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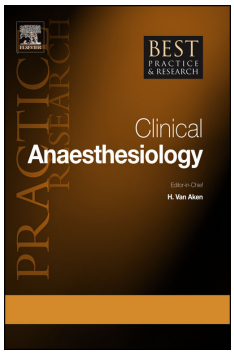

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Pathophysiology of AKI

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Abstract

Acute kidney injury (AKI) is common in the perioperative and intensive care setting. Although AKI is usually multifactorial, haemodynamic instability, sepsis and drug toxicity are commonly implicated. Independent of the exact aetiology, several different pathophysiologic processes occur simultaneously and in sequence, including endothelial dysfunction, alteration of the microcirculation, tubular injury, venous congestion and intrarenal inflammation. A multitude of different immune cells from within the kidney and the systemic circulation play a role in the development, maintenance and recovery phase of AKI.

In this review we describe the common processes involved in AKI and their connections with particular emphasis on the perioperative and critical care setting.

Key words: acute kidney injury, pathophysiology, inflammation, endothelial dysfunction, tubular injury, microcirculation

Introduction

Acute kidney injury (AKI) is a syndrome that encompasses many different aetiologies. In fact, most cases of AKI are multifactorial. Following an inciting event, various different pathophysiologic processes occur simultaneously as well as in sequence [1-3]. Not surprisingly, a multitude of different cell types from within the kidney and the systemic circulation are involved.

In the following review, we will summarise key components of normal renal physiology and describe the most common processes leading to AKI, with a particular focus on the perioperative and critical care setting.

Normal renal physiology

In health, the kidneys receive 20% of the cardiac output. Blood flow within the kidneys is selectively distributed. Branching renal arteries terminate in glomerular afferent arterioles and form a capillary network responsible for glomerular filtration. Subsequent efferent arterioles follow one of two paths. Those that arise from glomeruli within the outer and mid-cortex give rise to a dense network of capillaries that run alongside the proximal and distal convoluted tubules. Efferent arterioles that arise from the inner or juxtamedullary glomeruli form the vasa recta which run parallel to the loops of Henle.

Under these conditions, blood flow to the outer cortex is approximately 5-6 ml/g tissue/min whereas the outer and inner medulla only receive 1 and 0.5ml/g/min, respectively. In contrast to the outer cortex, where much of the blood flow is directed to glomerular filtration, the key roles of the peritubular microcirculation are to off-load oxygen, deliver nutrients to the tissues, return reabsorbed solutes and water to the systemic circulation and participate in the counter-current mechanisms that are necessary to permit the conservation of water.

The complex arrangement of the microvasculature generates a gradient of decreasing oxygen tension between the renal cortex and the papillary tip that results in a state of relative hypoxia within the renal medulla. In addition, the counter-current

arrangement of arteries and veins facilitates arterial-to-venous oxygen shunting in the renal cortex and also from descending to ascending vasa recta in the renal medulla, both of which contribute to deoxygenation of the medulla [4, 5].

The Na/K ATPase in the proximal tubules is responsible for active reabsorption of sodium and also transport processes for glucose, amino acids and other solutes; it is a major determinant of the oxygen requirement of the kidney (~80%) [6, 7]. As most of the reabsorption is dependent on the filtration rate, the majority of oxygen consumption is therefore directly dependent on the glomerular filtration rate (GFR).

In health, renal blood flow is maintained in a wide range of renal perfusion pressures (60 – 100 mmHg) [8]. Autoregulation of renal blood flow is mediated chiefly through changes in pre-glomerular vascular tone of the afferent arteriole in response to an increase of the NaCl concentration in the tubular fluid, ie. the tubuloglomerular feedback (TGF) [9, 10]. Several neurohormonal processes are involved, including complex interactions between the sympathetic nervous system, vasodilators such as nitric oxide (NO) and prostaglandin E2 and vasoconstrictors such as endothelin, angiotensin II and adenosine [7]. Thus, when systemic arterial pressure falls within the autoregulatory range, renal blood flow, GFR and kidney oxygenation can be maintained by a combination of afferent arteriolar dilatation and efferent arteriolar constriction. When renal artery pressure is reduced further, the impact on kidney oxygenation depends on the balance between changes in renal blood flow on the one hand, and changes in GFR and sodium delivery to the renal tubule on the other.

