammatory counterpart of SIRS (32) (Fig. 1). These anti-inflammatory cytokines cause pathogenicity in septic/SIRS states by producing a state of immunoparalysis or cell hyporesponsiveness (33,34). This is a critical factor associated with the inappropriate immune response in inflammatory/septic states. Treatments that can restore immune responsiveness or control cell apoptosis may just be the answer in the treatment of septic states (35,36).

Complicating this issue is the fact that the allocation of various cytokines to either pro- or anti-inflammatory roles is not so simple. Recent literature demonstrates that individual cytokines can function as both (37). The cytokine story remains perplexing; however, the isolation of single pathogenetic mediators responsible for the deleterious systemic complications is unlikely. Various strategies used to target incriminated factors such as cytokines, lipid mediators, and complement or bacteria-derived products (endotoxins and exotoxins) have unfortunately failed (38).

One question that needs to be addressed is, what is the relevance of circulating cytokines in sepsis? The sensitivity of monoclonal antibodies and assays to detect cytokines in plasma, the bound versus free ratio, and their renal clearance are the most important factors influencing their plasma levels. In fact, the presence or absence of detectable levels of cytokines within biological fluids reflects a rather complex balance between enhancing and inhibitory signals acting on producer cells, between production and catabolism, and between their binding to the target cells and the modulation of their receptors on the cell surface (14). Furthermore, their presence does not necessarily parallel their activity, and a possible interplay between a given cytokine and its relative inhibitor (if known) should be considered (14). Despite the fact that high plasma levels may reflect an exacerbated production, these levels do not necessarily represent enhanced bioactivity. There are several factors that may help to explain the incongruities seen in the cytokine-bioactivity story. One such factor is genotypic predisposition. Endotoxin-

