Sepsis-induced acute kidney injury

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Introduction

- Progress understanding of the incidence, detection, pathobiology, and treatment of kidney dysfunction in sepsis
- RIFLE definition of acute renal failure in 2004
- KDIGO definition of acute kidney injury
- Changes in kidney function with traditional methods (creatinine, urine output) has grown
- Many serum and urinary biomarkers: earlier detection of AKI
- Potential to improve supportive care and clinical outcomes

Definitions

- AKI as a complication of critical illness associated with mortality
- Consensus definition similar to sepsis
- Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group in 2004
- RIFLE classification (risk, injury, failure, loss, end stage kidney disease): decreased urine output and rise in serum creatinine
- acute kidney injury: underscores the importance of the injury and consequent change in the renal function

Definitions

- Acute Kidney Injury Network (AKIN 2007): initial injury previously deemed risk, injury, and failure of the RIFLE classification → stage 1, 2, and 3 AKI
- Loss and end stage kidney disease in the RIFLE system were removed with the partial reliance on glomerular filtration rate (GFR)
- AKIN criteria included small changes in serum creatinine (>0.3 mg/ dL increase in 48 hours) in the definition of stage 1 AKI
- RIFLE and AKIN: increasing severity of AKI was associated with increasing risk of death

Definitions

- The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines: the most recent consensus definitions
- Extending criteria: a rise in serum creatinine of 50% or greater over the presumed baseline within seven days of assessment
- 57.3% of ICU patients met KDIGO criteria for AKI. The adjusted odds ratio for in-hospital mortality was 1.68 (0.89 to 3.17) for stage 1, 2.95 (1.38 to 6.28) for stage 2, and 6.88 (3.88 to 12.23) for stage 3

Intensive Care Med 2015;41:1411-23

Sepsis associated acute kidney injury

- Sepsis is associated with up to 50% of AKI, and up to 60% of patients with sepsis have AKI
- Patients with sepsis complicated by AKI have a significantly increased mortality relative to patients without AKI.
- Patients with AKI associated with sepsis have a significantly increased mortality relative to those with AKI of another etiology

Clin J Am Soc Nephrol 2007;2:431-9

Epidemiology

- Accurate estimation of the incidence and trend of AKI secondary to sepsis challenging
- AKI attributable to sepsis remains difficult given the many confounders common in critically ill patients
- Incidence of sepsis and related morbidity seems to be rising, whereas the mortality rate of patients with sepsis seems to be falling

N Engl J Med 2003;348:1546-54

Risk factors for development of sepsis associated AKI

- Pre-morbid risk factors for AKI: advanced age, chronic kidney disease, cardiovascular disease
- Acute illness most commonly linked to AKI included cardiovascular failure, liver failure, sepsis
- AKI may predispose patients to increased risk of sepsis
- 243 (40%) patients developed sepsis a median of five days after AKI
- AKI increases the risk of sepsis and associated adverse outcomes

Intensive Care Med 2011;37:241-8

Early detection of SA-AKI

- Sepsis and AKI are associated with increased morbidity, mortality, length of stay, cost of care
- Early detection is critical to providing opportunities for successful intervention
- Increases in serum creatinine or decreases in urine output
- limitations that underscore the need for newer methods to detect AKI and SA-AKI

Limitations of serum creatinine and urine output

- Establishing a baseline serum creatinine
- No consensus method exists to establish pre-AKI baseline serum creatinine in the absence of previous values
- Changes in serum creatinine are delayed by renal reserve and the kinetics of AKI
- Urine output is insensitive measured accurately only in the ICU setting
- Same stage of AKI diagnosed by serum creatinine and urine output may confer differential risk.

Emerging SA-AKI detection techniques

- Urinalysis score above 3: predictive of severe AKI and correlated with biomarkers of tubular injury.
- New albuminuria: associated with odds ratio of 1.87 (1.21 to 2.89) for developing SA-AKI.
- No widely accepted risk score validated for risk of SA-AKI
- The RAI is score in which patients are assigned points based on their risk of AKI (comorbidities) and their degree of injury (change in creatinine clearance)
- RAI: AUC of 0.80 (0.75 to 0.86) for KDIGO stage 2 or 3 on ICU day 3.

