Med Intensiva. 2011;35(7):424–432

medicina intensiva

www.elsevier.es/medintensiva

REVIEW

Physiopathology of acute renal failure during sepsis☆

T. Regueira[a,*], M. Andresen[a], M. Mercado[a], P. Downey[b]

[a] *Departamento de Medicina Intensiva, Hospital Clínico Universidad Católica de Chile, Pontificia Universidad Católica de Chile, Santiago, Chile*
[b] *Departamento de Nefrología, Hospital Clínico Universidad Católica de Chile, Pontificia Universidad Católica de Chile, Santiago, Chile*

Received 9 December 2010; accepted 24 March 2011

KEYWORDS
Sepsis;
Acute renal failure;
Renal blood flow

Abstract Acute renal failure (ARF) is an independent risk factor associated with increased mortality during sepsis. Recent consensus definitions have allowed the standardization of research on the subject. The understanding of the physiopathology of ARF during sepsis is limited by the scarcity of histological studies and the inability to measure renal microcirculatory flows. Historically, ARF during sepsis has been considered to be a consequence of diminished renal blood flow (RBF). Indeed, in early stages of sepsis or in sepsis associated to cardiogenic shock, RBF may decrease. However, recent studies have shown that in resuscitated sepsis, in which cardiac output is characteristically normal or even elevated and there is systemic vasodilatation, RBF is normal or even increased, with no associated histological evidence of significant tubular necrosis. Thus, other factors may participate in the genesis of ARF in sepsis. These include apoptosis, glomerular and medullary microcirculatory disorders, cell changes in response to the pro-inflammatory cascade characteristic of sepsis, oxidative stress, mitochondrial dysfunction and damage induced by mechanical ventilation, among others. Sepsis-associated ARF treatment is supportive. In general, renal replacement therapies can be grouped as intermittent or continuous, and as those whose primary objective is the replacement of impaired renal function, versus those whose main objective is to secure hemodynamic stability through the clearing of pro-inflammatory mediators.

PALABRAS CLAVE
Sepsis;
Insuficiencia renal aguda;
Flujo sanguíneo renal

Fisiopatología de la insuficiencia renal aguda durante la sepsis

Resumen La insuficiencia renal aguda (IRA) es un factor de riesgo independiente asociado a mayor mortalidad durante la sepsis. Definiciones de consenso recientes han permitido estandarizar los trabajos de investigación en el tema. La comprensión de la fisiopatología de la IRA durante la sepsis está limitada por la escasez de estudios histológicos y por la

☆ Please cite this article as: Regueira T, et al. Fisiopatología de la insuficiencia renal aguda durante la sepsis. Med Intensiva. 2011;35:424–32.

* Corresponding author.
E-mail address: regueira@med.puc.cl (T. Regueira).

2173-5727/$ – see front matter

imposibilidad de medir los flujos microcirculatorios renales. Históricamente se ha considerado a la IRA séptica como una patología dependiente de la caída del flujo sanguíneo renal (FSR). Efectivamente, en las etapas precoces de la sepsis o en la sepsis acompañada de shock cardiogénico existe compromiso del FSR; sin embargo, estudios recientes han demostrado que en la sepsis reanimada, aquella en que característicamente se observa un gasto cardiaco normal o alto y vasodilatación sistémica, el FSR es normal o incluso aumentado y no existe evidencia histológica significativa de necrosis tubular. Otros factores, distintos al puramente hemodinámico, participan en la génesis de la IRA en la sepsis. Entre éstos están la apoptosis celular, los trastornos microcirculatorios glomerulares y medulares, los cambios celulares en respuestas a la cascada proinflamatoria propia de la sepsis, el estrés oxidativo, la disfunción mitocondrial y el daño a distancia inducido por ventilación mecánica, entre otros. En la actualidad, el tratamiento de la IRA en la sepsis es de soporte. En general, las terapias de reemplazo renal pueden ser clasificadas como intermitentes o continuas, y en las que buscan primariamente el reemplazo de la función renal deteriorada, frente a aquellas cuyo objetivo principal es lograr la estabilidad hemodinámica de los pacientes mediante la remoción de mediadores proinflamatorios.

Epidemiology

The incidence of acute renal failure (ARF) in critical patients is variable, depending on the definition used and the population studied, but ranges from 30 to 50%.[1] Sepsis and its most severe presentation, septic shock, are the main causes of ARF in the Intensive Care Unit (ICU), accounting for up to 50% of all cases.[2] Mortality due to sepsis remains high, particularly when associated to organ dysfunction such as ARF (with mortality rates of 20–35%) or in the presence of hemodynamic alterations (mean mortality 60%). The development of ARF during sepsis is an independent risk factor associated to increased patient mortality[2]; in this context, the FRAMI study, involving 43 Spanish ICUs, showed the appearance of ARF in critical patients to be independently associated to increased mortality, with an odds ratio (OR) of 2.51.[3]

Definition

Until recently there was no clear consensus-based definition of ARF in sepsis. The ADQI (Acute Dialysis Quality Initiative) group has proposed a consensus-based diagnostic classification that has been favorably viewed by clinicians, and has made it possible to standardize research work in this field.[4] The mentioned classification is known as the RIFLE (in reference to Risk, Injury, Failure, Loss, and End-stage renal failure) (Table 1). Patients are classified according to the loss of glomerular filtration (GF) (with respect to the baseline reference of each patient) and/or urinary flow (UF) into 5 categories (selecting the criterion yielding the poorest classification): risk (R), injury (I), failure (F), loss (L) or end-stage renal failure (E). ARF in sepsis is diagnosed in all patients meeting the criteria of sepsis,[5] meeting some of the RIFLE criteria, and lacking other conditions or causes capable of accounting for ARF, such as the use of contrast media or nephrotoxic drugs.

