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The Pathogenesis of Acute Kidney Injury

Nicholas A. Barrett and Marlies Ostermann
Department of Critical Care,
Guy's and St Thomas' NHS Foundation Trust, London
UK

1. Introduction

Acute kidney injury (AKI) is common in critically ill patients affecting 20 - 60% of patients (Chertow, et al., 2005; de Mendonca, et al., 2000; Mehta, et al., 2005; Ostermann & Chang, 2008; Silvester, et al., 2001; Uchino, et al., 2005). The exact incidence varies depending on patient population, associated comorbid factors and criteria used to define AKI. Sepsis induced AKI accounts for approximately 50% of cases and AKI is commonly a manifestation of multiple organ dysfunction (Chertow, et al., 2005; de Mendonca, et al., 2000; Mehta, et al., 2005; Ostermann & Chang, 2008; Silvester, et al., 2001; Uchino, et al., 2005). Many patients with AKI have a mixed aetiology where the presence of sepsis, ischaemia and nephrotoxicity co-exist. Current management of AKI is supportive, ensuring adequate perfusion pressures, correction of fluid depletion, avoidance of nephrotoxins and when required institution of renal replacement therapy (RRT). Despite the widespread use of RRT in the intensive care unit (ICU), AKI is associated with an associated mortality risk of 40 – 90% depending on patient population (Chertow, et al., 2005; Ostermann & Chang, 2008; Silvester, et al., 2001). Furthermore, evidence has emerged that AKI survivors have an increased risk of chronic kidney disease, long-term dialysis, increased mortality and reduced quality of life (Johansen, et al., 2010; Lo, et al., 2009; Lopes, et al., 2010; Wald, et al., 2009). AKI is no longer viewed as a reversible bystander of critical illness but a significant contributor to short and long-term morbidity and mortality.

2. Renal physiology

2.1 Renal blood supply and oxygenation

The chief function of the kidneys (ie. filtration of plasma and formation of urine) dictates the renal flow to be much higher than necessary to meet the metabolic needs. The kidneys receive blood via the renal arteries which supply them with approximately 25% of cardiac output. The vascular supply of nephrons consists of glomerular afferent and efferent arterioles which branch into the peritubular arteries and vasa recta. Oxygen tensions in the kidney are low, decreasing from 70 mmHg in the cortex to 20 mmHg in the medulla. The unique microvasculature of the kidneys coupled with high oxygen demand from the tubular salt-water reabsorption make the kidneys, in particular the medulla highly sensitive to hypoxia (Brezis & Rosen, 1995; Evans, et al., 2008). As a result, the renal microcirculation is recognised as a key actor in the initiation and development of AKI.

Basal renal oxygen consumption is approximately 400mmol/min/100g. Due to the high renal blood flow, there is a low oxygen extraction (Valtin & Schafer, 1995). Energy dependent processes in the kidney are those related to basal cellular metabolism and those related to filtration and reabsorption of solutes. In conditions associated with decreased renal blood flow, there is a reduction in both glomerular filtration and tubular reabsorption followed by a reduction in oxygen consumption. This relationship holds until the threshold of approximately 150mL/min/100g blood flow at which point oxygen extraction increases. At a blood flow of approximately 75mL/min/100g tissue the capacity for increased oxygen extraction is exceeded and anaerobic metabolism and cellular ischaemia occur (Schlichtig, et al., 1991).

2.2 Renal energy utilisation

Aside from basal metabolic requirements the major energy dependent process in the kidney is the reabsorption of solute, especially sodium. From animal studies, it is well established that there is a linear relationship between the reabsorption of sodium and oxygen consumption within the kidney (Gullans & Mandel, 1992). The predominant method of ATP production within the kidney is oxidative metabolism. In the cortex, oxidative metabolism accounts for over 97% of ATP production whereas in the medulla, up to 33% of energy comes from glycolysis (Bernanke & Epstein, 1965). In the presence of renal cortical hypoxia, the predominant form of energy production changes to glycolysis, however, this can not sustain significant function of the renal cells above homeostasis (Gullans & Mandel, 1992).

3. Ischaemic Acute Kidney Injury

Ischaemic AKI can occur in several clinical settings ranging from hypotension due to fluid depletion, blood loss, sepsis or reduced cardiac output to the use of vasoactive drugs. Following a reduction in effective kidney perfusion, tubular cells are unable to maintain adequate intracellular ATP. This depletion of ATP leads to rapid disorganization of the cytoskeletal structure and disruption of tight intercellular junctions (Sharfuddin & Molitoris, 2011). in case of severe depletion, apoptosis or necrosis occur and cells die. All segments of the nephron can be affected during an ischaemic insult but the most commonly injured sites are the proximal and distal tubular cells. Sloughed tubular cells and cellular debris can obstruct the tubule lumen and ultimately cease glomerular filtration in that functional nephron.