Nephrol Dial Transplant 2012;27:582-8, Nephron Clin Pract 2014;128:373-80, Clin J Am Soc Nephrol 2014;9:654-62

Emerging SA-AKI detection techniques

- Proenkephalin and cystatin C: associated with AKI and GFR. Increase before serum creatinine in critically ill patients with sepsis.
- Urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein-7 to predict the development of stage 2 or 3 AKI.
- NGAL: up regulated along the renal tubule in the setting of ischemic injury, nephrotoxins, and inflammation

Ann Lab Med 2017;37:388-97, Crit Care Med 2016;44:1851-60.

Emerging SA-AKI detection techniques

- NGAL: elevated in patients with sepsis even in the absence of AKI.
- Elevations of plasma NGAL even in the absence of elevated serum creatinine.
- Data have been inconsistent in SA-AKI
- Real time data from electronic health record to identify patients with either sepsis or AKI
- Electronic risk score and biochemical biomarkers will be incorporated

Biomark Med 2013;7:415-21, J Am Coll Cardiol 2011;57:1752-61

Pathobiology of SA-AKI

- Renal hypotension and ischemia
- Tubular cell injury and expression of markers such as KIM-1, inflammation, apoptosis
- Macrovascular and microvascular dysfunction, immunologic and autonomic dysregulation
- Disconnect between human and animal data
- limitations of our understanding of the relation between RBF and renal function
- Kidney biopsies from patients with AKI to create a kidney tissue atlas, define disease phenotypes, and identify critical cells, pathways, and targets.

ANZ J Surg 2001;71:15-20

Pathobiology of SA-AKI

- Disturbances in microcirculatory oxygen delivery
- Decreased flow and diffusion limitation
- Inflammatory cytokines and leukocyte activity→ may result in capillary plugging and micro-thrombi
- Reactive oxygen species and induction of nitric oxide synthase → may damage endothelial barrier and the glycocalyx.

Crit Care 2015;19:26.

Prevention and medical treatment

- Endothelial failure and consequent loss of veno-motor tone and barrier function
- Reduction in mean systemic pressure and relative hypovolemic state, paired with decreased systemic vascular resistance→ results in hypotension.
- Administration of intravenous fluids is key component of sepsis management
- Excessive administration and accumulation of fluids is common and harmful

BMJ 2016;353:i1585

Prevention and medical treatment

- Harms of excess fluid during and after development of AKI.
- Cardiac overload with falling cardiac output, resultant renal venous hypertension, increasing resistance, and decreased renal perfusion pressures
- Edema rises in intra-abdominal pressure may inhibit renal venous drainage, further exacerbating elevation of renal vascular pressure.
- Risks of under-resuscitation, volume overload from aggressive over-resuscitation is also harmful, creating J or U shaped curve for resuscitation and mortality.

Crit Care 2008;12:R74, Nat Rev Nephrol 2014;10:193-207, Kidney Int 2009;76:422-7.

Selection of resuscitation fluids

- Hydroxyethyl starches: associated with increased risk of AKI and need for RRT compared with crystalloid solutions.
- Albumin had higher central venous pressures over first 3 days and non-significant trend to decreased mortality but no difference in RRT rates across the two groups.
- Cannot be recommended over less costly crystalloid solutions

N Engl J Med 2012;367:124-34, *Intensive Care Med* 2011;37:86-96

Selection of resuscitation fluids

- Hyperchloremic solutions may be associated with increased AKI and mortality.
- Patients receiving exclusively isotonic saline had higher inpatient mortality than those who were co-administered balanced solutions.
- A pragmatic, cluster randomized, multiple crossover trial at single center with 15,802 patients showed no difference in primary endpoint of hospital-free days
- However, balanced solutions were associated with lower rate of composite endpoint of major adverse kidney events.