The RIFLE classification has been validated by a number of studies. In a study involving 20,126 patients admitted to a university hospital, 10%, 5% and 3.5% of the subjects reached the maximum R, I and F scores in the RIFLE classification, respectively. Mortality among the patients increased linearly with the severity of the RIFLE score, making it possible to independently predict mortality.[6] Another study involving 41,972 patients admitted to the ICU reported an ARF incidence of 35.8%. The mortality in the group without ARF was 8.4%, versus 20.9%, 45.6% and 56.8% in those with class R, I and F acute renal failure, respectively. The presence of ARF of any category was found to be an independent mortality risk factor.

With the purpose of improving sensitivity, the RIFLE criteria were modified by the Acute Kidney Injury Network (AKIN) group, which defined ARF as an increase in serum creatinine of $\geq$0.3 mg/dl or a percentage increase of $\geq$1.5 times from baseline as recorded in the previous 48 h (Table 2).[7] Urine output as a criterion of ARF was maintained, though the glomerular filtration rate and RIFLE L and E scores were excluded. AKIN, in contrast to RIFLE, requires two creatinine measurements spaced 48 h apart in order to establish a diagnosis of ARF.

Some authors have compared RIFLE versus AKIN in patients subjected to heart surgery[8] or admitted to the ICU.[9] In general, mortality is comparable with both methods and tends to increase with the severity of ARF–thus confirming that acute renal damage is correlated to patient mortality.

Pathogenesis

The study of the mechanisms involved in the development of ARF in sepsis is limited by the few histological studies in humans, due to the risk involved in the process and its frequently irreversible nature, and by the impossibility of measuring renal microcirculatory flow values.

Renal blood flow in sepsis

The classical position in septic patients is that the principal mechanism underlying ARF is ischemia or hypoperfusion–suggesting that the decrease in renal blood flow (RBF) and renal vasoconstriction are the characteristic events of sepsis. Furthermore, the main interventions for the management of ARF in sepsis have been volume replacement in already resuscitated patients,[10] and the use of renal

Table 1 RIFLE criteria for classifying acute renal dysfunction.

Category	GF criteria	UF criteria	
Risk	↑ Creatinine × 1.5 or GF decreased >25%	UF < 0.5 ml/kg/h × 6 h	
Injury	↑ Creatinine × 2 or GF decreased >50%	UF < 0.5 ml/kg/h × 12 h	
Failure	↑ Creatinine × 3 or GF decreased >75% or ARF over CRF: creatinine >4 mg/dl with acute ↑ ≥0.5 mg/dl	UF < 0.3 ml/kg/h × 24 h or anuria × 12 h	High sensitivity High specificity
Loss	Persistent ARF = complete renal function loss >4 weeks		
ESKD (CRF)	End-stage renal failure (>3 months)		

GF: glomerular filtrate; UF: urinary flow; ARF: acute renal failure; CRF: chronic renal failure; ESKD: end-stage kidney disease.

vasodilators such as dopamine and fenoldapam–though there is little evidence of their usefulness.[11]

In effect, the physiopathological processes inherent to sepsis, such as absolute and relative hypovolemia due to vasoplegia (pathological vasodilatation) and capillary leakage, myocardial dysfunction and impaired oxygenation, among other aspects, suggest that decreased oxygen transportation may be a relevant mechanism in ARF–mainly in the early stages or in sepsis accompanied by cardiogenic shock. However, most studies suggesting an ischemic etiology for ARF in sepsis are derived from animal models of ischemia and reperfusion.[12,13] These models are not consistent with the classical physiopathology of resuscitated sepsis, characterized by high cardiac output (CO) and low peripheral resistance.

The study of RBF in human sepsis is complex, due to the difficulty of measuring it on a continuous basis. Studies in septic animals have yielded contradictory results in relation to RBF. Some studies indicate that during the early phases of sepsis, or after a bolus dose of endotoxin, RBF decreases.[14,15] These models of endotoxemia induce an initial proinflammatory state that is not found in true sepsis, where the increase in inflammatory mediators is gradual rather than explosive as in the mentioned models.[16] Other more recent studies underscore the fact that under normal conditions, RBF is several times greater than that required by the actual renal metabolic needs – since RBF is destined more to glomerular filtration than to renal oxygen transport. These studies show that in resuscitated sepsis, i.e., where a normal or high cardiac output and systemic vasodilatation are characteristically observed, RBF is normal or even increased.[17,18]

A study involving a porcine model of hyperdynamic sepsis found RBF to be generally increased, and particularly increased towards the renal medulla.[19] Another study in 8 septic patients in which RBF was estimated invasively via thermodilution showed ARF to develop in the absence of alterations in RBF.[20] A systematic review of 160 experimental studies of sepsis and ARF found the principal determinant factor of the normality of RBF in sepsis to be cardiac output (CO). A high or normal CO is associated to preserved RBF, while a low CO–i.e., non-resuscitated sepsis or sepsis associated to cardiogenic shock–is associated to low RBF.[18]

Thus, even though renal hypoperfusion may play a role in low-flow states such as non-resuscitated sepsis, recent studies show that once the hyperdynamic state characteristic of sepsis has been established, hypoperfusion or renal ischemia are not relevant mechanisms.[17]

Renal histology in sepsis

The renal histological changes observed in sepsis are few and nonspecific.[15] A systematic review found only 22% of 184 patients to show evidence of acute tubular necrosis (ATN), and concluded that the existing experimental and human clinical evidence does not support the idea of ATN as the manifestation or mechanism characteristic of septic ARF.[21] The histology of septic ARF is heterogeneous–relevant findings being leukocyte infiltration (predominantly mononuclear cells), some degree of tubular cell vacuolization, loss of the brush border, and apoptosis.[22,23] Other described alterations are dysfunction of the intercellular tight junctions, favoring tubular fluid

Table 2 AKIN criteria for classifying acute renal dysfunction.