A marked decrease in total kidney perfusion may cause global ischaemia, but more often, ischaemic injury occurs due to decreased regional perfusion without major change in global perfusion. Both ischaemia and sepsis can have profound effects on renal endothelial cells, resulting in microvascular dysregulation and continued ischaemia and further injury. Ischaemic injury results in endothelial cell activation, endothelial swelling, up-regulation of adhesion molecules and shedding of components of the glycocalyx. This, in combination with leucocyte activation, platelet aggregation, red cell trapping and activation of the coagulation pathway serve as the basis for vascular congestion of the microvasculature (Le Dorze, et al., 2009). In response, a range of inflammatory mediators are being released, including prostaglandins, endothelin and nitric oxide, that alter the balance of

vasodilatation and constriction within the renal vasculature (Bonventre, 2004; Le Dorze, et al., 2009). Although the ultimate aim is to control intrarenal damage and to promote repair, these activated leucocytes and proinflammatory mediators are also thought to be responsible for distant effects in non-renal organs, in particular lungs, heart and brain (ie. principle of organ cross-talk).

4. Septic Acute Kidney Injury

Sepsis is a pathological state characterised by a systemic inflammatory response to infective agents. Septic shock is characterised by inadequate tissue perfusion and significant hypotension is usually present. There are a number of proposed mechanisms regarding the pathogenesis of septic AKI, including hypoperfusion at the systemic and/or microcirculatory level, apoptosis mediated by either the infective agents or cytokines released in response to infection as well as renal mitochondrial hibernation triggered by sepsis.

4.1 Histopathology

Our progress in understanding the pathogenesis of AKI in sepsis has been limited due to the paucity of histopathological studies performed in well-defined patient populations with sepsis. Results from studies have been inconsistent with varying reports of cellular necrosis, glomerular infiltration and microvascular thrombosis (Solez, et al., 1979).

Autopsy studies have similarly reported variable and inconsistent findings in sepsis-induced AKI including interstitial oedema, swelling of the tubular cells, tubular cell apoptosis and regeneration, as well as focal necrosis and micro-abscess formation (Lucas, 2007). Part of the difficulty with autopsy series is that autolysis of the kidney occurs rapidly after death which leads to difficulties in interpreting findings. In one study reporting on rapid autopsies (within 6 hours) of 20 patients who died from sepsis and multiple organ dysfunction, there was no evidence of cellular necrosis or apoptosis (Hotchkiss, et al., 1999). However, a more recent study of immediate (within 30 minutes) post-mortem renal histology in patients with septic shock demonstrated acute tubular lesions, glomerular leukocyte infiltration and tubular cell apoptosis which affected 2.9% of tubular cells (Lerolle, et al., 2010). In this study these patients had died in states of profound shock. Hypovolaemia and hyperlactataemia, suggestive of poor tissue perfusion correlated with the degree of histological change seen and it is not clear that the changes seen were due to shock and hypoperfusion or sepsis *per se*.

Animal models of sepsis-induced AKI exist and have also demonstrated inconsistent changes in renal histopathology (Heyman, et al., 2002; Rosen & Heyman, 2001). Furthermore, the microvasculature of the rat kidney is markedly different from that of humans (Rosen & Heyman, 2001) and none of the models adequately account for the resuscitation and supportive management seen in critically ill patients, making data difficult to extrapolate (Heyman, et al., 2002).

4.2 Haemodynamic changes

Experimental evidence for renal haemodynamic changes due to sepsis is inconsistent. Animal models variably demonstrate that with preserved systemic blood pressures there is

either a reduction in renal blood flow causing decreased glomerular flow (Badr, et al., 1986; Kikeri, et al., 1986) or renovascular vasodilatation with a consequent increase in renal blood flow (Langenberg, et al., 2006; Ravikant & Lucas, 1977). In humans, techniques measuring renal blood flow using para-aminohippurate extraction and renal vein catheter thermodilution have demonstrated that renal blood flow is preserved in sepsis (Brenner, et al., 1990). A systematic review of human and animal trials found that the primary determinant of renal blood flow during sepsis was cardiac output and that even in the presence of preserved renal blood flow, there is a reduction in glomerular filtration and AKI continues to progress (Langenberg, et al., 2005). It remains unclear as to whether there is significant relative reduction in medullary blood flow in humans with sepsis but given that the renal medulla is normally exposed to relative hypoxia, it has been hypothesised that this may be exacerbated during sepsis leading to tubular cell dysfunction or death (Brezis & Rosen, 1995; Eckardt, et al., 2005). Sepsis also leads to damage of the endothelial glycocalyx which aggravates a breakdown of the vascular barrier and contributes to microcirculatory changes in septic AKI (Chappell, et al., 2009).