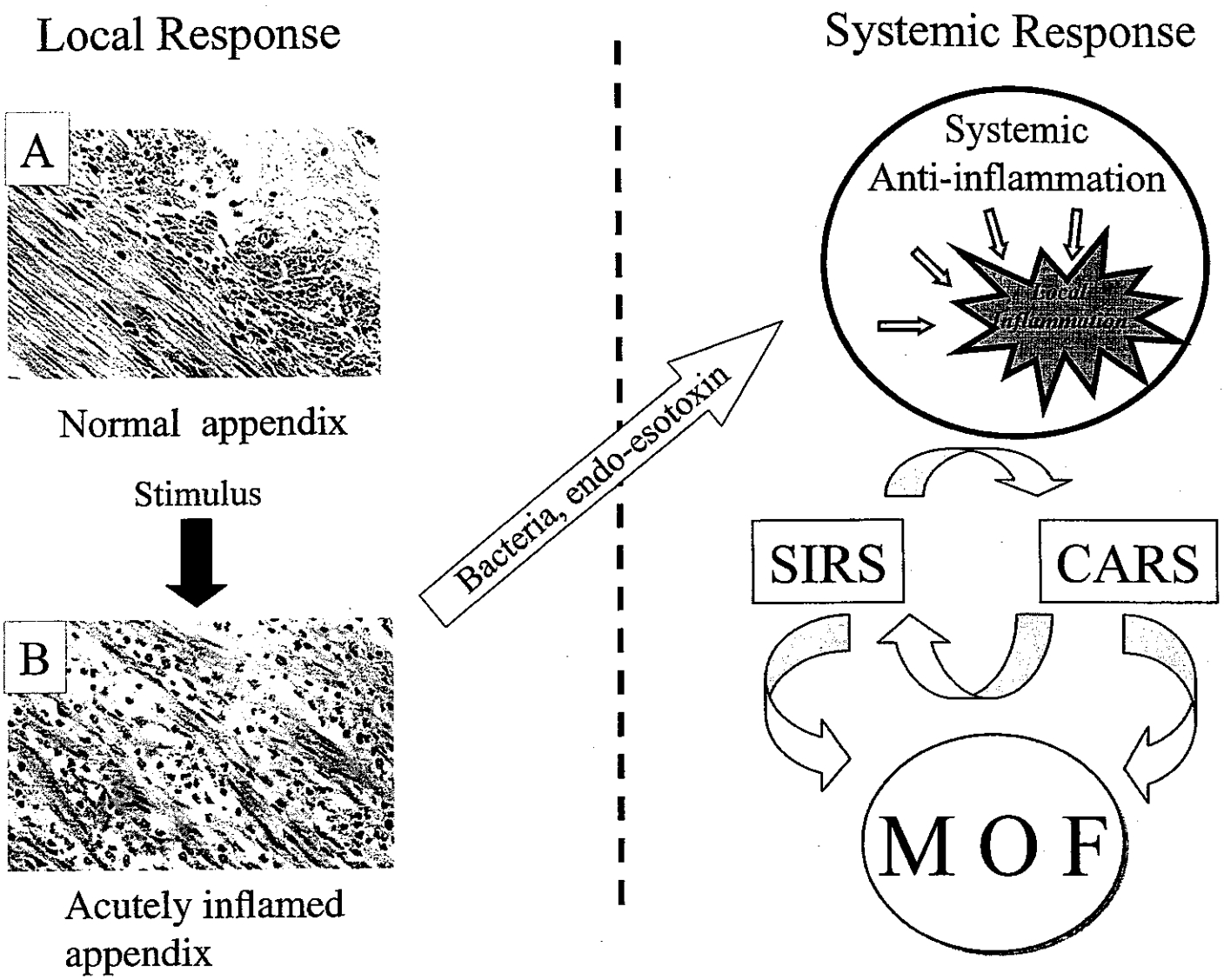

FIG. 1. Inflammation is the price the host pays for an efficient defense system. In the extreme, systemic inflammation may lead to death in the desperate try for an effective host response. We have to distinguish between local and systemic inflammation. Illustration A shows the histology of the muscle coats of the normal appendix. Illustration B shows a view of the same area in an acutely inflamed appendix. The muscle fibers have been separated by edema and numerous inflammatory cells. The passage of bacteria exo- and endotoxins into the bloodstream induces a massive activation leading to systemic inflammation. However, recent studies emphasize the role of the anti-inflammatory systemic response in limiting the pro-inflammatory response occurring at the local level. The alternate or simultaneous occurrence of SIRS and CARS is inherent to the development of MOF. This histology from the Department of Pathology, University of Birmingham, UK. Examples of Acute Inflammation, Acute appendicitis — high magnification histology. Available at: http://medweb.bham.ac.uk/http/mod/3/1/a/hp_example.html. Accessed Feb. 12, 2003.

induced cytokine production differs among individuals. This genetically determined trait is referred to as endotoxin responsiveness (14). Unfortunately, this theory, like most of the literature concerning inflammatory mediators and inflammation, is plagued by conflicting theories as subjects who are both highly endotoxin responsive (i.e., genetically inclined to produce larger amounts of pro-inflammatory cytokines such as tumor necrosis factor-α, TNFα) or less endotoxin responsive (i.e., lack of TNFα production but increased production of anti-inflammatory production such as IL-10) are predisposed to poorer prognoses (39).

In meningococcal sepsis, the paradigm for endotoxin-induced sepsis, despite variability in various cytokine concentrations, endotoxin levels, and capsular antigen levels, it seems that unimpeded bacteremia is probably much more important than endotoxin responsiveness. Therefore, in answering the question as to whether circulating cytokines are of any relevance in understanding the complexity of the host response in sepsis, the correct response is no. Studying various biological functions (spontaneous or stimulated cytokine production, apoptosis, phagocytosis) in different physiologic compartments may help assess the severity and the course of sepsis in

patients. As a direct consequence, testing innovative extracorporeal techniques on the basis of an effect on circulating cytokines may overlook more clinically significant biological changes at the cell/organ level.

The search for a single causative mediator and attempt to neutralize its function—the magic bullet—may be a long and unrewarding process. One of the more novel approaches finding some success in the treatment of sepsis/SIRS is the use of extracorporeal therapies.

Acute renal failure and multiple organ failure

Originally, the concept of blood purification by extracorporeal therapies stemmed from the assumption that in sepsis and other inflammatory syndromes nonspecific removal of several inflammatory mediators would improve outcome in septic shock (40). However, useful convective removal of mediators from the human septic circulation has not been achieved to date, although many cytokines have a molecular weight below the theoretical cutoff point of commercial membranes currently in use (41). The development of acute renal failure (ARF) in the context of sepsis and septic shock imparts a particularly remarkable change in the biological expression of cytokines. The occurrence of ARF impedes a physiological control in the elimination of different cytokines (e.g., interleukin-8, 42) and their relative plasma modulators (e.g., interleukin-1 receptor antagonist, 43). Furthermore, the brisk accumulation of metabolically active compounds in a non-adapted host makes their contributory role in the pathophysiology of ARF of particular interest yet to be fully elucidated (44).

