



## Acute Dialysis Quality Initiative

**The Third International ADQI Consensus Conference**  
**Miami, Florida**  
**January 27-28, 2003**

***Blood Purification in Non-Renal Disease***

Co-Chairs: John A. Kellum, Nathan Levin

ADQI (Acute Dialysis Quality Initiative) started in response to concerns about the quality of care delivered to patients with acute renal failure (ARF) requiring renal replacement therapy. These concerns emanated from expert opinion and published data that demonstrate that acute renal failure requiring artificial renal support continues to have a high mortality, that there is an extraordinary degree of practice variation in its treatment, that prescribed and delivered supportive therapy vary significantly and that no coordinated "plan of attack" existed or exists in the world to try and address these problems.

The chosen initial ADQI strategy was to follow the path of Evidence Base Medicine by first achieving a critical analysis of the available evidence. The first goal of such critical analysis was to generate several consensus statements that would describe, classify and interpret the available evidence and define the issues and areas of clinical and laboratory research that require priority attention. The second goal was to achieve dissemination of such consensus statements through publication in the literature. The third goal was to use the focus and impetus provided by such statements to facilitate or conduct issue-orientated research in the field of ARF.

The first meeting of ADQI took place in New York (August 2000) and sought to tackle the topic of continuous renal replacement therapy. The meeting was successful and a comprehensive consensus document was generated, which has just been published (November issue of *Kidney International*). Targets for future research were defined and a large epidemiological study of current practice developed from the deliberations of the meeting (B.E.S.T. kidney), the results of which have just been submitted for publication. The second ADQI, meeting (Vicenza, Italy 2002) focused on developing consensus criteria for ARF, choosing clinical and physiologic endpoints for trials, animal models, fluid management methodology and information technology.

Future ADQI conferences are being planned to address Intermittent Hemodialysis and Nutrition Support in ARF. However, for the third International Conference we have selected the topic of Extracorporeal Blood Purification in Non-Renal Disease. Various forms of Extracorporeal therapy are being employed for the treatment of a wide variety of syndromes from sepsis to end-stage liver disease. Without a standardized approach to patient selection or therapy, differences in results cannot be attributed to any single factor and progress has been slow. Enthusiasm for a given therapy based on the reports of dramatic results has been tempered by concerns surrounding variation in practice and generalizability. Accordingly, we have sought to bring several of the world's experts together to reach consensus on important aspects of these therapies.

For ADQI IV, the organizing committee has selected four topics: 1. Hemofiltration and Hemoperfusion in Sepsis and Septic Shock; 2. Plasma Therapies in Thrombotic Syndromes; 3. Liver Assist Devices in Hepatic Failure; and 4. Hemofiltration in Cardiac Surgery and Heart Failure. As we have done before, each topic will be assigned a group of experts and have a facilitator. While the facilitator will be responsible for coordinating the efforts of the workgroup, each member will equally share the responsibility for the tasks as outlined. Furthermore, by participating in the plenary sessions, each member will have input into the outcome of other groups.

### *1. Hemofiltration and Hemoperfusion in Sepsis and Septic Shock*

In the wake of more than a decade of failed trials in which potent biological agents (antibodies, or soluble receptors) were used to selectively inhibit individual components of the inflammatory response, blood purification is receiving renewed interest. The failures of the "biologicals" have been interpreted by some as evidence that immuno-therapy is useless, or even harmful, as a treatment for sepsis. However, others have argued that while selective therapy in unselected patients is not helpful, better patient selection and/or broad-spectrum immuno-therapy may still prove effective. Hemofiltration as a blood purification system, offers important theoretical advantages over narrow-spectrum biologicals. First, hemofiltration can effect a wide array of inflammatory substances, indeed virtually every known cytokine can be removed by hemofiltration to some degree. Second, this strategy has the capacity to "auto-regulate" itself such that as one component of the response increases so too does the effect on that component. Third, hemofiltration only affects the circulating pool of mediators rather than influencing local concentrations where their activity may be beneficial. Finally hemofiltration may

be the ideal treatment for sepsis because both pro- and anti-inflammatory substances are removed from the circulation according to their relative concentrations.