Category	Serum creatinine criterion	Urine flow criterion
1	↑ Serum creatinine ≥0.3 mg/dl or ↑ ≥150–200% (1.5–2 times) from baseline level[a]	UF < 0.5 ml/kg/h × >6 h
2	↑ Serum creatinine >200–300% (>2–3 times) from baseline level[a]	UF < 0.5 ml/kg/h × >12 h
3	↑ Serum creatinine >300% (>3 times) from baseline level[a] or serum creatinine ≥4.0 mg/dl with sharp ↑ of at least 0.5 mg/dl	UF < 0.3 ml/kg/h × >24 h or anuria × 12 h

Only one criterion (creatinine or UF) needs to be met to classify a patient. Those receiving renal replacement therapy (RRT) are considered in category 3, independently of the stage in which they are at the time of starting RRT. Categories 1, 2 and 3 correspond to R, I and F of the RIFLE classification, respectively.

[a] AKIN requires two creatinine measurements spaced 48 h apart–the first being the baseline value.

reflux through the epithelium,[24] and dysfunction of the basal membrane–with the consequent detachment of cells into the tubular lumen. This in turn is associated to the appearance of tubular cells or cylinders in the urine sediment. These cellular cylinders produce micro-obstruction of tubular urinary flow (UF), with cessation of GF in the affected nephron unit. The absence of necrosis in 70% of the patients is compatible with the existing evidence that other mechanisms different from ischemia contribute to the development of ARF during sepsis.[8,10]

Apoptosis, or programmed cell death, which in contrast to necrosis does not induce local inflammation,[25] has been described as one of the physiopathological phenomena present during ARF in sepsis.[21,22,26] Apoptosis is observed in 2–3% of the tubular cells during sepsis, and is more frequent in the distal tubules.[22] Tumor necrosis factor-alpha (TNF-α) plays an important role in the induction of renal tubular apoptosis; however, the relevance of apoptosis as a mechanism of ARF *in vivo* remains the subject of study.

Glomerular filtration in sepsis

Since in most cases of sepsis cardiac output is either normal or elevated, RBF is seen to be normal. A recent study in septic sheep has shown that, in effect, RBF is elevated in association to hyperdynamic CO, though renal vascular resistance (RVR) is decreased, with a secondary reduction in glomerular filtration rate and an associated rise in plasma creatinine concentration.[27] The drop in RVR may be explained by an increase in nitric oxide (NO) release. The proinflammatory cascade induces expression of inducible nitric oxide synthetase (iNOS) in the renal medulla,[28] in the glomerular mesangial cells and in the endothelial cells of the renal blood vessels[28] – resulting in intense and prolonged NO release. On the other hand, the acidosis inherent to septic shock, and the decrease in ATP levels in the vascular smooth muscle cells, favor cellular hyperpolarization as a result of potassium release from the cell through ATP-dependent membrane potassium channels–this in turn contributing to renal vasodilatation through resistance to catecholamines and angiotensin II. Likewise, the recovery of renal function was associated to a recovery of RVR associated to a decrease in RBF. This study suggests that the loss of GF pressure regulation participates as a mechanism of ARF in sepsis, even in the presence of increased RBF.

Glomerular filtration pressure depends on the diameter of the afferent and efferent arterioles. Constriction of the afferent arteriole and/or vasodilatation of the efferent arteriole can give rise to reductions in GF and in UF. Afferent vasodilatation participates as a mechanism of ARF in sepsis, though the efferent arteriole plays an even greater role (hyperemic ARF)–generating a drop in GF and in UF. However, the lack of direct measurements of RBF in human sepsis limits the drawing of conclusions.

Intrarenal hemodynamics during sepsis

Despite preserved RBF in resuscitated sepsis, the intrarenal distribution of the blood flow may be altered, with a predominance of cortical flow over medullary blood flow–a situation known as ''corticomedullary redistribution'', and which is responsible for medullary hypoxia.[29] A recent study in animals established differentiated measurements of critical and medullary blood flow using intrarenal laser Doppler flowmetry during sepsis. Both flows remained stable, and the use of noradrenalin–an adrenergic vasoconstrictor–significantly increased the flow in both regions. This suggests that the compensation mechanisms are active during hyperdynamic sepsis.[30] There probably are modifications in intrarenal blood flow during sepsis, but the evidence suggests that the compensatory mechanisms are active, and that such modifications do not represent a predominant mechanism.

Inflammation and oxidative stress

Other mechanisms, apart from the hemodynamic mechanisms, also participate in the genesis of ARF in sepsis. The inflammatory response inherent to sepsis has been examined as a direct mechanism of ARF. Different mediators implicated in sepsis, together with the neuroendocrine response, participate in the pathogenesis of septic ARF.[31,32] The kidneys are particularly sensitive to mediator-induced damage. Both the mesangial cells and the tubular cells are able to express proinflammatory cytokines such as interleukin (IL)-1, IL-6 and TNF-α.[33] Both IL-1 and TNF-α have been found to act as inducers of ARF in sepsis.[34] Mice with TNF-α receptor deficiency are resistant to the development of endotoxin-mediated ARF, and exhibit less tubular apoptosis and lesser mononuclear cell infiltration.[35] However, the use of anti-TNF-α antibodies during sepsis has not been able to improve survival or prevent the development of ARF.[36]

The mechanisms proposed to explain how IL-1 and TNF-α produce ARF during sepsis include the induction of increased cytokine release, amplifying the inflammatory cascade; favoring of tissue factor expression, which promotes local thrombosis[37]; the induction of tubular cell apoptosis[38]; and principally the elevation of regional oxidative stress through an increased production of reactive oxygen species (ROS).

