Prevention and Treatment of Acute Renal Failure in Sepsis

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Acute renal failure (ARF) is a common complication of sepsis and carries an ominous prognosis. Mortality was reported higher in patients with septic ARF (74.5%) than in those whose renal failure did not result from sepsis (45.2%) (1). Although the presence of multiple organ dysfunction and other comorbidities certainly contributes to the high mortality, ARF independently increases morbidity and mortality (2).

Sepsis is characterized by a generalized inflammatory response and activation of the coagulation and fibrinolytic cascades, resulting in endothelial injury (2a, 2b). A broad array of humoral mediators are released in the systemic circulation, including cytokines, lipid mediators such as platelet activating factor and arachidonic acid metabolites, endothelin-1, and complement components. Systemic hypotension, resulting in renal ischemia, is a contributing — but certainly not the sole — factor in septic ARF. Intrarenal vasoconstriction, owing to an imbalance between vasodilatory and vasoconstrictory substances, results in a decline in renal blood flow (RBF) and abnormalities in intrarenal blood flow distribution that predominantly affect the outer medulla (3). Inflammatory cells infiltrate the kidney, causing local damage by release of oxygen radicals, proteases, and further production of inflammatory cytokines. Leukocyte-endothelial interactions result in physical congestion of the medullary vasculature and a further decreased regional blood flow. Dysfunction of the coagulation and fibrinolytic cascades contributes to intraglomerular thrombosis. Tubular injury leads to cell detachment with intratubular obstruction and tubular backleak. Recovery from ARF requires clearance of necrotic tubular cells and debris, as well as regeneration and repair of the nonfatally injured cells.

The present communication will discuss the attempts to pharmacologically interfere with each of these dysfunctional pathways to improve the course of septic ARF, including inhibition of inflammatory mediators, improvement of renal hemodynamics by amplifying vasodilator mechanisms and blocking vasoconstrictor mechanisms, interruption of leukocyte infiltration, inhibition of the coagulation cascade, and administration of growth factors to accelerate renal recovery. Furthermore, the available supportive measures including dialytic treatment will be highlighted.

Treatment with Fluids, Vasopressors, and Diuretics

Few studies addressed the issue of treatment with fluids, vasopressors, and diuretics specifically in patients with septic ARF. However, conclusions can probably be safely inferred from studies performed in patients with ARF in general, which will be included in the discussion below.

Volume Expansion

It is common knowledge that optimization of systemic hemodynamics and effective intravascular volume is important to prevent ARF in patients with sepsis. Unfortunately, what constitutes optimal hemodynamics remains largely undefined. In a multicenter randomized trial, volume expansion and vasopressor therapy aimed at achieving supranormal values for cardiac index and normal values for mixed venous oxygen saturation had no effect on mortality or on the incidence and severity of ARF (4). In contrast, early institution of treatment to increase central venous oxygen saturation to 70% or higher resulted in a lower mortality and less severe organ dysfunction in patients with severe sepsis or septic shock (5).

Furthermore, the nature of the optimal fluid resuscitation regimen has not been defined. Three systematic reviews of randomized controlled trials comparing crystalloids with colloids have yielded conflicting results (6–8). A meta-analysis of trials comparing administration of albumin with no administration or with administration of crystalloids in critically ill patients found a strong suggestion that albumin increases mortality (6). A meta-analysis of trials comparing colloid with crystalloid solutions reported that resuscitation with colloids was associated with an absolute increase in the risk of mortality of 4% (7). In contrast, another meta-analysis of trials comparing isotonic crystalloids with colloids did not find a difference in mortality (8). Although the controversy over the choice of crystalloids or colloids as the ideal resuscitation fluid persists, a recent randomized trial in 129 patients with severe sepsis or septic shock demonstrated that the use of hydroxyethylstarch as plasma-volume expander was associated with a significantly higher risk of ARF than gelatin (9). In keeping with these findings, the use of hydroxyethylstarch in brain-dead kidney donors was associated with renal dysfunction in the kidney transplant recipients (10). However, a randomized trial of 300 trauma or postoperative patients with sepsis found no differ-
ence in mortality or incidence of renal failure between patients resuscitated with hydroxyethylstarch or albumin (11).

In conclusion, despite the importance of fluid therapy in the prevention and treatment of ARF, the nature and targets of an optimal fluid resuscitation regimen continue to be an unresolved issue.

**Vasopressors**

When appropriate volume expansion fails to restore BP in patients with sepsis, vasopressors are indicated. Physicians have been concerned about their use for fear that intrarenal vasoconstriction would abrogate the benefits of increased BP.

Norepinephrine, indeed, reduces RBF in healthy animals and humans (12). The ultimate effect of norepinephrine on renal perfusion depends, however, on a complex interplay of its actions on different vascular beds and the underlying condition of the patient. Norepinephrine increases BP by an $\alpha_1$-mediated increase in systemic vascular resistance and a $\beta_1$-mediated increase in cardiac output. An excessive rise in systemic vascular resistance with an increase in cardiac afterload may have a potential negative impact on cardiac output. The net effect on renal vascular resistance hinges on (1) the increase in systemic BP with a decreased renal sympathetic tone through a baroreceptor response, resulting in vasodilatation; (2) an autoregulatory vasoconstriction owing to a rise in renal perfusion pressure; (3) a direct $\alpha_1$-mediated renal vasoconstriction, which is of minor importance (12). Thus, in a patient with sepsis, characterized by systemic vasodilatation and impaired renal autoregulation, norepinephrine administration may be expected to improve RBF. Several non-controlled studies in patients with sepsis have, indeed, shown that norepinephrine augmented urine output and GFR (12). The only randomized trial available reported that norepinephrine administration in 32 patients with septic shock resulted in a higher BP, systemic vascular resistance, and diuresis than high-dose dopamine (13). A prospective observational study in 97 patients with septic shock found a lower mortality in patients treated with norepinephrine than in those treated with other vasopressors — mainly high-dose dopamine (14).

Vasopressin, a hormone secreted by the posterior pituitary, increases systemic vascular resistance through activation of $V_1\alpha$-receptors on vascular smooth muscle cells. Arginine vasopressin administration in 16 patients with septic shock and hyporesponsiveness to catecholamines increased BP, systemic vascular resistance, and urine output (15). A randomized trial in 24 patients with septic shock demonstrated that a 4-h infusion of arginine vasopressin improved urine output and creatinine clearance with similar effects on BP and cardiac output, as compared with norepinephrine (16).

