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Sepsis induced AKI

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Epidemiology

- Sepsis and septic shock are important causes of AKI in critically ill patients.
- ***More than 50 % of cases of AKI in the ICU .***
- The mortality associated with AKI can be extraordinarily high and extends beyond in-hospital mortality to longer-term outcomes.

NORMAL RESPONSE TO INFECTION

- Initiated when innate immune cells, particularly macrophages, recognize and bind to microbial components by several pathways:
  - Toll-like receptors (TLRs)
  - Nucleotide-oligomerization domain (NOD) leucine-rich repeat proteins
  - Retinoic-acid-inducible gene I (RIG-I)-like helicases

NORMAL RESPONSE TO INFECTION

Proinflammatory cytokines:
[TNFa]
[IL-1])
chemokines
[ICAM-1]
[VCAM-1]
nitric oxide.

Microbial insult
+
Innate I Cells
(macrophage)

Antiinflammatory mediators :
inhibit the production of TNFa and IL-1
Such mediators suppress the immune system by inhibiting cytokine production by mononuclear cells and monocyte-dependent T helper cells.

(PMNs) become activated and

Inflamation due to: release of mediators by PMNs at the site of infection i

balance between pro and antiinflammatory mediators regulates the inflammatory processes,

Tissue injury or Healing

TRANSITION TO SEPSIS

- ***Sepsis occurs when the release of proinflammatory mediators in response to an infection exceeds the boundaries of the local environment, leading to a more generalized response***

Sepsis

- ***Sepsis is a severe and dysregulated inflammatory response to infection characterized by :***
  - ***end-organ dysfunction such as AKI distant from the primary site of infection***

J Am Soc Nephrol 22: 999–1006, 2011

Sepsis can be conceptualized as malignant intravascular inflammation

- Malignant because it is uncontrolled, unregulated, and self-sustaining
- Intravascular because the blood spreads mediators that are usually confined to cell-to-cell interactions within the interstitial space
- Inflammatory because all characteristics of the septic response are exaggerations of the normal inflammatory response

The clinical diagnosis of sepsis

- Requires finding a focus of infection and at least two signs of systemic inflammatory-response syndrome
  - Body temperature (higher than 38°C or less than 36°C)
  - Heart rate > 90 beats/min
  - Respiration >20 breaths/min or CO_2 < 32 mmHg
  - WBC counts (greater than 12 000/mm3, less than 4 000/mm3, or greater than 10% bands).

The clinical prediction of sepsis related mortality

- SOFA (sequential sepsis related organ failure assessment)
  - The SOFA severity score is based upon the following measurements of organ function (http://clincalc.com/IcuMortality/SOFA.aspx):

    ●Respiratory system : (PaO2/FiO2)
    ●Cardiovascular system : the amount of vasoactive medication necessary to prevent hypotension
    ●Hepatic system : the bilirubin level
    ●Coagulation system : the platelet count
    ●Neurologic system : the Glasgow coma score
    ●Renal system : serum creatinine or urine output

  - The SOFA score has been endorsed by the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) as a tool to facilitate the identification of patients at risk of dying from sepsis

DEFINITION, CLASSIFICATION, AND STANDARDIZATION

	RIFLE criteria	
	sCreatinine	Urine output criteria
Risk	↑ sCrea × 1.5	< 0.5 ml/kg per h × 6 h
Injury	↑ sCrea × 2	< 0.5 ml/kg per h × 12 h
Failure	↑ sCrea × 3 or ⩾ 0.5 mg/dl if baseline sCrea ↑ > 4.0 mg/dl	< 0.3 ml/kg per h × 24 h or anuria × 12 h
Loss	Complete loss of renal function > 4 weeks	
End-stage	End-stage renal disease	