4.3 Apoptosis

Apoptosis has been demonstrated to occur in animal models of AKI (Bonegio & Lieberthal, 2002; Sharfuddin & Molitoris, 2011; Wan, et al., 2003). Apoptosis is thought to occur in response to a variety of insults including sepsis, ischaemia, inflammatory cytokines and bacterial lipo-polysaccharide. However, there is inconsistent evidence for the presence of significant apoptosis in kidneys from patients with sepsis at autopsy (Hotchkiss, et al., 1999; Lerolle, et al., 2010; Lucas, 2007). It remains uncertain that apoptosis, estimated at less than 3% in a recent study (Lerolle, et al., 2010), is occurring on a scale that would result in significant organ dysfunction and failure.

4.4 Bioenergetics

A recent hypothesis is that the organ dysfunction including AKI observed in sepsis is secondary to bioenergetic changes with mitochondrial down-regulation and hibernation (Singer, 2007a, 2007b; Singer, et al., 2004). There is some evidence that there is reversible mitochondrial dysfunction resulting in inadequate ATP generation and that this may underlie the organ dysfunction seen in sepsis (Singer, et al., 2004). Although not conclusively demonstrated in humans, there is evidence of decreased ATP and a reduction in activity of respiratory chain complexes associated with sepsis and septic shock (Brealey, et al., 2002).

4.5 Immune mechanisms

Another mechanism of renal failure associated with infection is that of immune-mediated glomerulonephritis (Naicker, et al., 2007). This occurs as a post-infectious condition and is usually related to streptococcal or viral diseases. The pathophysiological mechanism is immune-complex deposition leading to inflammation within the glomerulus and glomerulonephritis. Although well characterised following infection, there is no evidence that this mechanism is responsible for AKI associated with acute sepsis.

5. Repair of AKI

Renal tubular epithelial cells have high potential to regenerate after an ischaemic, septic or toxic insult. Minimally injured cells are repaired when blood flow is re-established. Viable cells proliferate and spread across denuded basement membrane and later regain their characteristics as tubular epithelial cells (Sharfuddin & Molitoris, 2011). There is evidence that progenitor cells, stem cells and mesenchymal stem cells have an important role in promoting tubular epithelial repair but also lead to chronic fibrosis. The benefit of infusions of mesenchymal cells to promote recovery of renal function in humans is currently under investigation (Humphreys & Bonventre, 2008). Endothelial cells have less regenerative capability. Decrease of peritubular capillary density has been observed several months after an episode of AKI (Basile, et al., 2001).

6. Conclusion

AKI is a common manifestation of multiple organ dysfunction observed in critically ill patients, especially in relation to sepsis and ischaemia. There is increasing evidence that independent of the exact aetiology, AKI should be regarded as an inflammatory condition with secondary effects on other organs. However, the exact underlying pathophysiology and pathology of human AKI remains incompletely understood.

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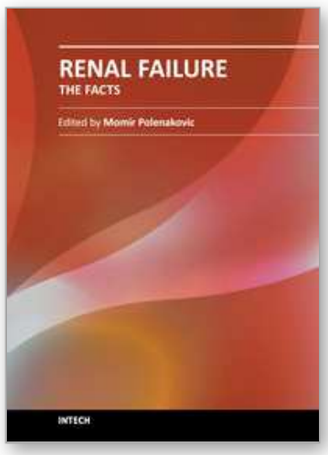

Renal Failure - The Facts

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The book "Renal Failure - The Facts" consists of some facts about diagnosis, etiopathogenis and treatment of acute and chronic renal failure. Acute, as well as chronic renal failure is great medical problems and their treatment is a burden for the budget of each government. The purpose of the chapters is to present some important issues of diagnosis and causes of AKI, as well as caused by snakes and arthropods, after cardiac surgery, as well as some therapeutic achievements in AKI. Well presented are the psychological condition in patients on haemodialysis, as well as the treatment of diabetic uremics. The book is aimed at clinicians with a special interest in nephrology, but it should also prove to be a valuable resource for any generalists who encounter a nephrological problems in their day-to-day practice.

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University Campus STeP Ri
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Phone: +86-21-62489820
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