In conclusion, vasopressors can be used safely to restore BP without compromising renal function in patients with septic shock. Norepinephrine is preferable to dopamine. In patients refractory to norepinephrine, early use of arginine vasopressin is recommended (17).

**Low-Dose Dopamine**

Low-dose dopamine (1 to 3 $\mu g/kg$ per min) increases RBF, diuresis, and natriuresis in healthy experimental animals and humans (18–19), actions that may be of potential benefit in patients with or at risk of ARF. Administration of low-dose dopamine has been examined in different models of experimental ARF, including ischemic ARF and sepsis, demonstrating protective or no beneficial effects (18–19). Studies examining the role of low-dose dopamine as a prophylactic agent in patients at high risk for ARF were generally negative but lacked statistical power due to limitations in study design, small patient numbers, or a low incidence of ARF in the control group (18–19). In established ARF, several uncontrolled case series or small randomized trials showed either no effect or a (usually transient) improvement of diuresis, natriuresis, or perhaps GFR with low-dose dopamine (18–19). In a study of 18 critically ill patients, short-term infusions of low-dose dopamine, low-dose dobutamine, and placebo were compared in a randomized, double-blind, crossover fashion. Dobutamine improved creatinine clearance without affecting diuresis, while dopamine induced diuresis without changing creatinine clearance (20). In a larger study, primarily investigating the value of atrial natriuretic peptide, patients not treated with dopamine were compared with those treated with either low-dose (3 $\mu g/kg$ per min) or high-dose (≥3 $\mu g/kg$ per min) dopamine. After adjustment for severity of illness, the use of dopamine was not associated with a lower risk for death or dialysis (21). Finally, in a randomized placebo-controlled trial in 328 critically ill patients with early renal dysfunction sufficiently powered to detect a small benefit, there was no effect of low-dose dopamine on renal function, need for dialysis, ICU or hospital length of stay, or mortality (22).

Furthermore, there is concern about the potential side effects of dopamine, even at low doses. Dopamine can depress respiratory drive and trigger tachyarrhythmias and myocardial ischemia (18–19). In a porcine model of hemorrhagic shock, dopamine accelerated intestinal ischemia owing to a shunting of blood away from the bowel mucosa (23). In addition, dopamine was found to suppress the circulating concentrations of all anterior pituitary-dependent hormones, except for cortisone (24), and to decrease T cell function (18–19).

In conclusion, the use of low-dose dopamine for renoprotective purposes should be abandoned, as there is no evidence supporting its effectiveness in this setting and dopamine can precipitate serious cardiovascular and metabolic complications in critically ill patients.

**Diuretics**

High-dose loop diuretics are commonly used in critically ill patients with early or established ARF. The rationale for their use rests heavily on the assumption that they decrease oxygen consumption in the tubular cells by inhibiting transcellular sodium transport and thus prevent or limit ischemic cell injury. In addition, loop diuretics may vasodilatate cortical blood vessels and improve oxygenation. Finally, augmentation of tubular flow may reduce intratubular obstruction and backleak of filtrate, thereby accelerating resolution of ARF.
Prophylactic administration of loop diuretics in patients at high risk for ARF contra-intuitively appeared to be deleterious to renal function (25–26). Although no specific information on septicemic patients is available, physicians should be discouraged from using diuretics in these patients in an effort to prevent ARF.

In patients with established ARF, several studies have found no benefit of loop diuretics (27–33) (Table 1). More particularly, loop diuretics did not accelerate renal recovery, reduce the need for dialysis, or decrease mortality. Most of these studies were, however, relatively small and lacked statistical power to entirely rule out a beneficial effect of diuretics.

Loop diuretics may convert oliguria to diuresis in a subset of patients with ARF. The mortality rate of non-oliguric ARF was found to be lower than that of oliguric ARF (33–34). There were, however, no significant differences in the clinical characteristics, the severity of renal failure, and the mortality rate between spontaneously non-oliguric patients and patients becoming non-oliguric after furosemide (33–34). These observations imply that patients responding to loop diuretics are characterized by a less severe form of renal failure, rather than a beneficial effect of therapy. In a recent retrospective survey of critically ill patients with ARF, diuretic use was associated with an increased risk of death and non-recovery of renal function (35). The authors suggested that the adverse outcome was due to either direct deleterious effects of diuretics or indirect effects owing to a delay in the recognition of the severity of ARF and institution of dialytic support. The higher odds for death or non-recovery of renal function was, however, borne largely by patients who were relatively unresponsive to diuretics (35), suggesting that diuretics were preferentially used in patients with an intrinsically more severe course of disease.

In conclusion, despite their ubiquitous use, only few and small studies have evaluated the role of loop diuretics in established ARF. This contrasts sharply with the testing of other pharmacologic agents in critically ill patients where mega-trials are the rule (see below), illustrating to what extent the scientific arena is dominated by the interests of the pharmaceutical industry. In the absence of data from a sufficiently powered multicenter randomized trial, high-dose loop diuretics should be used cautiously in critically ill patients with ARF. Intravascular volume depletion should be carefully corrected before and during administration of diuretics, as an already damaged kidney may be profoundly injured by a relatively mild decrease in perfusion pressure. In patients with sustained oliguria despite high doses of loop diuretics, this treatment should be withdrawn. In responders, continuous infusions are preferred because they are more effective and associated with less toxicity than bolus administrations (36).