Oxidative stress in sepsis is related to an increase in the production of ROS, and to the concomitant reduction of antioxidant levels through either consumption or diminished intake.[39–41] The proinflammatory cascade induces the expression of iNOS in the renal medulla,[28] in the glomerular mesangial cells, and in the renal vascular endothelial cells[28]–with the consequent rise in NO levels during sepsis. NO has both beneficial and deleterious effects during sepsis. Baseline levels of NO are necessary to maintain RBF and intrarenal flow during sepsis, particularly at afferent arteriolar level,[28] and to favor cellular mitochondrial biogenesis (re-synthesis).[42,43] However, NO is also a free radical, and when produced in excess is able to inhibit the oxidative phosphorylation chain and reduce oxygen consumption.[44] NO, moreover, can interact with other ROS to form more toxic reactive species such as peroxynitrite,[45–47] which can cause damage to DNA, proteins and membranes–resulting in an increase in mitochondrial permeability.[48,49] Increased mitochondrial permeability is associated to a decrease in electrochemical gradient and in ATP synthesis, as well as to the activation of apoptosis pathways.[50] The intensity of

oxidative damage is correlated to the intensity of mitochondrial damage and to survival.[48,51] A number of studies, including one by our own group, have shown that there is not only an increase in ROS during sepsis but also a decrease in antioxidant levels, related to the intensity of the septic process.[52–55]

Coagulation and microcirculation

Sepsis is characterized by a prothrombotic and antifibrinolytic state,[56] and the associated microcirculatory dysfunction has been described as a relevant mechanism in the development of multiorgan failure in sepsis, with an association to mortality.[57] Endothelial dysfunction is induced by the inflammatory cascade, and is characterized by an increase in the expression of tissue factor–which in turn activates the coagulation cascade. At renal level, fibrin deposits have been described in the glomerular capillaries during sepsis, though a recent study has shown that renal arterial/arteriolar thrombosis is not frequent in sepsis, and is not associated to the presence of disseminated intravascular coagulation.[22]

Mitochondrial dysfunction

Mitochondrial dysfunction is described as the incapacity of the cell to maintain its metabolic functions despite adequate oxygen transport, due to the impossibility of using the available oxygen for ATP synthesis.[58] Briefly, mitochondria must couple the transport of energy-rich substrates to the generation of a transmembrane electrochemical gradient allowing the synthesis of ATP. In order for this process to be efficient, there must be adequate function of the oxidative phosphorylation complexes (complexes I–IV plus ATP synthase),[59,60] structural integrity of the mitochondrial membrane (fundamentally the internal membrane),[61,62] a sufficient substrate supply,[63,64] and a sufficient number of mitochondria.[65,66] Few studies have evaluated cell function in septic ARF. Based on the continuous perfusion of lipopolysaccharide (LPS), one study observed no alterations in renal mitochondrial function,[67] though a more recent study in pigs with sepsis of intraabdominal origin reported an alteration in renal mitochondrial function, associated to an increase in oxidative stress marker levels.[68]

Distant damage caused by mechanical ventilation

The use of small tidal volumes (TV) (6 ml/kg ideal weight) in mechanical ventilation (MV) during acute respiratory distress syndrome (ARDS) reduces mortality among these patients.[69] One of the mechanisms proposed for explaining mortality associated to ARDS and MV is the release of systemic mediators generated at lung level in situations of high TV. An interesting study showed that animals ventilated with high TV values show greater tubular apoptosis and associated renal dysfunction. In fact, on cultivating renal cells *in vitro* with plasma from animals subjected to high TV, the cells likewise showed a higher apoptosis rate.[70]

Biomarkers in sepsis and ARF

The use of creatinine and UF for the diagnosis and prognosis of ARF during sepsis (RIFLE and AKIN criteria) poses several limitations. The rise in plasma creatinine is a late phenomenon, and in order for such an elevation to occur, it must be associated with an important decrease in GF capacity. The RIFLE classification does not clearly define the baseline value of patient renal function, in contrast to the AKIN classification, which requires the obtainment of two creatinine measurements spaced 48 h apart. On the other hand, UF as a diagnostic criterion of ARF is conditioned by patient volemia and the use of diuretics. Most studies included in the RIFLE and AKIN analyses are retrospective and did not measure UF every 6 or 12 h; accordingly, only 12% of them made use of both criteria (increase in creatinine and UF) for diagnosing ARF. The studies that used both criteria reported lesser mortality than those which used only creatinine as diagnostic criterion–this suggesting that the decrease in UF is more benign and/or reversible than the increase in creatinine.

The need to establish markers allowing an earlier and more sensitive diagnosis of ARF than creatinine elevation or a decrease in UF has led to the search for biomarkers of renal origin reflecting cellular damage in early stages of the disease.

Neutrophil gelatinase-associated lipocalin (NGAL) is a 24 kDa protein normally expressed in low concentrations in different human tissues (kidneys, lungs, stomach and colon), and is found in the secondary granules of neutrophils. NGAL is released when these cells are activated, particularly in response to bacterial infections. NGAL transcription and release is intensely induced in the presence of epithelial damage.