ARF is often a late and devastating complication of MOF with a mortality rate exceeding 70% (5). Isolated ARF is uncommon but has a frequency of 20–50% in severe sepsis (45). Since it is commonly associated with MOF, ARF is generally treated in the intensive care unit. No consensus guidelines for the treatment of ARF exist at this time, thus various modalities of renal replacement therapy are currently being used worldwide (B.E.S.T. Kidney study, Bellomo R et al., unpublished, personal communication). The targets of any renal replacement therapy in critically ill patients should mimic the functions and physiology of the native organ, ensure qualitative and quantitative blood purification, restore and maintain homeostasis, avoid complications, and have good clinical tolerance providing the kind of homeostasis that favors organ recovery. The more common types of continuous renal replacement therapy (CRRT) (for terminology, see ref. 46) used include continuous veno-venous hemofiltration (CVVH) and continuous veno-venous hemodiafiltration (CVVHDF).

CRRT is the preferred extracorporeal treatment once ARF develops as part of MOF. It has been demonstrated that CRRT has many benefits over intermittent therapies but to date, no suitably powered randomized controlled trials have been conducted to test whether CRRT decreases mortality (47). Compared to intermittent conventional hemodialysis, the most significant advantage of CRRT is the ability to provide continuous effective blood purification in septic/SIRS patients when hemodynamic instability is present (48). CRRT is very well tolerated, with minimal deviations in blood volume and mean arterial pressure (49). Hemodynamic events such as hypotension and hypovolemia can perpetuate ischemic-reperfusion injury and further exacerbate MOF. CRRT also achieves stricter fluid balance and allows the optimization of nutritional support without concern for fluid overload. CRRT offers superior control of uremia and of electrolyte and acid-base balance (50). Finally, it can help regulate core body temperature control.

As mentioned, CRRT seems the ideal modality of treatment for ARF in the setting of MOF. Today, approximately 25 to 50% of all patients with acute renal failure are treated with CRRT in some countries, but close to 100% are in Australia. Despite the increasing use, we must admit that there are presently no published standards for the application of this therapy and practice patterns vary widely. Results from recent clinical trials on selection of dialysis membranes and dialysis dose provide strong, yet conflicting, evidence to guide therapy. Other areas of uncertainty have not been sufficiently addressed by clinical studies, and directives for future research are needed. Finally, the success of multicentered clinical trials in supportive care in the ICU (transfusion thresholds and ventilator management) has intensified and renewed interest in the study of supportive care methods as a major target for future research. Recently, the Acute Dialysis Quality Initiative (ADQI, http://www.adqi.net) was created with the aim of establishing a methodology for a consensus process in this field, of describing current clinical practice and identifying important clinical and research questions in ARF. The final objective of ADQI is the development of evidence-based practice guidelines and directions for future research.

Among the several controversial points concerning CRRT, there is the question of who should be in charge of patient care and what should be the specific contribution of intensive care and renal

physicians. Furthermore, there are advantages and disadvantages of various modalities of replacement therapy other than CRRT (so-called hybrid techniques such as such as short daily or extended daily modalities have already been discussed, 51–55). In our opinion, this debate on the advantages/disadvantages of CRRT over intermittent therapies should be reconciled (56). Nephrologists should know more about critical care and the intensivists should do the same in the area of kidney function knowing what can be expected from extracorporeal therapies, and how to achieve prescribed goals. The need for an integrated approach has led to the concept of Critical Care Nephrology, not only as a new academic subject, but also as stimulus for the organization of dedicated teams in this challenging area of patient care.

Further indications might exist for CRRT beyond solely renal support. CRRT provides a degree of cytokine removal via filtration and adsorption (57). However, the clinical significance of such removal is still undetermined since multiple studies show that the plasma levels of these mediators remain unchanged, probably due to excessive production and saturation at the cellular level. In a randomized controlled clinical trial using CVVH versus no CVVH in early sepsis, Cole et al. demonstrated that the early use of CVVH at 2000 ml/h did not reduce circulating cytokine concentrations, anaphylatoxins, or organ dysfunction that followed severe sepsis (58). There is some evidence, however, of an immunomodulatory effect of CVVH in the porcine model of sepsis (59) and in human studies (60,61). Diffusion of suppressive "uremic toxins" may be important in acutely uremic patients (44). In agreement with this contention, a study in 12 critically ill patients with acute renal failure comparing low-volume CVVH (1500 ml/h) with a diffusive technique was performed in a nonrandomized, comparative fashion (60). High-flux bicarbonate dialysis amounting to 4200 ml/h was used, and the effect on monocyte responsiveness (ex-vivo endotoxin-stimulated TNF-production) was studied. Both techniques resulted in early improvement, but only the diffusive technique displayed persistent effects. Ultrafiltrate contained monocyte suppressive activity only with high-flux dialysis (60,61).