### Specific Pharmacologic Treatment

**Anti-TNF-α Therapy**

**Rationale.** Tumor necrosis factor-α (TNF-α) is a pleiotropic cytokine that plays a germane role in the host response to infection. Besides its well-documented systemic effects, TNF-α may have specific renal effects. Mesangial cells produced TNF-α when exposed to LPS (37). *In vivo* TNF-α infusion in rabbits (38)

### Table 1. Studies examining the value of loop diuretics in established ARF

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Design</th>
<th>Diuretic</th>
<th>Result*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(27)</td>
<td>47 ARF</td>
<td>Prospective, randomized</td>
<td>IV furosemide continuous or in bolus</td>
<td>↑ renal recovery ↓ number of dialyses = mortality</td>
</tr>
<tr>
<td>(28)</td>
<td>105 oliguric ARF</td>
<td>Retrospective</td>
<td>IV furosemide in bolus or no drug</td>
<td>= renal recovery ↓ number of dialyses = mortality</td>
</tr>
<tr>
<td>(29)</td>
<td>104 ARF</td>
<td>Retrospective</td>
<td>IV furosemide in bolus</td>
<td>= renal recovery = incidence of dialysis = mortality</td>
</tr>
<tr>
<td>(30)</td>
<td>66 oliguric ARF</td>
<td>Prospective, randomized</td>
<td>IV furosemide in bolus or no drug</td>
<td>= renal recovery = number of dialyses</td>
</tr>
<tr>
<td>(31)</td>
<td>14 ARF</td>
<td>Retrospective</td>
<td>IV furosemide in bolus or no drug</td>
<td>= renal recovery</td>
</tr>
<tr>
<td>(32)</td>
<td>56 ARF</td>
<td>Prospective, randomized</td>
<td>Continuous IV or PO furosemide or single dose furosemide</td>
<td>= renal recovery = number of dialyses</td>
</tr>
<tr>
<td>(33)</td>
<td>92 ARF</td>
<td>Prospective, randomized</td>
<td>IV furosemide in bolus or IV torasemide in bolus or placebo</td>
<td>= renal recovery = incidence of/time to/ duration of dialysis</td>
</tr>
<tr>
<td>(34)</td>
<td>552 ARF</td>
<td>Retrospective</td>
<td>Diuretics or no drugs</td>
<td>= mortality ↓ renal recovery ↑ in-hospital mortality</td>
</tr>
</tbody>
</table>

*a ↓, decreased; =, no difference; ↑, increased.*
or perfusion of the isolated rat kidney with TNF-α (39) decreased GFR. TNF-α caused leukocyte and fibrin accumulation in glomerular capillary lumens (38) and potently induced apoptotic cell death in glomerular endothelial cells (40).

**Experimental Studies.** A large number of studies in diverse animal models have shown that anti-TNF-antibodies confer protection against the morbidity and mortality from both Gram-positive and Gram-negative sepsis (41). Specifically for the kidney, passive immunization to TNF-α prevented renal cortical damage during endotoxemia in rhesus monkeys (42). Neutralization of TNF-α with a TNF-soluble receptor protected mice against LPS-induced renal failure (43). Mice with a targeted deletion of TNF receptor-1 (TNFR1−/−) were resistant to LPS-induced renal failure (44). Kidneys of TNFR1−/− mice had less tubular damage, less neutrophil infiltration, and a lower number of apoptotic cells than those of TNFR1+/+ mice. In addition, TNFR1+/+ mice transplanted in TNFR1−/− mice sustained severe renal failure after LPS injection, whereas TNFR1−/− kidneys transplanted in TNFR1+/+ mice were relatively protected. Finally, the fact that TNFR1−/− mice remain sensitive to the lethal effects of LPS (45) but are resistant to LPS-induced renal failure further supports a renal-specific role for TNF-α.

**Clinical Studies.** More than ten large phase III trials with neutralizing monoclonal anti-TNF-α antibodies or soluble TNF receptor fusion proteins failed to show survival benefits in patients with sepsis (41). Preliminary results of a recently completed trial with afelimomab were somewhat more encouraging. The monoclonal anti-TNF-α antibody conferred a 6.9% absolute and 14.3% relative reduction in risk-adjusted mortality in septic patients with interleukin-6 concentrations of more than 1000 pg/ml (46). Although the BAY 1351 monoclonal anti-TNF-α antibody did not improve survival in patients with septic shock, a reduction in the development of renal failure was observed (47).

**Conclusion.** Although TNF-α indirectly affects the kidney by inducing hypotension and releasing inflammatory mediators in the circulation, several lines of evidence point to direct TNF-mediated renal damage in sepsis. Despite the apparent success of anti-TNF therapies in animal models with prevention of both mortality and renal failure, the beneficial effects of these strategies in humans are marginal at best. A more profound knowledge of cytokine profiles in sepsis may allow for a better selection of patients that will most likely benefit from these therapies.

**Inhibition of Platelet-Activating Factor**

**Rationale.** Platelet-activating factor (PAF) is an endogenous phospholipid with vasoactive, platelet-aggregating and pro-inflammatory properties. Serum and urinary concentrations of PAF are elevated in septic patients and correlate with the severity of ARF (48). LPS and TNF-α stimulate the synthesis of PAF in mesangial cells, endothelial cells, and leukocytes. Intrarenal infusion of PAF in the rat results in renal vasoconstriction and a fall in GFR (49–50).

**Experimental Studies.** Several structurally unrelated PAF antagonists prevented the adverse renal hemodynamic effects of endotoxemia in the rat (49–50).

**Clinical Studies.** A large phase III trial with PAF acetylhydrolase, a recombinant form of the endogenous human enzyme that hydrolyzes PAF, has been initiated in patients with severe sepsis (51).

**Conclusion.** Although experimental studies are encouraging, no firm conclusions on the value of PAF antagonism in septic ARF can be drawn in the absence of information from clinical trials.

**Inhibition of Nitric Oxide Synthase**

**Rationale.** Nitric oxide (NO) is the metabolic product of l-arginine and is produced by three major NO synthase (NOS) isoforms that are expressed in a cell-type specific manner and each have a distinct functional role: endothelial NOS (eNOS), neuronal NOS (nNOS), and inducible NOS (iNOS). Within the kidney, eNOS is constitutively expressed in endothelial cells and plays a pivotal role in vascular relaxation, inhibition of leukocyte adhesion, and platelet aggregation. Sublethal endothelial injury and endothelial dysfunction, resulting in an impaired release of NO produced by eNOS, have been described in ischemic kidneys (52–53). On the other hand, iNOS is located in diverse cell types in the kidney but is normally not active. As regards septicemia, it is of interest that LPS exposure upregulates iNOS in the medulla and glomeruli (54). TNF-α and interleukin-1 induce the expression of iNOS in mesangial cells, vascular smooth muscle cells, and macrophages. Excessive generation of NO by iNOS has been implicated as an important mediator of the hemodynamic alterations in sepsis, particularly the vascular hyporesponsiveness and vasodilatation (55). These alterations in NOS expression and NO production in the systemic circulation and within the kidney have supported the extensive testing of NOS inhibitors in various models of sepsis and renal ischemia.