In ARF, NGAL is promptly released from the proximal renal tubules following ischemic[71] or toxic damage,[72] and its levels can be measured in plasma and urine. A recent review[73] involving over 4000 patients at risk of ARF due to sepsis, heart surgery, exposure to contrast media or transplantation, found NGAL to be significantly elevated in those individuals who develop ARF, and that this elevation significantly precedes the clinical diagnosis of ARF. Elevations in plasma and urine levels of NGAL have also been described in septic patients.[74] The plasma and urine concentrations of NGAL are correlated to the degree of renal dysfunction established by the RIFLE or AKIN.[75,76] However, a recent study suggests that urine NGAL elevation is a better predictor of ARF in sepsis than plasma NGAL elevation, which is less specific–possibly because of the activation of circulating neutrophils.[74]

Interleukin-18 is a proinflammatory cytokine transcribed and released in the proximal renal tubules, and which can easily be detected in urine following ischemic damage.[77] It does not appear to increase under conditions of infection, prerenal ARF or chronic renal failure. This marker was initially described in heart surgery patients in which IL-18 was seen to rise early before the clinical diagnosis of ARF, with an area under the curve (AUC-ROC) of 0.75.[78] IL-18 has also been described as a good predictor of ARF in critical patients in general, and in septic patients.[79]

KIM-1 (kidney injury molecule-1) is a transmembrane glycoprotein that shows a marked increase in expression on the

part of the cell of the proximal renal tubules in response to ischemic or toxic stimuli. Its concentrations can be detected in urine and are seen to increase in patients with ARF. This marker might be useful for predicting the need for dialysis or in-hospital mortality in patients with ARF of different origins and severity.[80]

Treatment

The limitations in establishing a physiopathological model of ARF have delayed the development of successful drug treatments, and at present much of the treatment of ARF in sepsis focuses on the support of kidney function. The management of ARF in septic patients is complicated, due to the existing hemodynamic instability and associated multiorgan dysfunction. As a result, in recent years many, both continuous and intermittent renal replacement therapy (RRT), techniques have been developed–though a lack of evidence in favor of one technique over the rest has largely precluded their clinical applicability.[81–85]

The different techniques developed are fundamentally based on two principles: diffusion and convection, or a combination of both. While diffusion techniques (hemodialysis) are preferentially used as non-antiinflammatory replacement therapy, and in hemodynamically stable patients, the convection techniques (hemofiltration) allow greater hemodynamic stability and the achievement of negative water balances, with lesser systemic repercussion.[86–88] However, more extended hemodialysis allows the replacement of renal function and the achievement of negative balances even in unstable patients. On the other hand, hemofiltration techniques not only allow renal support but also the possibility of modulating the inflammatory response through the removal of inflammatory compounds (cytokines) of greater molecular weight.[89,90] Hemofiltration with higher ultrafiltrate doses, referred to as high-volume hemofiltration (ultrafiltration rate >35 ml/kg/h), is mainly associated with a reduction in the need for vasopressors,[91–93] though some studies have also related it to improvements in microcirculation[94] and survival.[92]

However, although some studies suggest benefits from the use of continuous hemofiltration in hemodynamically unstable patients beyond those offered by intermittent hemodialysis techniques,[95] there is still not sufficient evidence of the superiority of continuous RRT over intermittent hemodialysis (IHD) in terms of mortality or the recovery of renal function.[96,97] The use of peritoneal dialysis is related to increased mortality, and thus is not recommended in ARF associated to sepsis.[98]

Conclusions

Acute renal failure associated to sepsis is frequent, and implies increased management complexity and mortality. A series of still poorly understood pathogenic mechanisms are involved–a fact that has limited the strategies for dealing with the disease. At present, renal support techniques make it possible to replace kidney function efficiently, and there is evidence that they can modulate the inflammatory response.

Financial support

Fondecyt 11100247 (Tomas Regueira).

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Ostermann M, Chang RW. Acute kidney injury in the intensive care unit according to RIFLE. Crit Care Med. 2007;35:1837–43 [quiz 1852].
2. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA. 2005;294:813–8.
3. Herrera-Gutierrez ME, Seller-Perez G, Maynar-Moliner J, Sanchez-Izquierdo-Riera JA. Epidemiology of acute kidney failure in Spanish ICU. Multicenter prospective study FRAMI. Med Intensiva. 2006;30:260–7.
4. Bellomo R, Ronco C, Kellum JA, Mehta Rl, Palevsky P. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8:R204–12.
5. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101:1644–55.
6. Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med. 2006;34:1913–7.
7. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11:R31.
8. Robert AM, Kramer RS, Dacey LJ, Charlesworth DC, Leavitt BJ, Helm RE, et al. Cardiac surgery-associated acute kidney injury: a comparison of two consensus criteria. Ann Thorac Surg. 2010;90:1939–43.
9. Joannidis M, Metnitz B, Bauer P, Schusterschitz N, Moreno R, Druml W, et al. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. Intensive Care Med. 2009;35:1692–702.
10. Regueira T, Andresen M. Management of oxygen delivery and consumption during sepsis. Rev Med Chil. 2010;138:233–42.
11. Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Lancet. 2000;356:2139–43.
12. Heyman SN, Lieberthal W, Rogiers P, Bonventre JV. Animal models of acute tubular necrosis. Curr Opin Crit Care. 2002;8:526–34.
13. Wan L, Bellomo R, Di Giantomasso D, Ronco C. The pathogenesis of septic acute renal failure. Curr Opin Crit Care. 2003;9:496–502.
14. Kikeri D, Pennell JP, Hwang KH, Jacob AI, Richman AV, Bourgoignie JJ. Endotoxemic acute renal failure in awake rats. Am J Physiol. 1986;250:F1098–106.
15. Badr KF, Kelley VE, Rennke HG, Brenner BM. Roles for thromboxane A2 and leukotrienes in endotoxin-induced acute renal failure. Kidney Int. 1986;30:474–80.