Common processes involved in the pathophysiology of AKI

i) Haemodynamic instability

Many observational clinical studies have demonstrated significant associations between systemic haemodynamic instability and the development and progression of AKI [8, 11-13]. Martin et al showed that adequate restoration of mean arterial pressure (MAP) in patients with septic shock was associated with restored urine output and improved creatinine clearance [12]. Similarly, the FINNAKI study demonstrated an

association between the time spent in relative hypotension and the development of AKI in patients with sepsis [13]. Asfar and colleagues showed that in patients with known chronic hypertension, a higher target blood pressure prevented the development of severe AKI during sepsis [15]. However, other studies have not reported an independent association between MAP and risk of AKI suggesting that the impact of hypotension may depend on the severity of illness and patient comorbidities [15, 16].

In the perioperative setting, several studies found an association between intraoperative hypotension and development of postoperative AKI [17-19]. In a large retrospective analysis of more than 30,000 non-cardiac surgeries, hypotension during surgery (defined as a MAP < 55 mm Hg) was associated with an increased risk of AKI [17]. The risk increased with duration of hypotension and was significant for durations as short as 1 – 5 minutes. These results have been largely confirmed in other studies [18, 19]. In an analysis of 57,000 patients, Salmasi et al showed that a duration of a few minutes of intraoperative MAP below 65 mmHg was associated with AKI [19].

Certain types of surgery are associated with a higher risk of renal hypoperfusion, in particular vascular surgery procedures in which the aorta is cross-clamped above the renal arteries. Though not as well described in human studies, in animal studies renal vein clamping also results in significant kidney injury [20]. In the setting of cardiac surgery, non-pulsatile flow during cardiopulmonary bypass may result in renal ischemia and contribute to the risk of AKI, together with systemic inflammation and release of free haemoglobin (as described below).

ii) Microcirculatory dysfunction

The concept of reduced renal blood flow as a main contributor to AKI is no longer valid since several studies in humans and animals demonstrated that AKI may develop during periods when renal blood flow was normal or even increased; instead, dysfunction of the intrarenal microcirculation appears to be more important [21].

There are two specialised microcirculatory structures in the kidney, the glomeruli and peritubular microcirculatory networks, both of which have crucial roles in the development and propagation of AKI [7]. Because peritubular capillaries are derived from the efferent glomerular arterioles, any disturbance of glomerular blood flow will impair peritubular perfusion even when global renal blood flow is unchanged or even increased [22].

Inflammatory diseases, including sepsis, can cause a profound alteration of microvascular function resulting in heterogeneous and sluggish flow. This may lead to patchy areas of hypoperfusion and micro-ischemia within the kidney even in the absence of global hypoperfusion. These focal perfusion deficits have been shown to be of greater magnitude in the highly vulnerable outer medulla compared with the cortex [22, 23]. Hypoxic zones may co-exist with intact regions with preserved tissue oxygenation, and interactions between these areas are thought to be associated with increased generation of reactive oxygen species (ROS) [24]. In addition, increased capillary permeability as a result of endothelial dysfunction can result in interstitial edema, which may both compromise microcapillary flow and increase the distance over which oxygen must diffuse. These alterations of microcirculatory flow can persist even when systemic hemodynamics are adequately corrected [25].

Recent experimental studies suggest that in septic AKI, there is also redistribution of flow away from the renal medulla to the renal cortex resulting in further medullary deoxygenation [26]. It is thought that activation of intra-renal shunting pathways may be responsible [1]. Although dysfunction of the microcirculation appears to play an important role in the pathogenesis of AKI, it remains unclear it is directly responsible for the development of AKI or rather an adaptive mechanism [27].

iii) Endothelial dysfunction

The endothelium is a natural barrier between intravascular and extravascular spaces. Under physiologic conditions, endothelial cells perform several functions to maintain homeostasis and integrity of the endothelial barrier. By producing prostacyclin, NO and

other vasoactive substances, they influence the tone of arterioles and venules and inhibit platelet aggregation, thereby regulating the microcirculation and glomerular filtration. The integrity of the endothelial barrier prevents the passage of albumin and larger endogenous molecules in the urine. A key component of the endothelial barrier is the glycocalyx, a network of glycoproteins that lines the extracellular surface of the endothelial cells. Damage to the glycocalyx contributes to microvascular dysfunction, capillary leakage and impaired GFR [27, 28].

