Original Article

SEVERE INFECTION, SEPSIS AND ACUTE KIDNEY INJURY

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ABSTRACT

Both severe infection and acute kidney injury (AKI) have a high, and rising incidence in critically ill patients admitted to the intensive care unit (ICU), and are associated with increased in-hospital mortality. Septic AKI patients are more severely ill compared to non-septic AKI patients and have worse outcome. Severe infection is a major cause of AKI in ICU patients, while conversely, AKI patients are at increased risk for infection. The dogma from the past relates the development of AKI in sepsis patients to decreased renal blood flow. However, current data suggest that there is no impairment of renal blood flow in patients with sepsis. The pathogenesis of AKI in sepsis is probably related to cytotoxic effects of inflammation, and impaired microcirculation. In addition, hyperglycaemia, and antimicrobial agent-induced drug nephrotoxicity may contribute to the development of AKI. On the other hand, AKI patients are at greater risk for infection as a result of volume overload, dialysis catheter insertion and secondary manipulation, inflammation of the kidneys leading to 'organ cross talk', and impaired host immunity.

INTRODUCTION

Severe infection and sepsis herald an important health treat with an increasing incidence rate in the western world. In the United Kingdom, the proportion of patients admitted to the ICU with severe sepsis increased from 23.5% in 1996 to 28.7% in 2004 (1). This corresponds to an increase in population incidence of 46 patients per 100,000 population admitted with severe sepsis in 1996 to 66 per 100,000 population in 2004. Also, mortality rose from 23 to 30 patients per 100,000 population over the same period. Similarly, in Australia and New Zealand, the population incidence of severe sepsis treated in the ICU is estimated to be 77 per 100,000 population (2). In the United States, the incidence of sepsis was estimated to have increased from 82,7 per 100,000 population in 1979 up to 240,4 per 100,000 population in 2000. Also, sepsis-related mortality decreased from 27.8% to 17.9%, while the total number of deaths increased (3). The considerable difference in population incidence between these 3 regions can probably be explained by differences in patient case-mix. In the United Kingdom, only patients

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with an admission diagnosis of severe sepsis were ir cluded, while in the United States, patients with les severe sepsis admitted to the hospital ward were ir cluded as well. The EPIC study demonstrated that 44.8% of ICU patients had infection, and in almost half of ther infection was acquired while in the ICU (4). Further, AK has a high incidence in ICU patients, and is associate with worse clinical and socio-economic outcome (5-7 Parallel to the increase in sepsis incidence, there is a increasing incidence of AKI (8-11). The epidemiology c AKI is extensively discussed in another paper in thi supplement of Acta Clinica Belgica (12). Sepsis is a important cause of AKI (13-15), and conversely, patient with AKI are also at increased risk for development of severe infection, and sepsis (16, 17). In this paper we will discuss the interaction between AKI and severe infection, and highlight some aspects of the underlying pathophysiology.

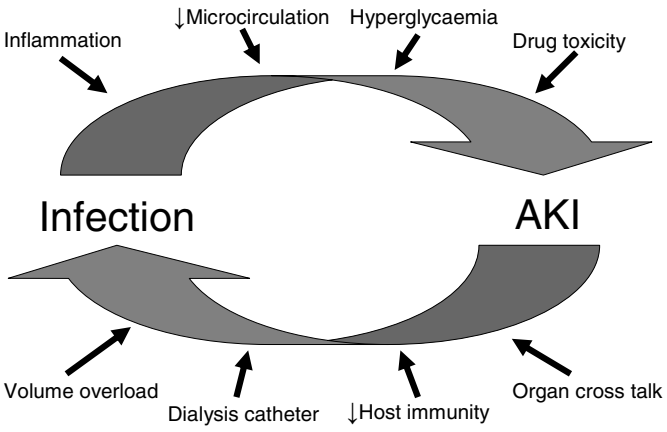

Figure 1

SEVERE INFECTION CAUSES AKI

In almost half of ICU patients with severe AKI, sepsis is the provoking underlying cause (13). Alternatively, 16% of patients who develop sepsis in the ICU will progress to AKI, defined by an increase of serum creatinine to a serum concentration greater than 2 mg/dL (14).