16. Zanotti-Cavazzoni SL, Goldfarb RD. Animal models of sepsis. Crit Care Clin. 2009;25:703–19, vii–viii.
17. Langenberg C, Bellomo R, May C, Wan L, Egi M, Morgera S. Renal blood flow in sepsis. Crit Care. 2005;9:R363–74.
18. Langenberg C, Wan L, Egi M, May CN, Bellomo R. Renal blood flow in experimental septic acute renal failure. Kidney Int. 2006;69:1996–2002.
19. Ravikant T, Lucas CE. Renal blood flow distribution in septic hyperdynamic pigs. J Surg Res. 1977;22:294–8.
20. Brenner M, Schaer GL, Mallory DL, Suffredini AF, Parrillo JE. Detection of renal blood flow abnormalities in septic and critically ill patients using a newly designed indwelling thermodilution renal vein catheter. Chest. 1990;98:170–9.
21. Langenberg C, Bagshaw SM, May CN, Bellomo R. The histopathology of septic acute kidney injury: a systematic review. Crit Care. 2008;12:R38.
22. Lerolle N, Nochy D, Guerot E, Bruneval P, Fagon JY, Diehl JL, et al. Histopathology of septic shock induced acute kidney injury: apoptosis and leukocytic infiltration. Intensive Care Med. 2010;36:471–8.
23. Doi K, Leelahavanichkul A, Yuen PS, Star RA. Animal models of sepsis and sepsis-induced kidney injury. J Clin Invest. 2009;119:2868–78.
24. Fink MP, Delude RL. Epithelial barrier dysfunction: a unifying theme to explain the pathogenesis of multiple organ dysfunction at the cellular level. Crit Care Clin. 2005;21:177–96.
25. Krown KA, Page MT, Nguyen C, Zechner D, Gutierrez V, Comstock KL, et al. Tumor necrosis factor alpha-induced apoptosis in cardiac myocytes. Involvement of the sphingolipid signaling cascade in cardiac cell death. J Clin Invest. 1996;98:2854–65.
26. Kaushal GP, Basnakian AG, Shah SV. Apoptotic pathways in ischemic acute renal failure. Kidney Int. 2004;66:500–6.
27. Langenberg C, Wan L, Egi M, May CN, Bellomo R. Renal blood flow and function during recovery from experimental septic acute kidney injury. Intensive Care Med. 2007;33:1614–8.
28. Spain DA, Wilson MA, Garrison RN. Nitric oxide synthase inhibition exacerbates sepsis-induced renal hypoperfusion. Surgery. 1994;116:322–30 [discussion 330–1].
29. Brezis M, Rosen S. Hypoxia of the renal medulla—its implications for disease. N Engl J Med. 1995;332:647–55.
30. Di Giantomasso D, Morimatsu H, May CN, Bellomo R. Intrarenal blood flow distribution in hyperdynamic septic shock: effect of norepinephrine. Crit Care Med. 2003;31:2509–13.
31. Abraham E. Neutrophils and acute lung injury. Crit Care Med. 2003;31:S195–9.
32. Marshall JC, Vincent JL, Fink MP, Cook DJ, Rubenfeld G, Foster D, et al. Measures, markers, and mediators: toward a staging system for clinical sepsis. A report of the Fifth Toronto Sepsis Roundtable. Crit Care Med. 2003;31:1560–7.
33. Camussi G, Ronco C, Montrucchio G, Piccoli G. Role of soluble mediators in sepsis and renal failure. Kidney Int Suppl. 1998;66:S38–42.
34. Knotek M, Rogachev B, Wang W, Ecder T, Melnikov V, Gengaro PE, et al. Endotoxemic renal failure in mice: role of tumor necrosis factor independent of inducible nitric oxide synthase. Kidney Int. 2001;59:2243–9.
35. Cunningham PN, Dyanov HM, Park P, Wang J, Newell KA, Quigg RJ. Acute renal failure in endotoxemia is caused by TNF acting directly on TNF receptor-1 in kidney. J Immunol. 2002;168:5817–23.
36. Rodriguez-Wilhelmi P, Montes R, Matsukawa A, Nariuchi H, Hurtado V, Montes M, et al. Tumor necrosis factor-alpha inhibition reduces CXCL-8 levels but fails to prevent fibrin generation and does not improve outcome in a rabbit model of endotoxic shock. J Lab Clin Med. 2003;141:257–64.
37. Thijs A, Thijs LG. Pathogenesis of renal failure in sepsis. Kidney Int Suppl. 1998;66:S34–7.
38. Messmer UK, Briner VA, Pfeilschifter J. Tumor necrosis factor-alpha and lipopolysaccharide induce apoptotic cell death in bovine glomerular endothelial cells. Kidney Int. 1999;55:2322–37.
39. Andresen HM, Regueira HT, Leighton F. Oxidative stress in critically ill patients. Rev Med Chil. 2006;134:649–56.
40. Wang W, Jittikanont S, Falk SA, Li P, Feng L, Gengaro PE, et al. Interaction among nitric oxide, reactive oxygen species, and antioxidants during endotoxemia-related acute renal failure. Am J Physiol Renal Physiol. 2003;284:F532–7.
41. Himmelfarb J, Mcmonagle E, Freedman S, Klenzak J, Mcmenamin E, Le P, et al. Oxidative stress is increased in critically ill patients with acute renal failure. J Am Soc Nephrol. 2004;15:2449–56.
42. Nisoli E, Clementi E, Paolucci C, Cozzi V, Tonello C, Sciorati C, et al. Mitochondrial biogenesis in mammals: the role of endogenous nitric oxide. Science. 2003;299:896–9.
43. Petros A, Lamb G, Leone A, Moncada S, Bennett D, Vallance P. Effects of a nitric oxide synthase inhibitor in humans with septic shock. Cardiovasc Res. 1994;28:34–9.
44. Radi R, Cassina A, Hodara R. Nitric oxide and peroxynitrite interactions with mitochondria. Biol Chem. 2002;383:401–9.
45. Kantrow SP, Taylor DE, Carraway MS, Piantadosi CA. Oxidative metabolism in rat hepatocytes and mitochondria during sepsis. Arch Biochem Biophys. 1997;345:278–88.
46. Unno N, Wang H, Menconi MJ, Tytgat SH, Larkin V, Smith M, et al. Inhibition of inducible nitric oxide synthase ameliorates endotoxin-induced gut mucosal barrier dysfunction in rats. Gastroenterology. 1997;113:1246–57.
47. Zingarelli B, Day BJ, Crapo JD, Salzman AL, Szabo C. The potential role of peroxynitrite in the vascular contractile and cellular energetic failure in endotoxic shock. Br J Pharmacol. 1997;120:259–67.
48. Brealey D, Karyampudi S, Jacques TS, Novelli M, Stidwill R, Taylor V, et al. Mitochondrial dysfunction in a long-term rodent model of sepsis and organ failure. Am J Physiol Regul Integr Comp Physiol. 2004;286:R491–7.
49. Radi R, Rodriguez M, Castro L, Telleri R. Inhibition of mitochondrial electron transport by peroxynitrite. Arch Biochem Biophys. 1994;308:89–95.
50. Murray AJ, Anderson RE, Watson GC, Radda GK, Clarke K. Uncoupling proteins in human heart. Lancet. 2004;364:1786–8.
51. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet. 2002;360:219–23.
52. Goode HF, Cowley HC, Walker BE, Howdle PC, Webster NR. Decreased antioxidant status and increased lipid peroxidation in patients with septic shock and secondary organ dysfunction. Crit Care Med. 1995;23:646–51.
53. Takeda K, Shimada Y, Amano M, Sakai T, Okada T, Yoshiya I. Plasma lipid peroxides and alpha-tocopherol in critically ill patients. Crit Care Med. 1984;12:957–9.
54. Andresen M, Regueira T, Bruhn A, Perez D, Strobel P, Dougnac A, et al. Lipoperoxidation and protein oxidative damage exhibit different kinetics during septic shock. Mediators Inflamm. 2008:168652.
55. Deneke SM, Lynch BA, Fanburg BL. Effects of low protein diets or feed restriction on rat lung glutathione and oxygen toxicity. J Nutr. 1985;115:726–32.
56. Messmer UK, Briner VA, Pfeilschifter J. Basic fibroblast growth factor selectively enhances TNF-alpha-induced apoptotic cell death in glomerular endothelial cells: effects on apoptotic signaling pathways. J Am Soc Nephrol. 2000;11:2199–211.
57. Elbers PW, Ince C. Mechanisms of critical illness—classifying microcirculatory flow abnormalities in distributive shock. Crit Care. 2006;10:221.