**Experimental Studies.** N-nitro-l-arginine methyl ester (l-NAME), a nonselective NOS inhibitor, prevented hypoxic cellular damage in isolated proximal tubules (56), whereas l-arginine enhanced the injury (56–57). NO thus appears to be cytotoxic to renal tubular cells. In contrast to the protective effects in isolated renal tubules, l-NAME resulted in an increase in proteinuria, a decline in renal function and a marked fibrin deposition and glomerular thrombosis during in vivo endotoxemic injury (58). Escherichia coli bacteremia in the rat increased cardiac output and caused renal hypoperfusion due to pregglomerular vasoconstriction. In this model, l-NAME normalized cardiac output but exacerbated pregglomerular vasoconstriction and further impaired glomerular blood flow (59). During Pseudomonas aeruginosa sepsis in sheep, l-o-mono-methyl-arginine (l-NMMMA) increased BP and systemic vascular resistance and decreased cardiac output, whereas RBF remained unchanged (60). N-methyl-l-arginine (l-NMA) fully reversed the decrease in BP and partially the decrease in RBF occurring in dogs after LPS infusion (61). These variable and contradictory results with nonselective NOS inhibitors suggest that alternative sources of NO in the systemic circulation and within the kidney exert opposite effects. It was therefore anticipated that the use of selective NOS inhibitors would produce less ambiguous results. Antisense oligodeoxynucleotides targeting iNOS improved renal function in rats subjected to...
renal ischemia (53). The effect was due to an attenuation of tubular injury, suggesting cytotoxic effects of NO produced by iNOS during renal ischemia. Similarly, the selective iNOS inhibitor L-N^6-(1-iminoethyl)lysine (L-NIL) conferred renoprotective effects during ischemia (62). Selective iNOS inhibition with S-methyl-isothiourea prevented hypotension through systemic vasoconstriction and maintained cardiac output and reduced the signs of renal dysfunction in rats challenged with LPS (63). In a hyperdynamic porcine model of sepsis, both L-NAME and S-methyl-isothiourea increased BP and caused comparable reductions of medullary and cortical blood flow (64). Only L-NAME was clearly detrimental to renal function by reducing GFR and increasing sodium excretion and renal oxygen extraction. S-methyl-isothiourea did not affect GFR and reduced sodium excretion. However, apart from increasing MAP, this selective inhibitor of iNOS offered little advantage in comparison with saline resuscitation (64). In agreement, the degree of renal failure after LPS infusion was similar in iNOS knockout mice as compared with wild-type mice (43).

Clinical Studies. Several small and uncontrolled studies demonstrated that short-term nonselective NOS inhibition increased both BP and systemic vascular resistance and decreased cardiac output in patients with septic shock (65–67). Beneficial effects on renal function were, however, not reported. A randomized, placebo-controlled trial with L-NMMA was discontinued early because of an increased mortality in the treated group.

Conclusion. The ubiquitous nature and the pleiotropic effects of the NO system, as well as its complex alterations in sepsis and ARF, likely explain why NOS inhibition fails to show straightforward laudable effects. NO release by the endothelial cells of the renal microcirculation is essential to counterbalance the vasoconstrictor influences and maintain RBF, to inhibit infiltration of leukocytes, and to prevent thrombosis. In contrast, excessive NO production in tubular cells exacerbates the injurious effects of ischemia on these cells. In addition, exaggerated NO-mediated systemic vasodilatation is deleterious for the kidney by reducing perfusion pressure. Future therapies that inhibit iNOS but amplify eNOS may prove to be beneficial.

Endothelin Antagonism

Rationale. Endothelin-1 (ET-1) is a peptide with potent vasoconstrictor effects on the renal microcirculation, thereby reducing RBF and GFR. Its effects are mediated by at least two types of receptors, the ETA and ETB receptors. Infusion of endotoxin greatly increases plasma ET-1 levels in experimental animals. TNF-α stimulates the synthesis of ET-1 in glomerular endothelial and epithelial cells. In humans with sepsis, plasma ET-1 levels are markedly elevated and correlate with morbidity and mortality (68).

Experimental Studies. Pretreatment with a nonselective ET receptor-antagonist, blocking both ETA and ETB receptors, did not improve hypotension but increased RBF, creatinine clearance, and diuresis in canine endotoxemia (69). Similarly, the nonselective ET receptor-antagonist tezosentan induced a significant fall in BP but prevented the reduction in RBF and GFR during endotoxic shock in neonatal piglets (70). Furthermore, an anti-ET-1 antibody improved renal function after endotoxin injection in rats (71). In contrast, renal hemodynamics were unaffected by a nonselective ET receptor-antagonist in porcine endotoxic shock (72), as well as by a selective ETA receptor-antagonist in conscious rats subjected to LPS infusion (73).

Clinical Studies. No studies with ET receptor-antagonists have been performed in patients with sepsis. A nonselective ET antagonist increased the risk of contrast nephropathy in patients with chronic renal failure undergoing coronary angiography. These negative effects were thought to relate to an intrarenal “steal” phenomenon, due to a predominant increase of the cortical blood flow with a worsening of medullary ischemia (74).

Conclusion. The mixed results in experimental models of sepsis and the deleterious effects in human contrast nephropathy dictate the need to reexamine the rationale for ET antagonism before embarking on clinical trials in patients with ARF and sepsis.

Inhibitors of Arachidonic Acid Metabolism

Rationale. Metabolism of arachidonic acid by cyclooxygenase results in the generation of prostaglandins and thromboxanes, whereas lipoxygenase yields leukotrienes. Both prostaglandin E2 and I2 (prostacyclin) induce renal vasodilatation and natriuresis, whereas thromboxane A2, leukotrienes, and stable keto-analouges of the endoperoxides prostaglandin F2α and prostaglandin H2 are potent renal vasoconstrictors. Spontaneous oxidation of arachidonic acid by oxygen-free radicals generates prostaglandin F2α-like compounds. One of these compounds, 8-epi-prostaglandin F2α, has an extremely potent selective renal vasoconstrictive effect through interaction with the thromboxane receptor (75). Endotoxin as well as various inflammatory cytokines stimulate the synthesis of thromboxane A2 and leukotrienes in the kidney and in inflammatory cells (75). The urinary excretion of thromboxane A2 and prostacyclin metabolites are increased several-fold in patients with sepsis (76).