JAMA 2012;308:1566-72, Anesthesiology 2015;123:1385-93, N Engl J Med 2018;378:829-39

Vasoactive drugs

- Norepinephrine: mainstay of treatment of septic shock, ability to increase mean arterial pressure (MAP) and improve renal perfusion
- First line agent for septic shock: better outcomes or fewer adverse events than with other vasoactives.
- Vasopressin: similar outcomes and no increased adverse events and survival benefit in subgroup analysis of patients with less severe shock.
- Vasopressin is viable first line alternative to norepinephrine

N Engl J Med 2010;362:779-89, N Engl J Med 2008;358:877-87

Vasoactive drugs

- phenylephrine and dopamine: should be avoided as first line treatment of septic shock.
- Angiotensin II led to significant increase in the MAP
- No difference was seen in inpatient mortality
- Patients treated with RRT showed that those receiving angiotensin II needed less RRT, were more likely to survive through day 28.

N Engl J Med 2010;362:779-89, Crit Care Med 2018;46:949-57

Drug treatment strategies for SA-AKI

- The prophylactic use of diuretics (furosemide) to prevent AKI: Unsuccessful and harmful in critically ill patients.
- Routine use of diuretics for the prevention or treatment of SA-AKI cannot be recommended
- Systemic administration of alkaline phosphatase has shown protection in SA-AKI
- Lower 28 day mortality: 17.4% in patients receiving 1.6 mg/kg compared with 29.5% of those in placebo group.

JAMA 2002;288:2547-53, JAMA 2018;320:1998-2009.

Renal replacement therapy

- The sepsis and SA-AKI specific data: timing of RRT point to potential harm with earlier initiation.
- Early start: increased adverse outcomes including worsening organ failure
- No difference in 60 day mortality between early and delayed arms. A significant increase in renal recovery, as measured by urine output, in patients in delayed arm.
- Not replicated by recent trial investigating timing of RRT in ICU patients.

N Engl J Med 2018;379:1431- 42, Am J Respir Crit Care Med 2018;198:58-66, JAMA 2016;315:2190-9

Renal replacement therapy

- No benefit of increased dosing of RRT.
- Higher doses (70 mL/kg/h) of continuous RRT: do not improve patients' survival.
- Limited data suggest benefit with any specific RRT modality
- No difference in renal recovery or 60 day mortality (56% *v* 55%)
- No data support use of intermittent hemodialysis over continuous RRT.

Intensive Care Med 2013;39:1535-46, N Engl J Med 2008;359:7-20, Crit Care 2014;18:R11

Renal replacement therapy

- Extracorporeal therapies to remove circulating endotoxin
- Patients randomized with 2 sessions of polymyxin B hemoperfusion (n=34) (compared with conventional therapy, n=30) had improved MAPs, lower critical illness scores, lower 28 day mortality.
- Polymyxin B hemoperfusion: not associated with significant difference in mortality at 28 days.
- Not enough evidence to recommend use of hemoperfusion in setting of septic shock or SA-AKI

JAMA 2009;301:2445-52, JAMA 2018;320:1455-63

Renal recovery and other long term outcomes

- No formally accepted definition of renal recovery
- Total recovery (return of serum creatinine to baseline) to persistent AKI requiring RRT which becomes end stage renal disease (ESRD)
- ADQI proposed concept of acute kidney disease, which separated out first 7 days of AKI (KDIGO guidelines), calling first week AKI but differentiating days 8-90 as acute kidney disease
- Recovery and potential progression to chronic kidney disease (CKD)/ESRD

Renal recovery and other long term outcomes

- Given lack of consensus for definitions of recovery from all cause AKI, data specific for SA-AKI recovery are lacking
- Sepsis: associated with increased risk of relapse.
- Americans aged 50 years or older with history of severe sepsis: showed to be 2.5 times more likely to be readmitted to hospital for AKI within 90 days than comorbidity matched patients without sepsis.

Am J Respir Crit Care Med 2017;195:784-91, JAMA 2015;313:1055-7

Summary

- Despite progress in understanding pathobiology of SA-AKI, it remains common and highly morbid complication
- Population change and continued intensive medical interventions are likely to increase its burden in epidemiologic data.
- Vigilance for risk factors for SA-AKI risks is essential
- Critical care practice (fluid, vasoactive, and ventilator management) affect the kidneys
- Understand factors involved in and likelihood of renal recovery and future risk after SA-AKI
- Novel translational animal models, electronic health records data, myriad novel clinical biomarkers

Thank you for your attention