Increasing severity

Outcome

	AKIN criteria	
	sCreatinine	Urine output criteria
Stage 1	↑ sCrea × 1.5 or ↑⩾0.3 mg/dl in sCrea	< 0.5 ml/kg per h × 6 h
Stage 2	↑ sCrea × 2	< 0.5 ml/kg per h × 12 h
Stage 3	↑ sCrea × 3 or ↑⩾0.5 mg/dl if baseline sCrea > 4.0 mg/dl	< 0.3 ml/kg per h × 24 h or anuria × 12 h
Patients who receive RRT are considered to have met stage 3 criteria, irrespective of the stage they are in at the time of RRT		

Increasing severity

Kidney International (2012) 81, 819–825

Pathogenesis of Sepsis-induced AKI

- Older studies were focused on inflammation and global renal blood flow
- Recently to :
  - Renal microvascular alterations :
    - Capillary leak
    - Leukocyte and platelet adhesion with endothelial dysfunction
    - Microthrombi formation
    - immunosuppression

RBF Alterations during Sepsis

- Based on animal studies :
  - RBF may be decreased ?
    - *If this is true, thus sepsis-induced AKI was mainly due to hypoperfusion of kidneys.*

RBF Alterations during Sepsis

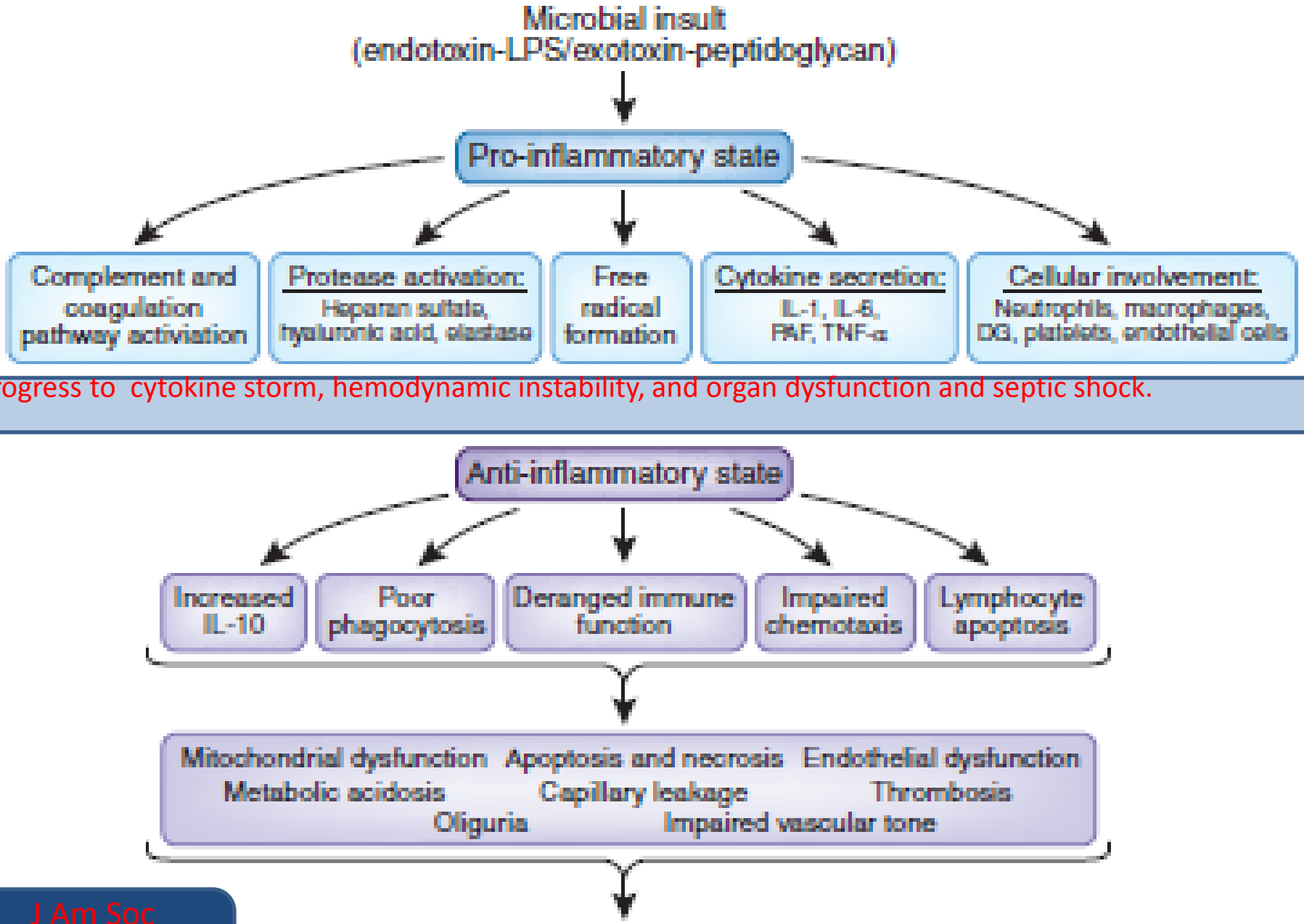
- RBF may be increased :
  - There was renal vasodilation accompanied by a increase in RBF.
  - Despite this increase in RBF, however, creatinine clearance decreased , and serum creatinine increased .
  - These findings strongly suggest that the actual AKI that occurs during sepsis is a hyperemic injury