Experimental Studies. Cyclooxygenase inhibition with indomethacin had a markedly protective effect on glomerular hemodynamics in endotoxemic rats (77). A selective thromboxane synthetase inhibitor attenuated the renal effects of LPS in the rat (78) and protected the kidney in sheep with hyperdynamic septic shock (79). Furthermore, leukotriene antagonism had beneficial effects on renal function in experimental endotoxemia in rats and dogs (75).

Clinical Studies. In patients with sepsis, cyclooxygenase inhibition with ibuprofen reduced the synthesis of thromboxane and prostacyclin, but it had no effect on the development of shock or renal failure and did not improve survival (76). Clinical studies with selective thromboxane or leukotriene inhibitors have not been performed.

Conclusion. Cyclooxygenase inhibition is expected to decrease both vasodilatory and vasoconstrictive derivatives of arachidonic acid metabolism. As vasodilatory prostaglandins may be important to maintain RBF by opposing the vasoconstrictive influences, the failure of ibuprofen to improve renal
function in sepsis is not surprising. In the absence of clinical studies with selective thromboxane or leukotriene inhibitors, no meaningful conclusions on their potential benefit can be drawn.

Natriuretic Peptides

**Rationale.** Atrial natriuretic peptide (ANP), a hormone synthesized in the cardiac atria, increases GFR through vaso-dilatation of the afferent arterioles and vasoconstriction of the efferent arterioles, inhibits reabsorption of sodium, and redistributes renal medullary blood flow, resulting in an improved supply and reduced demand of oxygen in the tubules. Urodilatin is synthesized in the renal tubular cells by differential processing from the same precursor as ANP and has similar biologic effects. Plasma ANP levels rise during endotoxic shock in the rat, resulting in an increased diuresis and natriuresis (80).

**Experimental Studies.** Exogenous administration of ANP increased RBF, GFR, and diuresis and improved renal pathology in different experimental models of ischemic ARF (81). In LPS-induced ARF in the rat, urodilatin induced a fall in BP but increased GFR, diuresis, and natriuresis (82). In contrast, ANP did not affect these parameters in a similar model of endotoxia in the rat (83).

**Clinical Studies.** In a noncontrolled study of 11 patients who developed ARF after cardiac surgery, long-term (>48 h) ANP infusion improved RBF and GFR (84). An open-label study of 53 patients with ARF showed that patients receiving ANP had transient increases in creatinine clearance during the infusion of the peptide (24-h) and a decreased need for dialysis as compared with control patients (85). In contrast, in a randomized placebo-controlled trial including 504 critically ill patients with ARF (31% with sepsis), a 24-h infusion of the synthetic ANP anaritide did not improve the overall rate of dialysis-free survival (81). A subgroup analysis indicated that anaritide improved dialysis-free survival rate in oliguric patients by reducing the need for dialysis but not by lowering mortality. In non-oliguric patients, however, anaritide worsened dialysis-free survival. To further examine the potential benefit of anaritide in oliguric patients, a randomized placebo-controlled trial was conducted in 222 oliguric ARF patients (35% with sepsis) (86). Anaritide (24-h) conferred a nonsignificant trend toward improved 14-d and 21-d dialysis-free survival, but 60-d mortality rates were similar to placebo. The study was criticized for administering anaritide too late, too shortly, and at an excessive dose, the latter leading to hypotension and jeopardizing renal perfusion. In two randomized placebo-controlled trials in critically ill patients with ARF, a long-term (>96 h and 5-d, respectively) infusion of urodilatine did not improve renal function or reduce the need for renal replacement therapy (87–88).

**Conclusion.** There is no convincing evidence to support the use of natriuretic peptides as adjunctive treatment in ARF.

Inhibition of Leukocyte Adhesion

**Rationale.** The recruitment of circulating leukocytes into a tissue is directed by specific adhesive interactions between the leukocyte and the vascular endothelium. Selectins (L-, P-, and E-selectin) and their carbohydrate-containing ligands mediate the initial contact between the leukocyte and the endothelium, the so-called “rolling,” facilitating exposure to tissue-derived chemokines and other activating stimuli. Firm adherence and transendothelial migration are mediated by interactions between integrins on the leukocyte surface (e.g., CD11a, CD11b) and their Ig-like receptors on the endothelium (e.g. ICAM-1). Renal ICAM-1 mRNA levels are increased after ischemia-reperfusion in the mouse (89). TNF-α upregulates renal E- and P-selectin and ICAM-1 expression. TNFR1−/− mice had fewer neutrophils infiltrating the kidney after LPS exposure than wild-type mice (44). Perfusion of isolated kidneys with neutrophils and LPS (90) or perfusion of ischemic kidneys with activated neutrophils (91) caused renal dysfunction that was prevented with a neutrophil elastase inhibitor and a free radical scavenger. Conversely, neutrophil-depleted animals were protected against ischemic renal failure (89). Taken together, these observations suggest during sepsis and ischemia leukocytes infiltrate the kidneys, resulting in renal dysfunction, and provide a rationale for the inhibition of leukocyte recruitment in these settings.

**Experimental Studies.** Treatment of experimental animals with anti-ICAM-1 antibodies (89,92) or with antisense oligonucleotides for ICAM-1 (93) provided protection from ischemic ARF. ICAM-1 knockout mice appeared resistant to acute renal ischemic injury (89). Similarly, anti-CD11a and anti-CD11b antibodies decreased injury after experimental renal ischemia in the rat (94). Furthermore, mice deficient for the Src-family kinases Hck and Fgr, required for integrin signal transduction, were resistant to the lethal effects of LPS-injection and had a marked reduction in renal damage (95). SialylLewis X, a soluble ligand for selectins, and an anti-P-selectin antibody attenuated renal dysfunction and histopathologic changes in LPS-induced ARF in rabbits (96). Finally, E-, P-, and E/P-selectin knockout mice were resistant to lethality and renal dysfunction during septic peritonitis (97).