However, critics argue that blood purification cannot be realized in sepsis because the generation rates of mediators are high and endogenous clearance is great. Further, it can be argued that many of the soluble substances important in the pathogenesis of sepsis may still be unknown. However, it is important to point out that these limitations are not significantly different for dialysis in acute renal failure. Despite more than 30 years of investigation, the key substances responsible for the clinical condition known as uremia are still unknown and thus generation and endogenous clearance rates cannot be determined. Nevertheless, dialysis is effective in the treatment of acute renal failure. Indeed, the effectiveness of dialysis is routinely measured not by the clinical response but by the concentration of marker substances (e.g. urea). If blood purification is to advance as a treatment for sepsis or related conditions, we must establish a means for patient selection and monitoring. We must develop methods to judge the effectiveness of therapy, both for clinical practice and for clinical trials.

#### **Group 1. Hemofiltration and Hemoperfusion in Sepsis and Septic Shock**

Rinaldo Bellomo (Melbourne) --*facilitator*

Claudio Ronco (Vicenza)

James Winchester (New York)

James Matson (Plano, Texas)

#### *2. Plasma Therapies in Thrombotic Syndromes*

As established by the nomenclature workgroup for ADQI, plasma therapies include any blood purification technique that requires the separation of plasma from the formed elements of blood. Typically these therapies include *plasma exchange* where plasma is removed and then replaced with donor plasma or *plasmapheresis* where plasma is removed and then replaced with fluid other than plasma, usually with human albumin. Plasma can be replaced as fresh frozen plasma or as cryosupernatant plasma (low in von Willebrand Factor [vWF] and fibrinogen). Plasma exchange can be performed by centrifugation or by plasma filtration (usually called plasma filtration or PF).

The basic rationale for the use of plasma therapies in multiple organ failure (MOF) is most apparent in patients with thrombotic microangiopathy and thrombocytopenia associated MOF. Thrombotic thrombocytopenic purpura (TTP) remains the classic model of this disease. In this

condition, systemic endothelial injury results in release of multiple mediators including some that are now strongly implicated in the pathogenesis of these disorders. One such mediator is the ultra large vWF fragment, which attracts platelets and causes platelet and then fibrin microthrombi in the microcirculation. Another is plasminogen activator inhibitor type-1 (PAI-1), which inhibits endogenous fibrinolysis resulting in further thrombosis and endothelial injury. These patients concomitantly produce antibodies to vWF cleaving protease. In the absence of cleaving protease, platelet microthrombi progress with inexorable secondary organ injury. Plasma exchange removes the harmful factors (e.g. ultra large vWF fragments, vWF cleaving protease antibodies, PAI-1, etc.) and replaces the good factor (vWF cleaving protease) with healthy plasma.

Thus, there is sound rationale for the use of plasma therapies in thrombotic microangiopathic diseases. But what about syndromes other than “classical TTP”? In many patients with severe sepsis thrombotic microangiopathy also occurs and in many communities, these patients are treated with plasma therapies. However, the experimental evidence has been, until recently, unconvincing. Natanson and colleagues performed an experiment in a canine model of experimental intraperitoneal sepsis. In this model, plasma exchange therapy 6 hrs after implantation of an E. coli infected clot unequivocally resulted in worse, not better survival. However, the experiment was performed according to the rigor of experimental design, not clinical utility. Inotropes and fluids were not used when the animals developed hypotension, and hypotension can be commonly associated with the use of plasma exchange. Plasma exchange removes circulating catecholamines, glucocorticoids and mineralocorticoids and may result in hypocalcemia (with citrate preserved plasma products) unless carefully monitored. It can also result in transient hypovolemia. For this reason it is notable that two subsequent experimental studies which used inotropic support to reverse hypotension, showed that plasma exchange improved outcome in septic shock. Thus, it appears that potential trials designed to evaluate the role for plasma exchange therapy must be careful to anticipate and treat hypotension associated with the therapy.