Endothelial dysfunction plays a central role in microcirculatory dysfunction during sepsis. Following exposure to a variety of systemic inflammatory mediators, the endothelium undergoes structural changes with loss of cell-cell contact and disruption of the glycocalyx, resulting in increased permeability. In addition, activated endothelial cells up-regulate the expression of adhesion molecules resulting in increased adherence of leukocytes and enhanced leukocyte-endothelium interactions which leads to leukocyte transmigration toward the renal interstitium [29, 30]. Leukocytes leaving peritubular capillaries have a close proximity to tubular epithelial cells and can directly induce tubular cell injury [2]. During this process, endothelial and tubular cells continue to release pro-inflammatory cytokines which ultimately triggers a vicious circle of inflammatory processes [27, 31]. Within the microvasculature, there is marked plugging and heterogenous flow mediated by adherence of leukocytes to the endothelium and formation of microthrombi [32, 33]. In the perioperative setting, although the degree to which the endothelium is affected will vary by type of surgery, the role of endothelial dysfunction in the pathogenesis of AKI appears to be more limited.

Apart from sepsis, the endothelium also plays an important role in primary renal diseases such as rapidly progressive glomerulonephritis or vasculitis. Histopathologically, the hallmark of these diseases is the formation of crescents. Crescents develop following the leakage of fibrin into the Bowman space as a result of increased permeability of the glomerular basement membrane. Fibrin stimulates the proliferation of cells of the Bowman capsule, and induces an influx of monocytes. As crescents grow, capillary loops are compressed and glomerular function ceases.

However, this is a unique class of kidney pathology that is uncommonly encountered in the perioperative setting but may be a potential cause of AKI in critically ill patients in the Intensive Care Unit (ICU). Typically, these diseases require a renal biopsy for diagnosis, in contrast to AKI that more typically occurs in the peri-operative setting or in the context of sepsis.

iv) Formation of microvascular thrombi

Under physiological conditions, endothelial cells inhibit blood coagulation through their interaction with protein C and thrombomodulin. Activation of coagulation is central to microcirculatory dysfunction. During an inflammatory response, many of the natural anticoagulants, including protein C, are degraded, or their production is decreased leading to a pro-coagulant state. Damaged endothelial cells may also undergo apoptosis which amplifies the coagulation cascade further. This disturbance of the procoagulant – anticoagulant balance is enhanced by pro-inflammatory cytokines, leads to formation of microthrombi and capillary plugging, and is typically seen in sepsis. Confocal microscopy studies in animal models of septic AKI have very elegantly demonstrated the presence of microvascular thrombi [34].

A thrombotic microangiopathy is also classically seen in diseases associated with complement activation, for instance, haemolytic uraemic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP) or pre-eclampsia [35]. In all cases, the thrombotic injury is often followed by an influx of inflammatory cells. Again, these conditions are rarely encountered in the perioperative setting but may be seen in patients admitted to the ICU.

v) Inflammation

Inflammation and recruitment of leukocytes are now recognised as key mediators of all phases of endothelial and tubular cell injury in the initiation and maintenance phase of AKI [3]. Immediately after endothelial or tubular epithelial cell injury, an immune response is triggered consisting of the activation of resident inflammatory cells and the

recruitment and subsequent invasion of white blood cells. Virtually all immune cells have been implicated in these pathophysiological processes of AKI. Most invading cells are thought to be deleterious (i.e., neutrophils, monocytes, dendritic cells) but some are likely protective (i.e., T regulatory cells) [36-38]. There are also some circulating cells whose role varies depending on the phase of the disease process [32]. For instance, M1 macrophages contribute to inflammation in the early phase, whereas M2 macrophages exert anti-inflammatory functions post-ischaemia and facilitate renal recovery [39].