Novel trends

In recent years there have been tremendous advancements in CRRT technology (62). There has been increasing awareness of the need for dedicated extracorporeal systems that are more in tune with the clinical needs of critically ill patients (Fig. 2).

Attempts to increase mediator clearance have been along two lines of research and development: either by increasing the rate of ultrafiltration, or by increasing the porosity or the membrane. Consequently, it was sought to improve the efficiency of the methodology regarding removal of soluble mediators of sepsis by increasing the amount of plasma water exchange, i.e., increasing ultrafiltration rates.

Animal studies provided great support for this concept. Starting in the early 1990s, several studies using different septic animal models examined the effect of high ultrafiltration rates (up to 300 ml/kg/h) on physiological parameters and outcome. In a landmark study, a porcine model of septic shock induced by endotoxin infusion was investigated (63). The animals developed profound arterial hypotension and a decrease in cardiac output, stroke volume, and right ventricular stroke work index. With high volume hemofiltration (HVHF, at 6 l/h), right ventricular function, blood pressure, and cardiac output showed a remarkable improvement compared to control and sham-filtered animals (63,64). The same group extended their findings in the same model by i.v. administration of ultrafiltrate from LPS-infused animals into healthy animals. The latter ones developed hemodynamic features similar to septic shock, while animals infused with ultrafiltrate from healthy animals showed a moderate blood pressure rise (63). In a further study by the same group, a bowel ischemia-reperfusion model in pigs was investigated. HVHF started before clamping of the superior mesenteric artery significantly diminished bowel damage and prevented hemodynamic deterioration (65). These studies established that a convection-based treatment can remove substances with hemodynamic effects resembling septic shock, when sufficiently high ultrafiltration rates are applied.

Closer to human sepsis has been the finding that the ultrafiltration dose is correlated to outcome in critically ill patients with ARF. In a large randomized, controlled study including 425 patients, an ultrafiltration dose of 35 ml/kg/h increased survival rate from 41% to 57% compared to a dose of 20 ml/kg/h (66). Eleven to 14% (per randomization group) of the patients had sepsis. In these subgroups there was a trend of a direct correlation between treatment dose and survival even above 35 ml/kg/h, in contrast to the whole group where a survival plateau was reached.

This lends support to the concept of a "sepsis dose" of hemofiltration in septic patients, contrasting to a "renal dose" in critically ill patients without systemic inflammation, the former being probably distinctly