A plausible explanation for this :

- *Afferent and efferent arterioles are essential regulators of renal perfusion. Simultaneous dilation of both arterioles (with greater efferent than afferent dilation) can lead to decreased glomerular pressure and subsequent decrease in filtration. This is very similar to the observed effects of ACEi and may account for the AKI that accompanies sepsis.*

During sepsis, microvascular dysfunction can occur by several mechanisms:

- 1-blood flow stagnation from altered circulatory cell function (loss of reticulocyte flexibility, increased leukocyte adhesion
- 2- endothelial cell injury
- 3- parenchymal cell injury with oxygen utilization abnormalities and mitochondrial dysfunction
- 4- increased coagulopathy (clotting factors, protein C, tissue factor
- In addition, severe capillary leakage can result in interstitial edema exacerbating low tissue oxygen perfusion, contributing to hypoxia and multiorgan dysfunction.



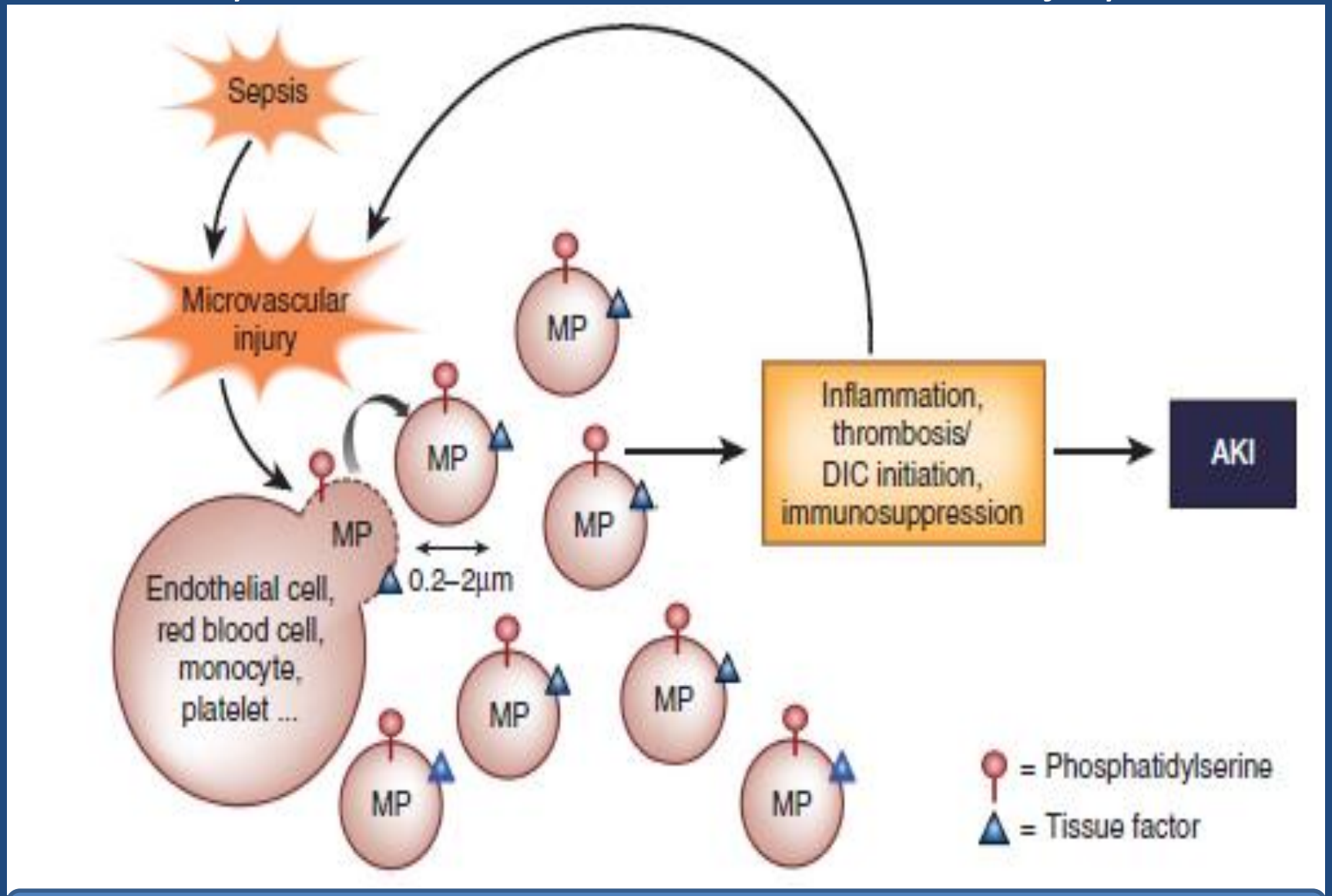
progress to cytokine storm, hemodynamic instability, and organ dysfunction and septic shock.

J Am Soc Nephrol 22: 999–1006, 2011

Microparticles are new class of markers and mediators in the pathogenesis of sepsis.