**Clinical Studies.** No results from human trials with antibodies to leukocyte adhesion molecules are available.

**Conclusion.** Inhibition of adhesion molecules on leukocytes or endothelial cells substantially ameliorated the functional and histologic injury associated with experimental ischemic or septic ARF. Several mechanisms may be operative in leukocyte-mediated renal injury. Leukocytes release reactive oxygen species and enzymes that may directly injure cells. The production of cytokines attracts additional inflammatory cells and upregulates adhesion molecules, creating a cycle of injury. Release of vasoconstrictor arachidonic acid metabolites, as well as physical congestion of medullary capillaries, contributes to persistent hypoxia. Inhibition of leukocyte recruitment is a potential promising approach in the treatment of septic ARF, but data in humans are required before relevant conclusions can be drawn.

Inhibitors of Coagulation

**Rationale.** Disseminated intravascular coagulation is common in septic patients and is associated with an adverse prognosis. It is characterized by a generalized activation of the coagulation cascade, resulting in the intravascular formation of
fibrin clots and endothelial damage. Impaired tissue blood supply contributes to organ dysfunction, including ARF.

The enhanced fibrin formation is caused by tissue factor-mediated thrombin generation. In addition, natural inhibitors of coagulation, including antithrombin III and the protein C–protein S system, as well as the fibrinolytic system, are deficient in sepsis. Several agents that block coagulation at different levels have been evaluated as adjunctive therapy in sepsis (51).

**Tissue Factor Pathway Inhibitor.** Tissue factor forms a complex with factor VIIa, which cleaves factor IX and factor X, initiating thrombin generation. Tissue factor is inhibited by a natural anticoagulant, tissue factor pathway inhibitor (TFPI). Specific blockade of the tissue factor–factor VIIa complex, with either TFPI or a site-inactivated factor VIIa, prevented renal injury during *Escherichia coli* sepsis in baboons. Fibrin deposition in glomeruli and tubuli and vessels occluded by fibrin clots were identified in control animals but were absent in treated animals (98). A phase II trial comparing placebo and recombinant TFPI in 210 patients severe sepsis showed a trend toward mortality reduction in the recombinant TFPI-treated group (51). However, a recently completed phase III trial failed to demonstrate a benefit of TFPI in patients with severe sepsis or septic shock (99).

**Antithrombin.** Antithrombin blocks several proteases involved in coagulation, but its inhibitory effect is most powerful against factor Xa and thrombin. Plasma levels of antithrombin are usually markedly reduced in patients with sepsis, which is associated with an increased mortality (100). Melagatan, a low–molecular weight thrombin inhibitor, protected against renal dysfunction in a porcine model of endotoxemia (101). A meta-analysis, aggregating data from 122 patients with sepsis supplemented with antithrombin, reported a 22% nonsignificant decrease in mortality in the treated patients (102). However, in a double-blind, placebo-controlled multicenter trial in 2314 patients with severe sepsis and septic shock, high-dose antithrombin had no effect on 28-d mortality and was associated with an increased risk of hemorrhage when co-administered with heparin (100). In a predefined subgroup of patients not receiving heparin, there was a trend toward a reduced 28-d and 90-d mortality (100).

**Activated Protein C.** Protein C is activated by the thrombin-thrombomodulin complex on endothelial cells. Activated protein C inhibits thrombin generation by inactivating factor Va and factor VIIIa. Besides its effects on coagulation, activated protein C has direct antiinflammatory properties, including impairment of leukocyte adhesion to the endothelium by binding selectins and inhibition of the production of inflammatory cytokines by monocytes. Furthermore, it stimulates the fibrinolytic response by inhibiting plasminogen-activator inhibitor type 1 (103). Reduced levels of protein C are found in patients with sepsis and are associated with a fatal outcome (103). The species specificity of activated protein C has limited its testing as a treatment for sepsis to studies in baboons. In these animals, administration of activated protein C prevented the procoagulant and lethal effects of Gram-negative sepsis (104). In a randomized, multicenter trial conducted in 1690 patients with severe sepsis, recombinant human activated protein C significantly reduced mortality (103). Its efficacy was most apparent in the most seriously ill patients, as assessed by the APACHE II score, the number of failing organs and the presence of shock (99). Activated protein C also decreased interleukin-6 levels, a finding consistent with its known antiinflammatory activity (103).

**Conclusion.** An intense and complex crosstalk exists between the pro-inflammatory, coagulation, and fibrinolytic networks that likely plays a germane role in organ damage in sepsis. Several strategies to inhibit coagulation have been evaluated as adjunctive therapies in sepsis, but only the administration of activated protein C has proved successful. The success of activated protein C may hinge on its combined effects on coagulation, fibrinolysis, and inflammation, rather than its anticoagulant action alone. Activated protein C is currently the first biologic agent approved by the FDA for the treatment of sepsis (99). As the benefit of activated protein C consistently increased with the risk of death, the FDA has restricted its use to patients with an APACHE score of 25 or more, until further data are available (99). In Europe, activated protein C will be approved for patients with sepsis and more than two failing organs (M. Bourgeois, personal communication).

**Growth Factors**

**Rationale.** The recovery from ARF depends on the ability of tubular cells to regenerate and restore the continuity of the tubular epithelium. This phenomenon requires the participation of growth factors, which stimulate cellular migration and proliferation and promote tubulogenesis. Epidermal growth factor (EGF) and insulin-like growth factor I (IGF-I) are known mitogens for tubular epithelial cells. The expression of EGF and IGF-I and their receptors are increased after experimental renal injury. Exogenous administration of these growth factors in ARF may thus accelerate renal epithelial regeneration and speed the time to recovery of renal function. In addition, IGF-I is a downstream mediator of growth hormone (GH) and has potent anabolic effects. Increased protein catabolism and a negative nitrogen balance are characteristic features of critically ill patients with ARF that are partly attributable to GH resistance with low IGF-I levels. These considerations provide a rationale for the use of EGF, IGF-I, or GH in the treatment of ARF in critically ill patients.