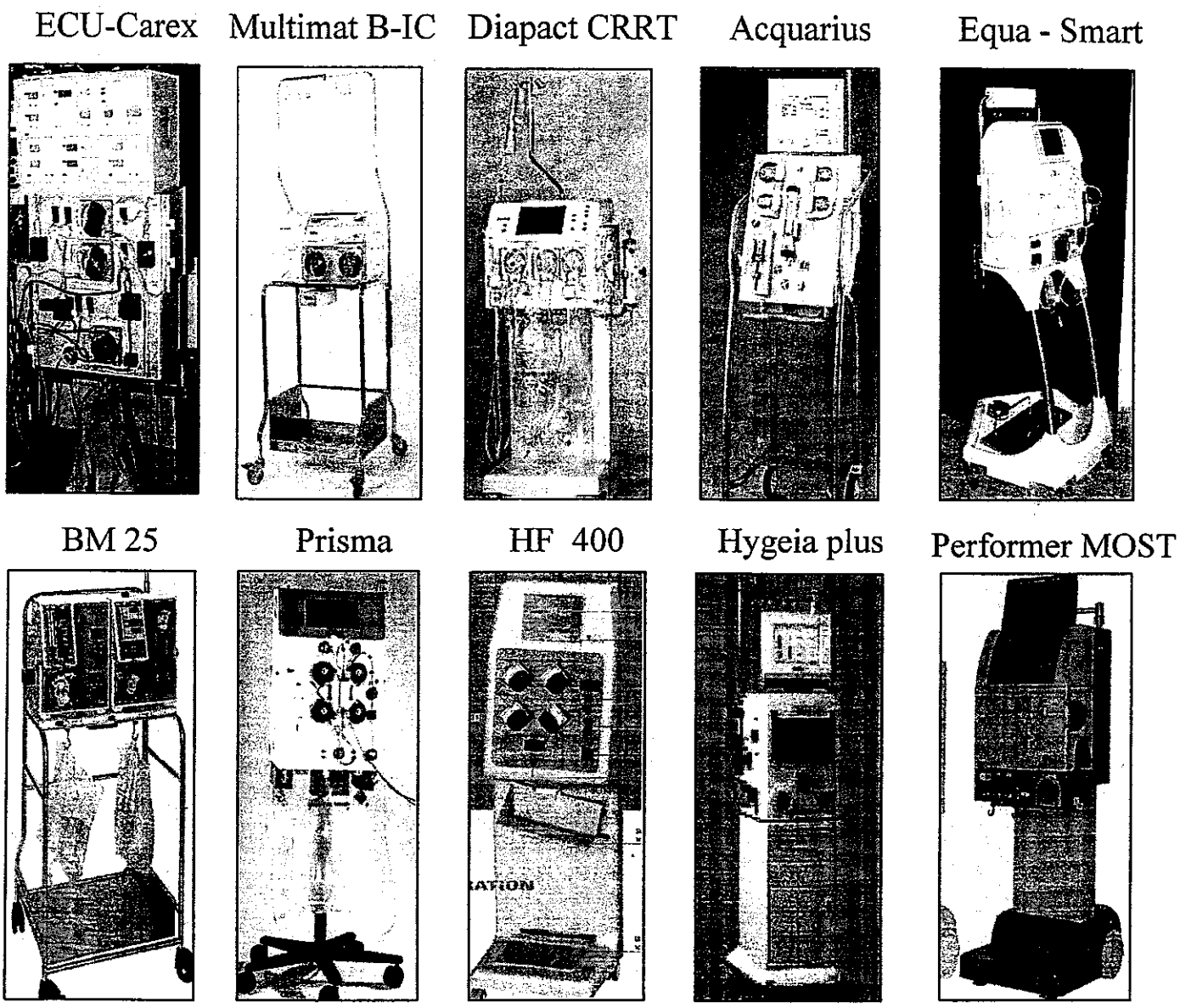

FIG. 2. Different dedicated machines for renal replacement therapies in critically ill patients are shown. From top left to bottom right, they are: BCU-Carex (Braun-Carex, Mirandola, Italy), Multimat B-IC (Bellco SpA, Mirandola, Italy), Diapact (B. Braun, Mesungen, Germany), Aquarius (Edwards Lifesciences, Brussels, Belgium), Equa-Smart (Medica, Medolla, Italy), BM-25 (Baxter, Brussels, Belgium), Prisma (Gambro, Lubd, Sweden), HF-400 (Infomed, Lausanne, Switzerland), Hygeia Plus (Kimmal, U.K.), and Performer MOST (also performing anti-cancer hyperthermia and loco-regional therapy) (91).

higher (without proven upper limit). Of note, there was no increase in adverse effects even with the highest ultrafiltration dose.

Journois et al. demonstrated improvements in several end points using zero balanced HVHF (UF rates of 7–9 l/h in a 70 kg person) in 20 children undergoing cardiac surgery (67). Honoré et al. (68) obtained impressive results in a group of catecholamine refractory septic shock patients with poor expected survival using short-term (4 hrs) HVHF and removing 35 L of ultrafiltrate replaced with bicarbonate-based fluid. These authors demonstrated an impressive survival, but unfortunately had no control group. Most interestingly, subjects with higher body weight did worse, possibly due to the smaller dose of ultrafiltration (68). Oudemans-van Straaten et al. also demonstrated better than severity score-predicted survival in a prospective cohort-analysis of 306 critically ill patients with varying underlying diseases using a mean ultrafiltration rate of 3.8 L/h (69). Despite the above-mentioned observations, the results of a recent prospective, randomized, controlled study of early HVHF on intensive care patients with ARF showed that survival at 28 days

and recovery of renal function were not improved using early high ultrafiltrate volumes (48.2 mL* $kg^{-1}*hr^{-1}$) (70). However, this study had very limited statistical power (only a 20% power of detecting a 20% relative reduction in mortality with HVHF!).

The only other alternative is to attain higher removal rates of middle molecular weight molecules using membranes with a larger pore size. Animal data (71,72) as well as preliminary clinical data (73) showed that the goal of attaining higher removal rates of selected cytokines could indeed be reached.

The pursuit of ultra-high-efficiency clearance has led to rediscovery of plasma exchange in the form of plasma filters. There appears to be little benefit from plasmafiltration, however, according to a recent clinical trial (74). Both high costs from excessive plasma substitution fluids and unregulated losses of beneficial plasma constituents may also be limits to this modality of treatment.