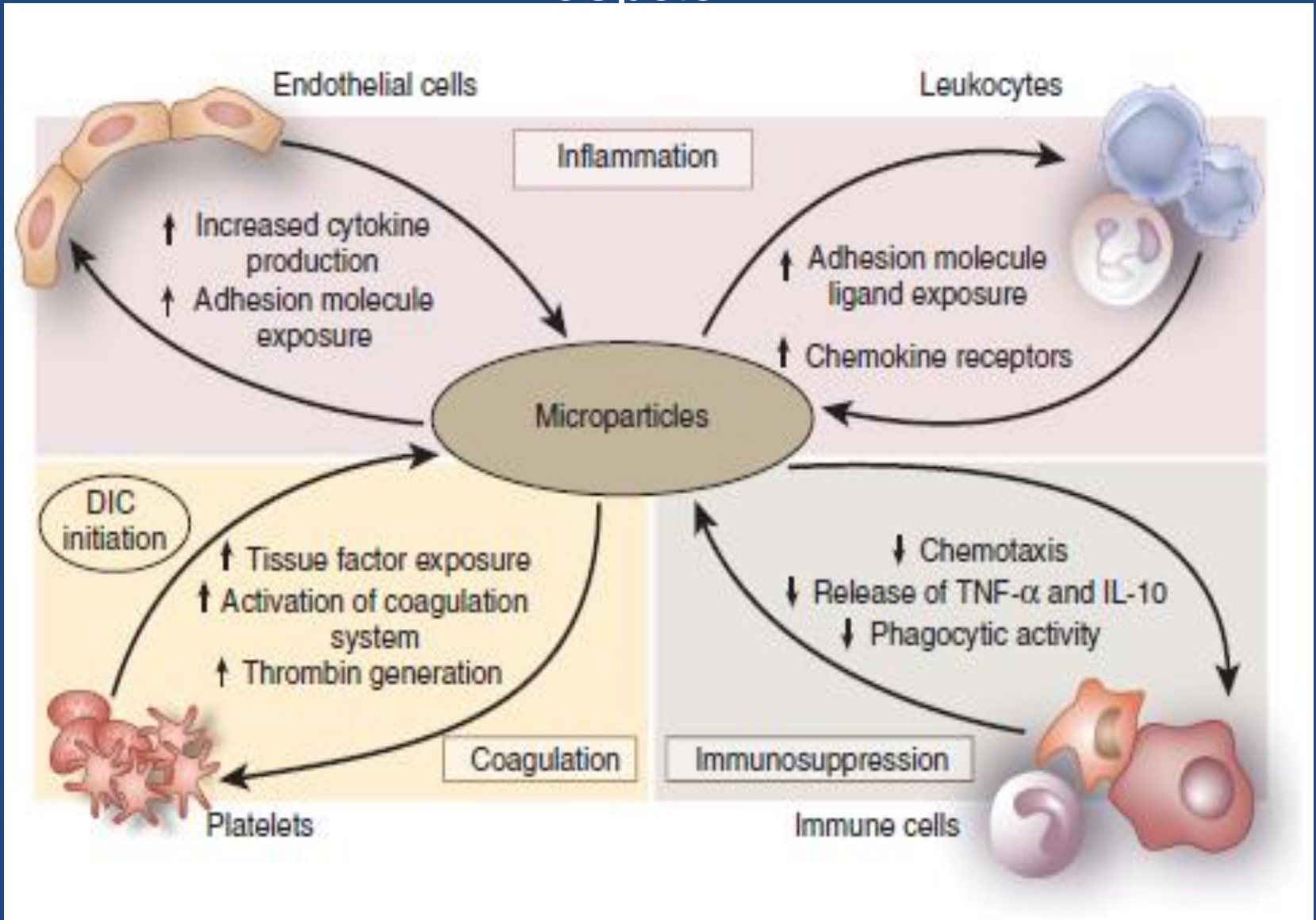
- Microparticles (MPs) are :
  - MPs retain cell membrane and cytoplasmic constituents of their parental cells, including two procoagulants: phosphatidylserine and tissue factor.
  - can promote coagulation
  - inflammation
  - angiogenesis
  - they can participate in cell-to-cell communication.

Schematic view of sepsis-induced microparticles (MPs) released into the systemic circulation after microvascular injury