Much like the experimental literature, the results of clinical studies on plasma therapies for septic shock, MODS and thrombocytopenia associated MOF are conflicting. Several uncontrolled case series from both sides of the Atlantic and Pacific Oceans have reported benefit using plasma exchange in patients with septic shock, renal failure, and DIC. Stegmayr's analysis of these studies is particularly informative. Interestingly, in the studies analyzed by this

author, patients who received the centrifugation method appeared to have had better outcomes than those who received the plasma filtration method. However, it must be pointed out that the plasma filtration technology has changed in recent years. Synthetic filters are used which are far less likely to induce inflammatory cell activation. Nevertheless, work remains to be done to evaluate whether there are any important differences between centrifugation based and filtration based plasma exchange. Two randomized controlled trials using plasmapheresis via plasma filtration (one for 36 consecutive hours, and the other for 1 –2 treatments ) rather than plasma exchange via centrifugation showed no benefit in adults with septic shock.

In a recent study presented in Intensive Care Medicine, Busund and colleagues treated hypotension if and when it occurred during plasma exchange therapy in patients with septic shock and used partial plasma exchange therapy. The authors showed a tendency to improved outcome in adults with septic shock. What explains the differences in outcomes in patients with septic shock described in these uncontrolled case series, and three underpowered randomized controlled trials? Is it plasma exchange vs plasmapheresis? Is it plasma centrifugation vs plasma filtration? Is it patient selection? Is it the hemodynamic management of the patient during the procedure? Is there some unmeasured treatment, practice or patient differences among the studies? Regrettably we simply cannot determine at this time.

The clinical literature suggests that plasma exchange therapy is unequivocally successful in improving outcome in patients with primary thrombotic microangiopathy also known as TTP. These patients are first treated with steroids for up to 24 hours and then plasma exchange therapy for a median of 18 days. Patients who remain unresponsive are plasma exchanged with cryosupernatant plasma and or started on vincristine to reduce antibody production against vWF cleaving protease. It is generally agreed that these therapies have decreased mortality in this disease from 90% to 10%. Case series report the successful use of prolonged plasma exchange therapy for adults with TTP associated with sepsis, infection, and cancer in the ICU. Investigators have now reported that adults with thrombocytopenia associated organ failure with uremia, sepsis, cirrhosis, or autoimmune disease have reduced vWF cleaving protease activity with as many as 50% having absent VWF cleaving protease activity. Some of these patients had antibodies to vWF cleaving protease while others did not. Recently, in a preliminary report, Nguyen and colleagues reported that children with thrombocytopenia (platelet count < 100,000) associated MOF had reduced to absent vWF cleaving protease activity along with markedly increased PAI-1 activity, both reversed by plasma exchange therapy. These patients required a

median of 11 days of plasma exchange to reverse MOF. These findings suggest that prolonged plasma exchange may be required to reverse the thrombotic microangiopathy of thrombocytopenia-associated sepsis as well. Hence, outcomes with plasma exchange therapy may also be related to length of treatment and presence of underlying thrombotic microangiopathy.

Based on the data to date, a multi-center randomized controlled trial of plasma exchange therapy would seem warranted. The design of the definitive trial for plasma therapy should consider and standardize three key features: i. modality (centrifugation vs. filtration) ii. replacement (plasma exchange vs. plasmapheresis vs. some combination of the two) and iii. details of supportive care. Finally, as with all, therapeutic trials, patient selection will be of great importance. The presence of thrombocytopenia appears to select patients who are likely to respond to plasma therapies. Whether more specific markers such as vWF cleaving protease or PAI-1 activity can be used to select patients with even great specificity is not known at this time.

#### **Group 2. Plasma Therapies in Thrombotic Syndromes**

Trung Nguyen/Joe Carcillo (Pittsburgh) –*facilitator*

Tim Bunchman (Birmingham Ala)

BG Stegmayr (Sweden)

R Busund (Torsmo, Norway)