These limitations have produced new enthusiasm for adsorbent technology (75–78). Uncoated adsorbents (i.e., maximizing their adsorptive ability) could, in fact, allow the regeneration of ultrafiltrate or plasma, which would then be used as reinfusion fluids without the need for exogenous supplementation. Historically, activated carbon represented the first adsorbent ever used in artificial organs for blood detoxification (79). Carbons per se represent a rather complex family of inert materials, which have very different characteristics and biocompatibility, as reviewed in ref. 78. Other adsorbents for nonspecific adsorption have been used with varying success

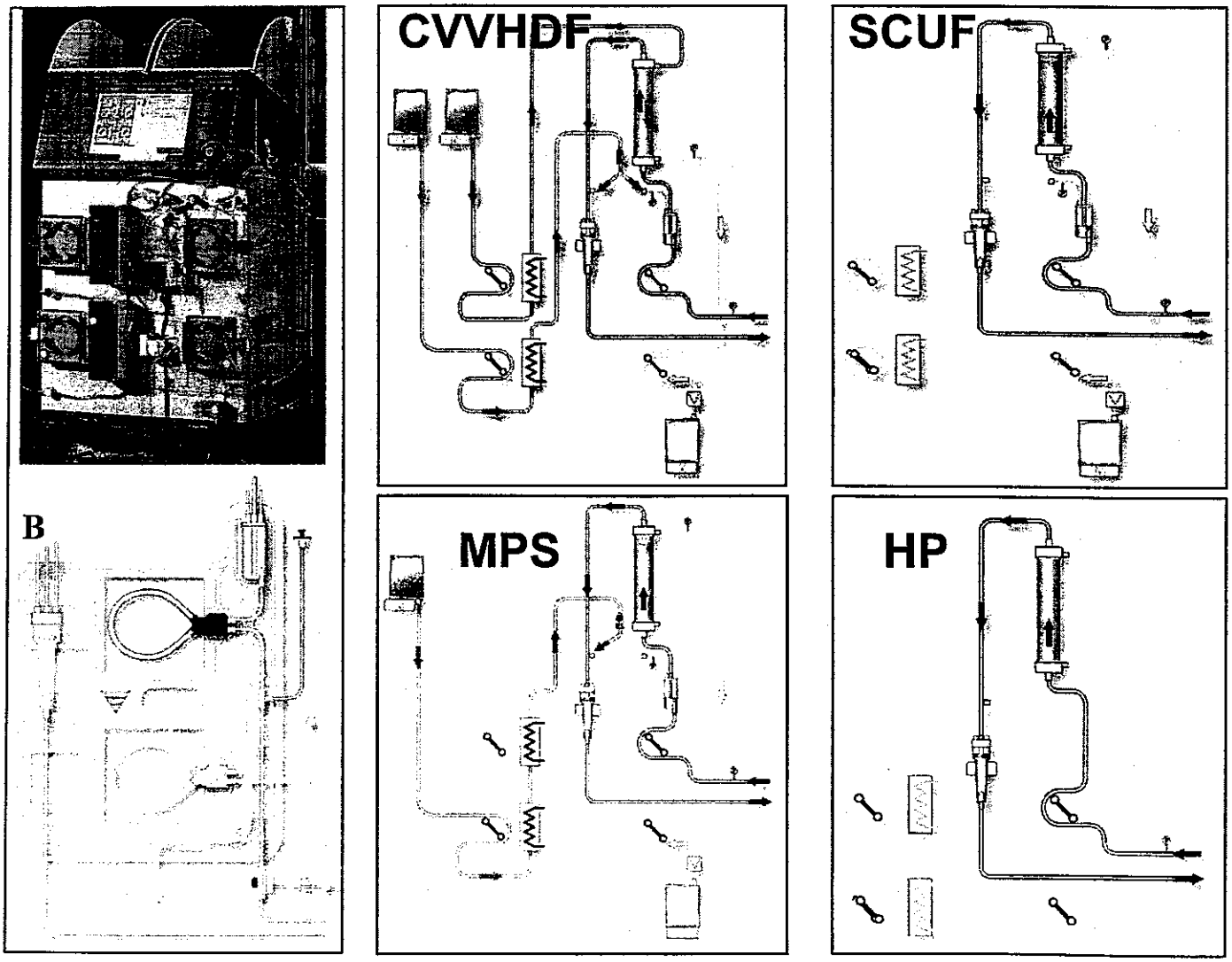

FIG. 3. Shown is a new generation machine (A) (MiltiFiltrate, Fresenius AG) where conventional treatments such as CVVHDF and SCUF (slow continuous ultrafiltration) may be performed simultaneously with new treatments such as MPS (membrane plasma separation), and hemoperfusion (HP) and the application of adsorbent technology. Diagram B shows a detail of a disposable ready-to-connect set of lines.