The predominant causes of sepsis-induced AKI are prerenal failure and acute tubular injury (18). Biopsy studies are very scarce, and the few existing studies suffer from selection bias, i.e. only those patients suspected to suffer from other causes of AKI underwent this invasive diagnostic technique (19, 20). Nevertheless, it seems reasonable that a certain number of patients will suffer from acute interstitial nephritis, secondary to antibiotic therapy.

Several pathophysiologic mechanisms can contribute to the development of AKI in a patient with severe infection (figure 1).

Renal perfusion

The classical textbook teaching of critical care nephrology dictates that sepsis-induced AKI is caused by a decreased perfusion of the kidneys, especially the outer medullar region where oxygen supply is limited, and energy demands are high (21). However, there is increasing evidence that renal blood flow, and even medullar blood flow are not decreased in patients with sepsis (22-24). In addition, it was anticipated that vasoconstrictor agents such as norepinephrine would cause deleterious effects on renal blood flow, however, the opposite is true. Norepinephrine leads to an improvement of renal blood flow, medullar blood flow, and creatinine clearance (24-26). The current evidence points more to a deficient microcirculation in the kidneys secondary to inflammation.

Inflammation

Pro-inflammatory cytokines such as tumour necrosis factor (TNF), interleukin (IL)-1, IL-6, and platelet activating factor (PAF) play an essential role in the development of sepsis, and the kidneys are especially vulnerable to cytokine-mediated injury. These cytokines induce a whole cascade of pro-, and anti-inflammatory cytokines, and induce vasoconstriction, neutrophil aggregation, production of reactive oxygen species (ROS), induction of tissue factor, and thrombosis (27, 28). Regional blood flow is also affected by increased concentrations of inducible nitric oxide synthase (iNOS), a vasodilator, and endothelins which are potent vasoconstrictors. Although decreased renal blood flow cannot be held responsible any longer for the development of AKI, deficient microcirculation in the kidney probably is an important factor for the development of AKI. The intra-renal microcirculation is affected by several inflammatory mediators.

Low levels of activated protein C

Activated protein C (aPC) concentrations are decreased in patients with sepsis, and supplementation leads to improved survival amongst the most severely-ill subgroup of ICU patients (29). In an animal model, it has been demonstrated that treatment with aPC results

in an improvement of the microcirculatory blood flow in the kidney, and reduced leucocyte rolling and adherence(30). In addition, substitution with aPC decreased iNOS, the renine-angiotensin system, and caspase-3 activity, and led to improvement of kidney function (30, 31). Whether treatment with aPC results in less AKI in septic patients, or in improved outcome for septic patients with AKI remains, until recently, uncertain.

Hyperglycaemia

Intensive insulin therapy aimed to maintain normoglycaemia has led to improved survival in both patients that were admitted to a surgical and a medical ICU (32, 33). In both studies, patients that were allocated to the intervention group also had less AKI. In the surgical ICU, less patients developed a peak serum creatinine concentration greater than 2.5 mg/dL (12.3% vs. 9.0%, P=0.04), and less patients were treated with renal replacement therapy (RRT) (8.2% vs. 4.8%, p=0.007(32)). In the medical ICU patients' study, the effect of tight glycaemia control on AKI was less prominent: less patients developed a peak serum creatinine concentration greater than 2.5 mg/dL (39.4% vs. 32.5%, P=0.04), and there was no effect on the requirement for RRT (22.7% vs. 20.8%, P=0.5) (33). In conclusion, intensive insulin therapy has a mitigating effect on the occurrence of AKI. The mechanisms of how intensive insulin therapy leads to less AKI are, however, unclear.