58. Regueira T, Andresen M, Djafarzadeh S. Mitochondrial dysfunction during sepsis, impact and possible regulating role of hypoxia-inducible factor-1alpha. Med Intensiva. 2009;33:385–92.
59. Szabo C. Poly (ADP-ribose) polymerase activation and circulatory shock. Novartis Found Symp. 2007;280:92–103 [discussion 103–7, 160–4].
60. Goldfarb RD, Marton A, Szabo E, Virag L, Salzman AL, Glock D, et al. Protective effect of a novel, potent inhibitor of poly(adenosine 5′-diphosphate-ribose) synthetase in a porcine model of severe bacterial sepsis. Crit Care Med. 2002;30:974–80.
61. Larche J, Lancel S, Hassoun SM, Favory R, Decoster B, Marchetti P, et al. Inhibition of mitochondrial permeability transition prevents sepsis-induced myocardial dysfunction and mortality. J Am Coll Cardiol. 2006;48:377–85.
62. Regueira T, Lepper PM, Brandt S, Ochs M, Vuda M, Takala J, et al. Hypoxia inducible factor-1 alpha induction by tumour necrosis factor-alpha, but not by toll-like receptor agonists, modulates cellular respiration in cultured human hepatocytes. Liver Int. 2009;29:1582–92.
63. Vary TC. Increased pyruvate dehydrogenase kinase activity in response to sepsis. Am J Physiol. 1991;260:E669–74.
64. Vary TC, Siegel JH, Nakatani T, Sato T, Aoyama H. Effect of sepsis on activity of pyruvate dehydrogenase complex in skeletal muscle and liver. Am J Physiol. 1986;250:E634–40.
65. Crouser ED, Julian MW, Huff JE, Struck J, Cook CH. Carbamoyl phosphate synthase-1: a marker of mitochondrial damage and depletion in the liver during sepsis. Crit Care Med. 2006;34:2439–46.
66. Fredriksson K, Hammarqvist F, Strigard K, Hultenby K, Ljungqvist O, Wernerman J, et al. Derangements in mitochondrial metabolism in intercostal and leg muscle of critically ill patients with sepsis-induced multiple organ failure. Am J Physiol Endocrinol Metab. 2006;291:E1044–50.
67. Porta F, Takala J, Weikert C, Bracht H, Kolarova A, Lauterburg BH, et al. Effects of prolonged endotoxemia on liver, skeletal muscle and kidney mitochondrial function. Crit Care. 2006;10:R118.
68. Kozlov AV, Van Griensven M, Haindl S, Kehrer I, Duvigneau JC, Hartl RT, et al. Peritoneal inflammation in pigs is associated with early mitochondrial dysfunction in liver and kidney. Inflammation. 2010;33:295–305.
69. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med. 2000;342:1301–8.
70. Imai Y, Parodo J, Kajikawa O, De Perrot M, Fischer S, Edwards V, et al. Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. JAMA. 2003;289:2104–12.
71. Mishra J, Ma Q, Prada A, Mitsnefes M, Zahedi K, Yang J, et al. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. J Am Soc Nephrol. 2003;14:2534–43.
72. Mishra J, Mori K, Ma Q, Kelly C, Barasch J, Devarajan P. Neutrophil gelatinase-associated lipocalin: a novel early urinary biomarker for cisplatin nephrotoxicity. Am J Nephrol. 2004;24:307–15.
73. Haase M, Haase-Fielitz A, Bellomo R, Mertens PR. Neutrophil gelatinase-associated lipocalin as a marker of acute renal disease. Curr Opin Hematol. 2011 [published ahead of print].
74. Martensson J, Bell M, Oldner A, Xu S, Venge P, Martling CR. Neutrophil gelatinase-associated lipocalin in adult septic patients with and without acute kidney injury. Intensive Care Med. 2010;36:1333–40.
75. Cruz DN, De Cal M, Garzotto F, Perazella MA, Lentini P, Corradi V, et al. Plasma neutrophil gelatinase-associated lipocalin is an early biomarker for acute kidney injury in an adult ICU population. Intensive Care Med. 2010;36:444–51.
76. Siew ED, Ware LB, Gebretsadik T, Shintani A, Moons KG, Wickersham N, et al. Urine neutrophil gelatinase-associated lipocalin moderately predicts acute kidney injury in critically ill adults. J Am Soc Nephrol. 2009;20:1823–32.
77. Melnikov VY, Faubel S, Siegmund B, Lucia MS, Ljubanovic D, Edelstein CL. Neutrophil-independent mechanisms of caspase-1- and IL-18-mediated ischemic acute tubular necrosis in mice. J Clin Invest. 2002;110:1083–91.
78. Parikh CR, Mishra J, Thiessen-Philbrook H, Dursun B, Ma Q, Kelly C, et al. Urinary IL-18 is an early predictive biomarker of acute kidney injury after cardiac surgery. Kidney Int. 2006;70:199–203.
79. Parikh CR, Abraham E, Ancukiewicz M, Edelstein CL. Urine IL-18 is an early diagnostic marker for acute kidney injury and predicts mortality in the intensive care unit. J Am Soc Nephrol. 2005;16:3046–52.
80. Liangos O, Perianayagam MC, Vaidya VS, Han WK, Wald R, Tighiouart H, et al. Urinary N-acetyl-beta-(D)-glucosaminidase activity and kidney injury molecule-1 level are associated with adverse outcomes in acute renal failure. J Am Soc Nephrol. 2007;18:904–12.
81. Mehta Rl, Mcdonald B, Gabbai FB, Pahl M, Pascual MT, Farkas A, et al. A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. Kidney Int. 2001;60:1154–63.
82. Lins RL, Elseviers MM, Van der Niepen P, Hoste E, Malbrain ML, Damas P, et al. Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: results of a randomized clinical trial. Nephrol Dial Transplant. 2009;24:512–8.
83. Augustine JJ, Sandy D, Seifert TH, Paganini EP. A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. Am J Kidney Dis. 2004;44:1000–7.
84. Bagshaw SM, Berthiaume LR, Delaney A, Bellomo R. Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: a meta-analysis. Crit Care Med. 2008;36:610–7.
85. Pannu N, Klarenbach S, Wiebe N, Manns B, Tonelli M. Renal replacement therapy in patients with acute renal failure: a systematic review. JAMA. 2008;299:793–805.
86. Tetta C, Bellomo R, Ronco C. Artificial organ treatment for multiple organ failure, acute renal failure, and sepsis: recent new trends. Artif Organs. 2003;27:202–13.
87. Honore PM, Matson JR. Extracorporeal removal for sepsis: acting at the tissue level—the beginning of a new era for this treatment modality in septic shock. Crit Care Med. 2004;32:896–7.
88. Di Carlo JV, Alexander SR. Hemofiltration for cytokine-driven illnesses: the mediator delivery hypothesis. Int J Artif Organs. 2005;28:777–86.
89. Honore PM, Joannes-Boyau O. High volume hemofiltration (HVHF) in sepsis: a comprehensive review of rationale, clinical applicability, potential indications and recommendations for future research. Int J Artif Organs. 2004;27:1077–82.
90. Cole L, Bellomo R, Journois D, Davenport P, Baldwin I, Tipping P. High-volume haemofiltration in human septic shock. Intensive Care Med. 2001;27:978–86.
91. Romero CM, Downey P, Hernandez G. High volume hemofiltration in septic shock. Med Intensiva. 2010;34:345–52.
92. Cornejo R, Downey P, Castro R, Romero C, Regueira T, Vega J, et al. High-volume hemofiltration as salvage therapy in severe hyperdynamic septic shock. Intensive Care Med. 2006;32:713–22.