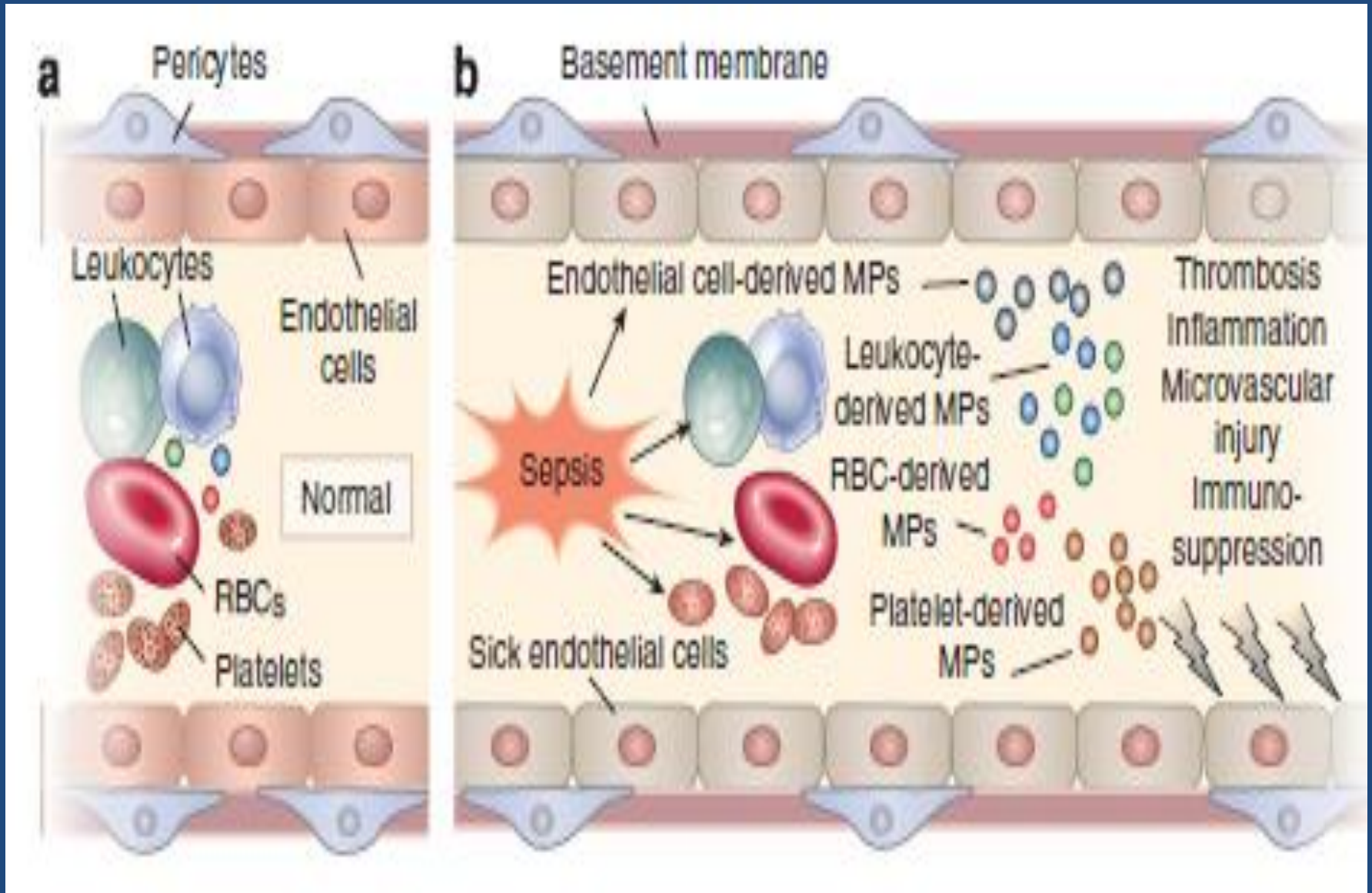


Kidney International (2015) 87, 1100–1108;