#### **3. Liver Assist Devices in Hepatic Failure**

The healthy liver is a detoxifying organ and it has also secretory function for coagulation factors, proteins and hormones. The liver hydrophilizes several toxins making their excretion possible through the kidneys. When this function is impaired, protein-bound hydrophobic substances tend to accumulate in blood and specific blood purification systems are required. The ideal blood purification system for liver support has not yet been found. It should be capable of removing lipid soluble toxins, water soluble toxins, protein bound toxins and achieve high clearances of these toxins. A complete liver support system should include a detoxification component and a secretory component, possibly capable of metabolic activity. While the first component can be accomplished by an inert mechanical system, the second one can only be performed by a hybrid artificial organ containing a mixture of synthetic materials and living

hepatocytes. Nevertheless, the first detoxifying component can be sufficient to perform liver support and to bridge the patients towards recovery of the native organ or transplantation. To perform such a task, a combination of membrane separation processes and adsorption mechanisms have been utilized. Different systems are today available for liver support, some of which utilize the direct contact of blood with adsorbent materials. This approach can be utilized in series with standard hemofiltration procedures but it has the limitations imposed by the partial adsorptive capacity of the sorbents. In fact, in order to place the sorbent in contact with blood, the material must be coated to improve biocompatibility and this process of coating often reduced the efficiency of the adsorptive process. On the other hand, more effective sorbent materials can be utilized and placed in contact with plasma, if the blood cells are previously separated through a plasma filter. In such condition, protein bound toxins can be removed by the adsorbent and blood can be reconstituted downstream after plasma has been purified. In these circumstances, uncoated resins and carbons can be utilized without any problem of bioincompatibility since there is no direct contact of the sorbent with the blood cells. The final expected physiological effects can be an improved neurological state, clearance of unconjugated bilirubin at 20-40 ml/min or more, clearance of some aromatic amino acids, decrease in serum ammonia and removal of some cytokines. Thus, although we have a long way to go, we are *already* making the first important steps toward clinically relevant liver support.

### **Group 3. Liver Assist Devices in Hepatic Failure**

David Kramer (Jacksonville, FL) –*facilitator*

Julia Wendon (London)

Kang Lee (Singapore)

Pierre Opolon (Paris)

### **4. Hemofiltration in Cardiac Surgery and Heart Failure**

Even when the kidneys are functioning, the demands of cardiac failure and volume overload may often be “too much” for the system. Furthermore, cardiac and respiratory management may require manipulation of intravascular volume beyond what can be achieved through pharmacology.

Myocardial dysfunction is common in the critically ill. It may be a consequence of a myocardial dilatation with reduced contractility, ventricular stiffness with diastolic dysfunction, or the consequence of myocardial injury or circulating myocardial depressant factors. In all cases, cardiac support can be achieved by the optimization of fluid balance, the reduction of organ edema and the restoration of desirable levels of pre-load and afterload. Several reports have shown that myocardial elastance can improve after hemofiltration with restoration of adequate fluid balance. In such conditions, the continuity of the extracorporeal therapy allows remarkable cardiovascular stability with maintenance of hemodynamic parameters including mean arterial pressure, heart rate and systemic vascular resistance. Such stability, which is achieved through the slow continuous ultrafiltration and continuous refilling of the intravascular volume from the interstitium, allows stability of circulating blood volume and the preservation of organ perfusion. This may be crucial in facilitating renal recovery during ARF.

The fundamental concept in patients with acute lung injury (ALI) is to provide adequate gas exchange without causing further barotrauma or volutrauma to the lungs as well as decreasing extravascular lung water. Mechanical ventilation is typically needed in the treatment of ALI but is injurious to the lungs. In such conditions, the possibility of removing carbon dioxide from the circulating blood by means of extracorporeal methods has been previously explored. Today, the idea of using a special carbon dioxide removing cartridge in series with the hemofilter might represent, in selected patients, a new chance for reducing the requirement for invasive mechanical ventilation allowing instead for a “non-invasive” approach. Special membranes are under evaluation utilizing a dry/wet gas exchange process leading to significant values of CO<sub>2</sub> clearance in the extracorporeal circuit. Such systems might reduce the morbidity and mortality of ALI in the future. Furthermore, by optimizing the patient's volume state and offering the ability to remove interstitial fluid extracorporeal therapy may offer additional support to the failing lung.

**Group 4. Hemofiltration in Cardiac Surgery and Heart Failure**

William Clark (Indianapolis) –*facilitator*

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Bob Bartlet (Ann Arbor)

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