Nephrotoxic injury by antimicrobial agents

Antimicrobial agents used in the treatment of severe infection may exert untoward effects to the tubules, interstitial space and vasculature, or may block the distal tubules (34). Tubular cell toxicity may be caused by aminoglycosides, amphotericin, and antiviral agents. Tubular cell toxicity is dependent on the dose, and duration of treatment. Increasing the dosing interval of aminoglycosides appears to result in reduced nephrotoxicity, while efficacy remains comparable (35). Tubular toxicity of amphotericin is reduced when the rate of administration is prolonged to a 24-hour infusion (36). Interstitial nephritis may be caused by a whole range of antimicrobial agents, such as betalactam antibiotics, fluoroquinolones, rifampicin, sulfonamides, tetracyclines, macrolides, and antivirals (37). Interstitial nephritis is an allergic phenomenon, and is independent of the dose of the antimicrobial agent. Finally, crystal deposition in the renal tubules may occur with antiviral agents and sulfonamides (38). Volume depletion exacerbates the nephrotoxic effects on the proximal tubules and crystal deposition in the distal tubules.

AKI CAUSES INFECTION

It is a well-established fact that patients with chronic kidney disease are at greater risk for infection (39). Many of the presumed pathogenic factors of increased risk for infection are also present in AKI patients. It seems, therefore, plausible that also AKI patients are at increased risk for infection. There are only limited data that support this presumption. A greater proportion of patients with AKI after cardiovascular surgery developed infection compared to patients without AKI (58.5% vs. 23.7%, P<0.001) (16). In addition, our group found that AKI patients who are treated with RRT have a greater risk for bloodstream infection compared to ICU patients without AKI (8.8% vs. 3.5%, p<0.001) (17). On top of that, a large proportion of bloodstream infections in this cohort is caused by antimicrobial-resistant pathogens (40), incurring an important economic burden (41, 42). Several factors are responsible for the increased risk for infection in these patients (figure 1). Volume overload may cause pleural effusion and pulmonary oedema, on its turn leading to atelectasis, and pneumonia. Also, intra-abdominal hypertension may develop as a consequence of fluid accumulation in the retroperitoneal compartment, formation of ascites, and bowel oedema. Intra-abdominal hypertension leads to elevation of the diaphragm, atelectasis, and as such, also contributes to the increased risk for pneumonia. In addition, patients may develop bloodstream infection by bacterial translocation from the gut lumen to the bloodstream, and peritonitis secondary to bowel ischaemia. Wound healing will be impaired in patients with volume overload (43). RRT by means of a temporal dialysis catheter increases the risk for catheter-related bloodstream infection (17). Also, retention of uraemic compounds may impair the immune response, as has been demonstrated in patients with chronic kidney disease (39, 44, 45). Finally, inflammation may cause AKI, but AKI may also cause inflammation to other organs, also called 'organ cross talk' (46). For instance, the inflammatory response mediated by the kidney, and/or uraemia may lead to pulmonary oedema, by altered expression of heat shock proteins, down regulation of pulmonary epithelial sodium channels, and aquaporin-5, increased pulmonary vascular permeability, and increased expression of adhesion molecules, and neutrophil infiltration (47-49).

SEPTIC AKI VERSUS NON-SEPTIC AKI

AKI is caused by sepsis in 45% to 50% of patients, and this proportion seems to be stable over the last 10-years (50, 51). Patients with sepsis as a cause of AKI are more severely ill on admission (51). Sepsis patients who develop AKI have a more positive fluid balance, and higher central venous pressure compared to sepsis patients who do not develop AKI (14). Despite this, more AKI patients with sepsis had oliguria at time of diagnosis (51), and more patients had late onset AKI during their ICU stay (50). Prognosis for septic AKI patients is worse compared to non-septic AKI patients (50, 51). However, there is a trend towards greater renal recovery in septic AKI patients (51) .

CONCLUSIONS

Severe infection and sepsis are the most important underlying causes in the development of AKI among ICU patients. Also, septic AKI carries a worse prognosis compared to non-septic AKI. We discussed the different pathogenic mechanisms that all contribute in the development of AKI due to sepsis, but also vice versa, mechanisms that lead to increased risk for infection in AKI patients.

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