Systemic inflammation may also contribute to the pathogenesis of AKI – for example, elevated levels of interleukin-6 have been associated with the development of AKI in the setting of severe sepsis, cardiac surgery, and in critically ill patients with the acute respiratory distress syndrome [40-42]. Finally, intrarenal inflammatory processes can induce inflammatory changes in other non-renal organs, including the heart, lung and liver. These distant organ effects appear to be mediated through cytokines and activated immune cells [43].

vi) Tubular cell injury

Microcirculatory dysfunction leads to tubular cell injury. Another mechanism for tubular cells to get injured is through direct exposure with substances in the filtrate. By nature, tubular epithelial cells are at the frontline of filtered exogenous products (i.e., drugs) and endogenous molecules such as cytokines, danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) [44]. During cardiac surgery with cardiopulmonary bypass, free haemoglobin may be released and cause tubular damage through direct toxicity as well as intratubular crystal formation [45, 46]. Independent of the exact aetiology, tubular cell injury often manifests itself in structural changes including apical membrane blebbing, opening of tight junctions, loss of polarity, cell detachment from the basement membrane and cell swelling. Mitochondrial damage may occur, too [46-48]. Increased mitochondrial fragmentation promotes the excess production of reactive oxygen species, release of cytokines and cellular death, all of which contribute further to the progression of AKI [49]. As such,

tubular cells have diverse roles in AKI. They are the victims as well as promoters of inflammatory processes. In addition, they try to protect neighbouring cells by spreading alarm signals in a paracrine fashion [2, 51].

At its extreme, tubular cell injury will result in cell death through a number of mechanisms, including necrosis and apoptosis. In human AKI, tubular cell injury typically predominates over frank cell death. As described, a number of mechanisms that contribute to tubular cell injury occur in the perioperative setting, and may culminate in AKI.

Tubular damage itself can be associated with a significant decline in GFR despite a lack of damage to the glomerulus per se. A likely mechanism linking both processes is TGF. In the event of tubular cell damage or dysfunction, Na reabsorption in the proximal tubule is impaired resulting in increased delivery of NaCl to the macula densa. This triggers the TGF and leads to pre-glomerular vasoconstriction of the afferent arteriole resulting in a decline in GFR.

vii) Renal venous congestion

The kidney is an encapsulated organ. Elevated central venous pressure (CVP) and the resultant increased backward pressure negatively impact on renal function, mainly due to renal congestion and increased pressure along the renal vascular tree. This can lead to compression of tubules and a decrease in the net pressure gradient across the glomerulus, resulting in a fall in GFR [52, 53]. Most evidence stems from patients with congestive heart failure, cardiovascular disease and critical illness where an association between venous congestion and the development of AKI has been repeatedly shown [54-60]. Relevant to the perioperative setting, renal venous clamping has been shown in animal models to result in significant kidney injury, too [20].

viii) Tubular obstruction

Obstruction at any level from the tubules to urethra can cause AKI. A typical example

of tubular obstruction is crystal nephropathy following administration of drugs that are insoluble in urine, such as indinavir, acyclovir, sulfadiazine or methotrexate [61]. In addition to insolubility, factors such as urine pH, sluggish tubular urine flow rates, and rapid parenteral or excessive dosing enhance the risk for precipitation and crystal formation in the distal tubular lumen. Other examples of obstructive nephropathy are ureteric obstruction from nephrolithiasis or retroperitoneal fibrosis, or bladder outflow obstruction.

In the perioperative setting, myoglobinuria and/or hemoglobinuria as a result of extensive tissue injury, hemolysis or extracorporeal circuits may also lead to intratubular cast formation and obstruction.

ix) Auto-immune processes

Several primary renal diseases are caused by circulating or newly formed immune complexes that deposit in the glomeruli and lead to an inflammatory reaction. Typical examples are lupus nephritis, post-infectious glomerulonephritis or Goodpasture syndrome. These are relatively rare causes of AKI in the peri-operative setting but may occasionally be encountered in patients in the ICU.

x) Hypersensitivity immune reactions

The high blood flow to the kidneys renders the tubular cells at increased risk of exposure to endogenous and exogenous substances, including drugs that may induce hypersensitivity reactions resulting in acute tubulo-interstitial nephritis [62]. In the first phase, either the resident peritubular interstitial cells or injured tubular epithelial cells can function as antigen presenters. The normally quiescent resident dendritic cells when exposed to antigens or damage signals are activated and endocytose, process, and express the incriminated antigenic components as peptides located on their surface. Once activated, dendritic cells migrate through the renal lymphatic vessels to regional lymph nodes where they present the antigen to the residual naïve T cells, which are then activated and migrate to the antigenic source or injury emitting the

danger signal. Dendritic cells have also been shown to take up small potentially antigenic molecules directly from the tubular lumen. In addition to the dendritic cells, the renal interstitium contains dormant macrophages and fibroblasts that may also be activated and contribute to an inflammatory response within the interstitium. The glomeruli and blood vessels are usually spared.