**Experimental Studies.** In rat models of renal ischemia, EGF (105) and IGF-I (106–107) buttressed the recovery of renal function and reduced mortality. While IGF-I is known to increase RBF (106), the beneficial effects were due to an accelerated regeneration of tubular epithelial cells, resulting from a rapid repopulation of cellular ATP levels, a reduction in the incidence of apoptosis and an increased mitogenesis (107). In addition, IGF-I reduced protein catabolism and stimulated protein synthesis in skeletal muscle (106). In contrast to the beneficial effects in rat models, EGF failed to affect renal ischemic injury in the pig, a model of ARF that more closely resembles the human condition (108). In fact, animals treated with EGF had higher serum creatinine levels than the control group (108).

**Clinical Studies.** In a multicenter randomized placebo-controlled trial, IGF-I did not reduce time to renal recovery or
activated protein C, by virtue of its combined actions on the development of multitargeted interventions. The success of intervention may lose their efficacy later on. Finally, the therapeutic strategies that are appropriate early in the disease process may differ from those that are appropriate later. It is important to note that growth factors and ARF are dynamic processes and the relative role of the different mediators varies with time. Consequently, pharmacologic interventions that are effective in ameliorating ARF in animal models may not be effective in human patients. In addition, sepsis and ARF are not just a single disease but rather a spectrum of diseases with different underlying pathophysiologic mechanisms.

**Conclusion.** Despite ample evidence that growth factors accelerate renal recovery in experimental ARF in the rat, a study in a large animal model more representative for human ARF as well as several clinical studies in critically ill patients demonstrate no beneficial or even detrimental effects.

**Conclusion.** The conclusion of this overview on the potential treatments of ARF in critically ill patients with sepsis is gloomy. Several decades of research efforts have been successful in unraveling the complex pathophysiology of sepsis and ARF and have resulted in the development of different pharmacologic interventions that are effective in ameliorating experimental ARF but have failed to come up with a treatment that works in humans. Several possible explanations for this discrepancy have been forwarded. The most important is perhaps the failure of animal models to reproduce human disease. Renal artery occlusion in the rat is not a good model for human acute tubular necrosis, as the importance of hemodynamic factors may be overestimated. Furthermore, many endotoxemic models do not mimic the hyperdynamic state associated with human sepsis. Large animal models such as the pig may be more appropriate. In this respect, it is important to note that growth factors reported to accelerate renal recovery in the rat, failed to provide benefit in both pigs and humans. Second, ARF in critically ill patients is notoriously heterogeneous, resulting from a combination of sepsis, ischemia, nephrotoxic drugs, and radiocontrast agents. Some investigators have therefore stressed the need to combine insults in animal models. A third obvious problem is the timing of intervention. Experimental studies usually administer the drug before the renal insult, a convenience not often encountered in critically ill patients. In addition, sepsis and ARF are dynamic processes and the relative role of the different mediators varies with time. Consequently, therapeutic strategies that are appropriate early in the disease process may lose their efficacy later on. Finally, the complex and multifactorial nature of septic ARF may require the development of multitargeted interventions. The success of activated protein C, by virtue of its combined actions on the inflammatory, coagulation, and fibrinolytic cascades, clearly illustrates this point.

**Dialytic Treatment.** A comprehensive discussion of all aspects of dialytic treatment in ARF, including timing of initiation, dose of dialysis, adequacy measurements, and type of dialyzer membrane, is beyond the scope and space limitations of this report. Instead, two controversial issues of special relevance to the treatment of ARF in critically ill patients with sepsis will be highlighted: the choice of renal replacement modality and the concept of extracorporeal inflammatory mediator removal.

**Intermittent Hemodialysis (IHD) Versus Continuous Renal Replacement Therapy (CRRT).** For several years, the choice of renal replacement modality in ARF has engendered controversy. The theoretical advantages and disadvantages of both CRRT and IHD have been listed numerous times and will not be repeated here. An important potential benefit of CRRT is its better hemodynamic tolerance, due to a more gradual fluid and solute removal. Although CRRT is empirically felt to induce less hemodynamic instability than IHD in critically ill patients, this contention is not supported by firm evidence. A randomized crossover trial compared 24-h continuous arteriovenous hemofiltration with a 24-h period encompassing a 4-h IHD session in 27 critically ill patients and found no difference in the incidence of BP drops and vasopressor requirements. Another trial randomized 30 patients with septic shock to either continuous venovenous hemofiltration (CVVH) or IHD (114). CVVH induced a mild increase in systemic vascular resistance and a decrease in cardiac output, but splanchic regional perfusion parameters were not different between the groups. The hemodynamic changes appeared to be related to a fall in core temperature. Indeed, the heat loss that occurs during CRRT may result in mild hypothermia with an increase in systemic vascular resistance and venous tone and thus provide an alternative explanation for the reported laudable hemodynamic effects of CRRT. It should be noted that the hemodynamic tolerance of IHD in critically ill patients was substantially improved after implementation of guidelines derived from chronic hemodialysis, including dialysate sodium modeling, ultrafiltration profiling, and cooling of dialysate.

Several studies have attempted to address the question of whether the choice of renal replacement modality affects patient outcome. A recent meta-analysis of 13 studies published between 1977 and 1998 including 1400 patients treated with either IHD or CRRT, found no difference in mortality between both techniques (117). After adjustment for study quality and severity of illness, mortality was lower in patients treated with CRRT. Due to methodologic limitations, however, no firm conclusions could be drawn. Two large observational studies including 349 (118) and 587 (119) patients reported higher crude mortality rates with CRRT than with IHD, because patients with an adverse prognosis were more likely to receive CRRT. After adjust-
ment for severity of illness, choice of renal replacement modality had no bearing on outcome (118–119). Only two randomized trials comparing IHD with CRRT have been published, one of which in abstract form only (120–121). The first, performed in 166 patients, excluded subjects with a mean arterial pressure below 70 mmHg. ICU mortality was significantly higher in the IHD group, but severity of illness was not evenly distributed, with more nonrenal disease in patients randomized to CRRT (120). The second randomized patients with a mean arterial pressure as low as 50 mmHg and found no difference in outcome between IHD and CRRT (121). Of note is the important crossover in both trials: 18% and 15% crossed over from IHD to CRRT and 20% and 20% crossed over from CRRT to IHD, respectively (120–121).