93. Boussekey N, Chiche A, Faure K, Devos P, Guery B, D'Escrivan T, et al. A pilot randomized study comparing high and low volume hemofiltration on vasopressor use in septic shock. Intensive Care Med. 2008;34:1646–53.
94. Ruiz C, Hernandez G, Godoy C, Downey P, Andresen M, Bruhn A. Sublingual microcirculatory changes during high-volume hemofiltration in hyperdynamic septic shock patients. Crit Care. 2010;14:R170.
95. Rabindranath K, Adams J, Macleod AM, Muirhead N. Intermittent versus continuous renal replacement therapy for acute renal failure in adults. Cochrane Database Syst Rev. 2007; CD003773.
96. Vinsonneau C, Camus C, Combes A, Costa de Beauregard MA, Klouche K, Boulain T, et al. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. Lancet. 2006;368:379–85.
97. Baeza-Roman A, Latour-Perez J, Gomez-Tello V, Garcia-Garcia MA. Hemofiltration in sepsis: what is the evidence? Med Intensiva. 2010;34:571–2 [author reply 572–3].
98. Phu NH, Hien TT, Mai NT, Chau TT, Chuong LV, Loc PP, et al. Hemofiltration and peritoneal dialysis in infection-associated acute renal failure in Vietnam. N Engl J Med. 2002;347:895–902.