TABLE 1. *Adsorbents used in extracorporeal modalities*

	Adsorbent	Modality
Non-selective	Carbon { coated (Various) (79) / uncoated (Bellco) (78)	Hemoperfusion Hemodiafiltration
	Powdered carbon + Ion-exchange resins (HemoCleanse) (80)	Hemodiadsorption
	Hydrophobic resins (Bellco) (86,87)	Coupled plasma filtration adsorption (CPFA)
	Non-ionic resin (BetaSorb™/CytoSorb™, RTI) (77,82)	Hemoperfusion
Selective	Microphere-based Detoxification system (81)	Regenerative push-pull Pheresis; polystyrene-derivative figers
	Engineered matrices: Polymyxin-B (83)	Macroporous cellulose (beads)
	Engineered matrices: Polyethyleneimine (81)	Macroporous cellulose (beads)

(Table 1). The use of microparticles may result in greater accessibility and higher adsorption capacity due to smaller diffusion distances. Several ingenious schemes have been proposed. The first clinically used microadsorbent system was designed for temporary extracorporeal liver support, and later tested for the removal of cytokines in septic patients and incorporated in the so-called Biologic DT (80). Plasma filtration and applied microspheres showed excellent removal rates for different target molecules such as endotoxin, cytokines, and bilirubin (as reviewed in ref. 81). These approaches look promising. However, their real benefit in human sepsis awaits the result of randomized, clinical trials. Recent technology has also allowed the development of new "coated" adsorbents for direct contact with blood (CytoSorb, RenalTech Intl., New York, NY, U.S.A.) (82). In the field of specific adsorption in the context of sepsis, various adsorbents have been proposed for the removal of endotoxin from whole blood using a dialyzer incorporating Polymyxin B immobilized fiber (PMX-B), commercialized as Toraymyxin by Toray Ind (Kyoto, Japan). This is used particularly in Japan for severe sepsis and septic MOF. PMX-B treatment improves the symptoms related to the septic state and cytokine levels including tumor necrosis factor, interleukin (IL)-6, and IL-10, with a decrease in endotoxin levels. Phase II trials with extracorporeal endotoxin removal by PMX-B revealed that endotoxin removal might be helpful in the treatment of septic patients (as reviewed in ref. 83). LPS adsorption was carried out by hemoperfusion over high-affinity polymethacrylate-bound albumin (Matisse sepsis adsorber, Fresenius Hemocare, Bad Homburg, Germany) (84,85) and the preliminary results on 141 septic patients were recently presented in abstract form (http://www.colloquium.fr/waa-sfh/program.htm, see also "matisse in sepsis" under http://www.google.com, "images").

Using plasma filtration, another approach has been to use a hydrophobic resin in a cartridge placed on the plasmafiltrate path, so-called coupled plasma filtration adsorption (CPFA). The hydrophobic resin has been shown to avidly bind different cytokines. The binding was shown to be at least in part mediated by α2-macroglobulin, an acute phase response protein with carrier function for different cytokines in plasma (86,87). In a rabbit model of septic shock, CPFA showed improved survival (88). A prospective, crossover study with 10 patients randomized to 10 hours of CPFA vs. 10 hours CVVHDF with an overnight washout period, showed that CPFA significantly improved hemodynamics (mean arterial pressure, cardiac index) with a significant reduction in vasopressor requirement (56). The potential for CPFA in the treatment of sepsis/SIRS seems exciting, but once again one must await large-scale prospective randomized clinical trials to ascertain its real benefit.

What will be the future of these different extracorporeal modalities? Their efficacy, if proven, will increase our armamentarium. However, a new concept is already emerging based on the ever-more critically ill population: the multiple organ support therapy (89,90). The need for simultaneously treating pulmonary, hepatic (91), or kidney failure with specific assist devices will have to be met by the performance of a new generation of dedicated machines (MultiFiltrate, Fresenius AG, Bad Homburg, Germany) (Fig. 3). Different options should be available in order to tailor the best extracorporeal therapy suited for the patient at any time (Fig. 4). In the future, a more precise definition of the biological and clinical pattern for the application of the different therapies will provide the necessary