Acute tubulo-interstitial nephritis is typically caused by a reaction to drugs but can also occur in the context of other inflammatory diseases like sarcoidosis, Sjögren's syndrome or neoplastic diseases. As a result of interstitial expansion and tubular damage, renal function deteriorates. Importantly, the reaction is not dose-related but recurs on re-exposure to the same drug or one of its congeners. Common causes of interstitial nephritis that may be encountered in the operating theatre include non-steroidal anti-inflammatory drugs and antibiotics, in particular pencillins and cephalosporins.

xi) Intra-abdominal hypertension

As intra-abdominal pressure increases, venous drainage of abdominal organs diminishes and venous congestion occurs [63]. For most patients, the critical intra-abdominal pressure at which microcirculatory disturbance is observed is 10 to 15 mmHg. In case of elevated renal vein pressure, intrarenal vascular congestion may induce AKI. If the intra-abdominal pressure continues to rise over 20mmHg (ie. abdominal compartment syndrome), additional factors, including reduction in cardiac output and elevated levels of catecholamines and inflammatory cytokines contribute to multi-organ failure, including AKI.

Sequelae of AKI

Under ideal conditions, renal function recovers fully after an episode of AKI. The timeline and trajectory of the renal recovery process will depend on reversal of the pathophysiological processes involved. However, it appears that under many circumstances, pro-fibrotic signals result in maladaptive repair and chronic kidney disease (CKD). Risk factors for maladaptive repair include increasing age, reduced

baseline renal function and prolonged duration and severity of AKI [64]. In the ICU setting, close follow-up of patients who suffer an episode of AKI is needed because these patients are at increased risk of multiple adverse events including CKD, end-stage renal disease, re-hospitalizaton and death. However, the causal relationship between AKI and subsequent CKD remains controversial. In a recent secondary analysis of data from the CORONARY study, a large randomized clinical trial comparing off-pump vs on-pump coronary artery bypass graft (CABG) surgery, off-pump CABG was associated with a lower rate of AKI but there was no difference in the incidence of CKD at one year [65]. Thus, whether AKI is causal or a marker of risk of CKD progression still needs to be further elucidated.

Summary

In most forms of AKI, the pathogenesis is characterised by an exacerbated inflammatory response, endothelial dysfunction, altered microcirculation and tubular injury. (Figure 1) An orchestra of different cells, inflammatory mediators and oxidative processes play a role, acting simultaneously as well as in sequence.

Although most pathophysiological processes and relationships can explain the development of AKI in humans, it is important to remember that the majority of data stem from animals undergoing experiments that induce AKI. More work is necessary to verify current concepts in humans.

Practice points

1. During the perioperative period, haemodynamic instability and hypotension are strongly associated with the development of postoperative AKI and should be avoided.
2. AKI may develop during periods when renal blood flow is normal or even increased due to altered microcirculation within the kidney.
3. Recruitment of leukocytes and intrarenal inflammation are key mediators of all phases of AKI but the role of anti-inflammatory therapies is unknown.
4. Fluid overload and raised right atrial pressure are associated with the development of AKI, mainly due to renal congestion and increased intrarenal pressures and should be avoided or corrected.

Research agenda

- It is essential that knowledge acquired in idealized animal models is evaluated in human subjects with common comorbidities.
- There is an urgent need to identify and measure inflammatory processes in human AKI in order to study the role of anti-inflammatory therapies for AKI.
- It is important to identify the pathways implicated in microcirculatory dysfunction in humans to identify targets for therapeutic interventions.
- There is a need to develop novel real-time methods to monitor the renal microcirculation in humans at risk of AKI.