In conclusion, although physicians intuitively prefer CRRT to IHD in critically ill patients with severe fluid overload and cardiovascular instability, there is no conclusive evidence to support the superiority of either technique. Comparative studies were either methodologically flawed or showed no differences in outcome. As for today, a reasonable approach is to choose a technique according to individual patient characteristics, nursing proficiency, and technical resources. The high crossover from one modality to another indicates that IHD and CRRT should be regarded as complementary, rather than competitive, techniques in the care of the critically ill patient with ARF.

Two recently developed modifications of standard dialysis techniques deserve further attention: high-volume hemofiltration (HVHF) and extended daily dialysis (EDD). HVHF is an adaptation of CVVH, using ultrafiltration rates of 2 to 4 L/h. A prospective cohort analysis of 306 patients treated with HVHF found a lower observed mortality rate than that predicted by illness severity scores (122). A randomized trial in 425 critically ill patients with ARF compared three different ultrafiltration rates: 20 ml/h per kg, 35 ml/h per kg, and 45 ml/h per kg. Survival in the first group (41%) was significantly lower than in the second (57%) and third (58%) group (123). In contrast, a randomized trial in 106 severely ill ventilated and oliguric patients found no difference in time to renal recovery or 28-d mortality between early started HVHF (48.2 ml/h per kg), early-started low-volume hemofiltration (20.1 ml/h per kg), and late-started low-volume hemofiltration (19.0 ml/h per kg) (124). EDD is a hybrid technique, designed to combine the theoretical advantages of IHD (flexibility of the dialysate composition, patient mobility, low cost) and of CRRT (better hemodynamic tolerance) (125–127). Dialysis with standard IHD equipment is performed daily over an extended treatment time, using low dialysate and blood flow rates. Preliminary experience has been promising (125–127), but the technique has not been prospectively compared with other renal replacement modalities. In conclusion, HVHF and EDD should be subject to the same criteria for acceptance as any new technique or agent seeking approval for clinical use, that is a randomized controlled comparison with standard techniques. Their generalized use can, therefore, at present not be recommended.

### Extracorporeal Inflammatory Mediator Removal

The failure of the anti-cytokine strategies has fueled the conviction that nonspecific elimination of humoral mediators of the inflammatory response with CRRT could be an adjunctive treatment option in septic patients. This contention rests heavily on the assumptions that (1) cytokines can be effectively removed by these techniques; and (2) nonselective mediator removal from the systemic circulation is beneficial for patients. Despite of numerous studies, neither assumption has been supported by convincing evidence (128–129). Several studies reported elimination of inflammatory mediators with CRRT (128). A detailed quantitative analysis revealed that cytokines were mainly removed by adsorption, but that ongoing adsorption was limited by a rapid saturation of the dialyzer membrane (130) (Figure 1). Despite evidence for convective, diffusive, or adsorptive removal, most studies do not show a significant and sustained effect on cytokine plasma concentrations with CRRT (128). Furthermore, equivalent removal rates of inflammatory cytokines and inhibitors of inflammation have been reported (130). Whether simultaneous elimination of anti-inflammatory cytokines may abrogate the potential benefits of inflammatory mediator removal remains moot.

Taking into account the high endogenous turnover rates of inflammatory mediators, it has been calculated that an effective mass removal is only possible with a highly permeable membrane (sieving coefficient approximately 1), a high ultrafiltration rate (more than 2 L/h), and provided that the half-life of the substance is greater than 60 min (131). Several strategies to...
increase mediator removal are currently being evaluated, including combined plasma filtration with adsorption (CPFA) and HVHF.

CPFA uses a plasmafilter in series with a hydrophobic resin. The plasmafiltrate is circulated through the sorbent device and re-infused into the circulation. CPFA improved survival in a rabbit model of endotoxic shock (132). Ten patients with hyperdynamic septic shock were treated with 10-h CPFA or CVVH in random order (133). BP was higher and norepinephrine requirements were lower during CPFA. Although plasma TNF-α and interleukin-10 levels did not change during either treatment, ex vivo spontaneous and LPS-induced TNF-α production from patients whole blood increased over time with CPFA (133).

HVHF at a rate of 8 L/h (!) was associated with a temporary decrease in vasopressor requirements and a greater reduction in C3a and C5a concentrations compared with CVVH with an ultrafiltration rate of 1 L/h (134). It should be noted that the reduction in body temperature was larger during HVHF, although not to a significant extent (134). In a randomized trial of 24 patients with septic shock without renal dysfunction, early start of CVVH at an ultrafiltration rate of 2 L/h failed to affect the plasma concentrations of inflammatory mediators or any clinical outcome parameter (135). Combined use of a superflux hemofilter and ultrafiltration rates of 6 L/h was found to achieve high cytokine clearances in addition to a substantial loss of albumin (136). Cytokine plasma concentrations were, however, not reported (136).

In conclusion, assuming that effective clearance of humoral mediators of inflammation were achievable, it is far from clear which mediators should be removed at which time point and under which conditions this might be advantageous for the patient. The respective roles of inflammatory mediators and counter-regulatory antiinflammatory systems and their dynamics during the course of sepsis are insufficiently clarified. It appears non-sequitur to restore the endogenous TNF-α production by leukocytes with CPFA (133) in the same patients who may be considered for treatment with anti-TNF-α molecules (41). In addition, any attempt to substantially increase nonspecific mediator removal will almost certainly deplete valuable nutrients, albumin, hormones, vitamins, trace elements, and antibiotics, with potential detrimental effects for the patient.

**Conclusion**

Unfortunately, treatment of ARF in sepsis is as yet exclusively supportive. Thousands of patients have been randomized in industry-sponsored trials of sophisticated pharmacologic therapies, yielding very little or no tangible results, with the exception of activated protein C. In sharp contrast, clear guidelines on basic therapeutic attitudes such as the optimal fluid resuscitation regimen, use of diuretics, dose of dialysis, and timing of initiation of dialysis are still lacking. As these issues continue to be mooted, we should urgently call on public resources to support trials to clarify these questions. Governments should be convinced that any significant advance in the treatment of ARF will save money and, most importantly, patient’s lives.

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