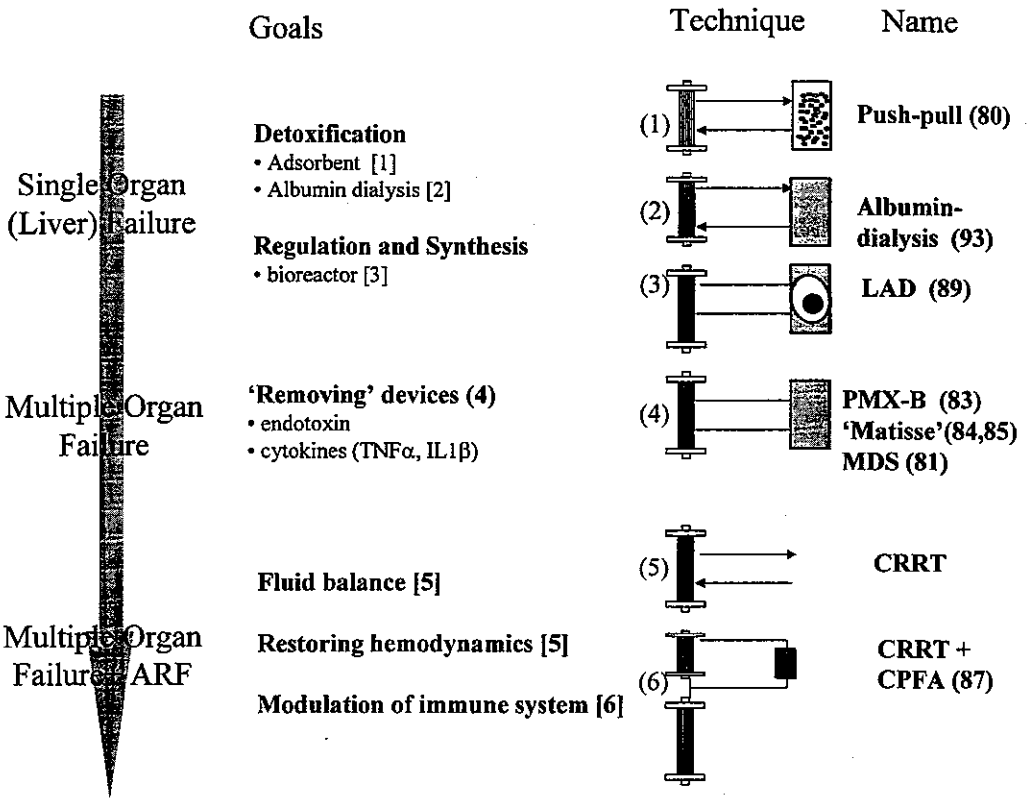

FIG. 4. Shown are the different options that could ideally fit in the progression of multiple organ failure. In the case of one organ failure (e.g., liver), the extracorporeal liver support system has to support or substitute for the main functions of the liver. Artificial detoxification systems such as the push-pull adsorbent system (75) or the albumin dialysis (86) may be used in parallel with a more specific liver bioreactor (LAD: Liver Assist Device) (83). It is anticipated that organ (including the lung) specific support systems will be available in the near future. Other extracorporeal therapy not included in the figure might be the endotoxin-specific removing devices (76,78,79). Once multiple organ failure develops, extracorporeal modalities should maintain fluid and electrolyte homeostasis, and restore hemodynamics. Recent evidence indicates that the biologic expression of an effective "blood purification" resides in the modulation of the leukocyte responsiveness, leading to an enhanced responsiveness of circulating leukocytes (56). Abbreviations used are: LAD, liver assist devices; PMX-B, polymyxin B; and MDS, microphere detoxification system.

criteria to prove their efficacy. Bedside diagnostics and recognition of pro-inflammatory vs. anti-inflammatory responses in a given patient would greatly benefit the understanding of whether one or more of the extracorporeal therapies should be used alone or in combination, for how long, and for what goals. A clear definition of efficacy is needed today to balance cost-benefit ratios and to prove superiority in relation to drug therapies such as APC (8) or low-dose hydrocortisone and fludrocortisone (92).

CONCLUSIONS

Sepsis/SIRS is a common problem encountered in the hospital population that is responsible for a large amount of hospital resources. When uncontrolled, it is associated with multiple organ failure and impressive mortality rates. Despite vast resources spent on sepsis research, the condition remains complex and poorly understood, and to this day treatment consists essentially of critical organ support. Multiple therapies have failed in the past. Recently, one of the latest modalities showing great promise is extracorporeal blood purification therapies. CRRT, plasmafiltration, and CPFA demonstrate exciting potential for improving outcome in critically ill septic subjects. Data so far is impressive; we await the results of further large-scale randomized studies to clarify their usefulness.

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