Conflict of interest statement

Conflict of interest: none

Figure legend

Figure 1: Important pathophysiological processes involved in acute kidney injury

Abbreviations: DAMPs = danger-associated molecular patterns; PAMPs = pathogen-associated molecular patterns

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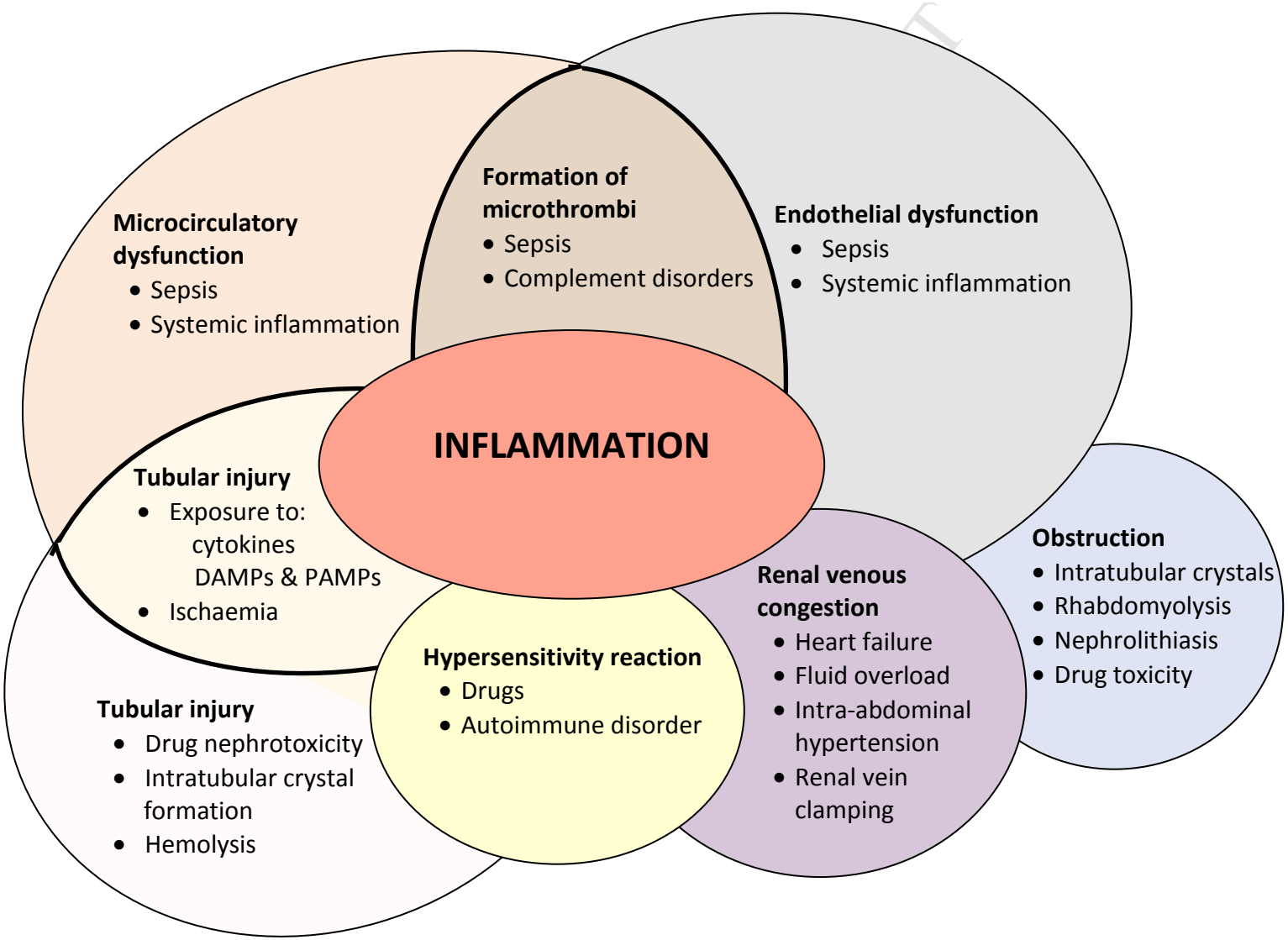
Figure 1


Microcirculatory dysfunction
• Sepsis
• Systemic inflammation
Formation of microthrombi
• Sepsis
• Complement disorders
Endothelial dysfunction
• Sepsis
• Systemic inflammation
INFLAMMATION
Tubular injury
• Exposure to: cytokines DAMPs & PAMPs
• Ischaemia
Obstruction
• Intratubular crystals
• Rhabdomyolysis
• Nephrolithiasis
• Drug toxicity
Renal venous congestion
• Heart failure
• Fluid overload
• Intra-abdominal hypertension
• Renal vein clamping
Hypersensitivity reaction
• Drugs
• Autoimmune disorder
Tubular injury
• Drug nephrotoxicity
• Intratubular crystal formation
• Hemolysis