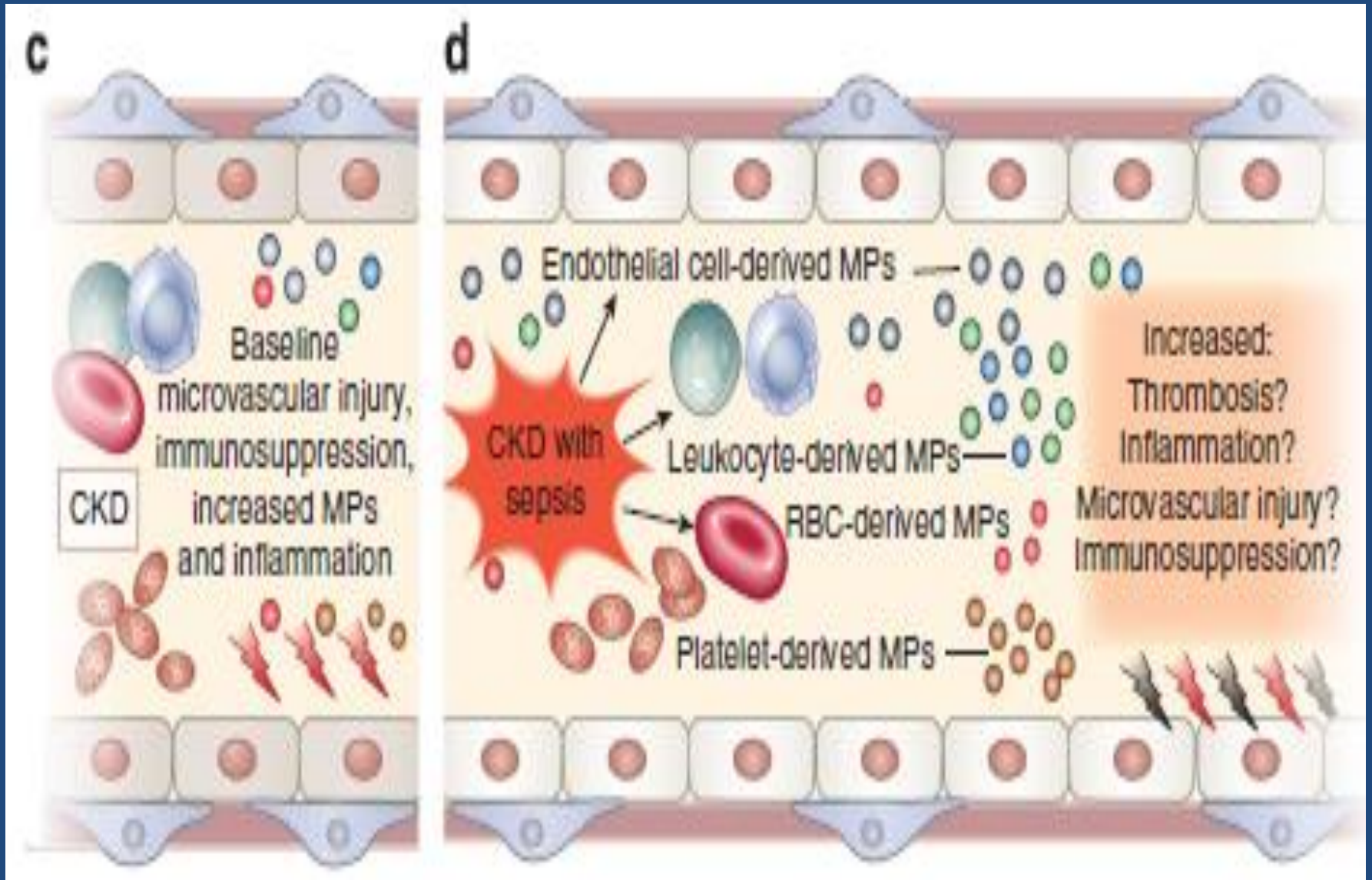
Schematic representation of functions attributable to microparticles (MPs) during sepsis



Schematic representation of proposed roles of microparticles as an accelerant of microvascular injury when sepsis-AKI occurs



Schematic representation of proposed roles of microparticles as an accelerant of microvascular injury when sepsis-AKI occurs with underlying CKD.



Limitations on changes in creatinine as a reliable marker of AKI

- AKI can be diagnosed by small changes in serum creatinine or acute reductions in urine output BUT
  - with delay
  - sepsis decreases production of creatinine without major alterations in body weight, hematocrit, or extracellular fluid

New biomarkers in Sepsis-induced AKI

- Excretion of IL-18 is higher in septic AKI than in non septic AKI.
  - Moreover, an increased level of IL-18 predicts deteriorating kidney function approximately 24 to 48 hours before clinically significant AKI.
- A recent study demonstrated that septic AKI have higher plasma and urine NGAL compared with non septic

Table 1. A partial list of emerging biomarkers for early detection of acute kidney injury

Biomarker	Source of Sample	Elevation in Sepsis-induced AKI	Reference
Cystatin C	Plasma	Intermediate	44,76
L-FABP	Urine	Early	45,49
IL-18	Urine	Intermediate	35,36
NGAL	Plasma	Early	42,77
KIM-1	Urine	Intermediate	44,48,76
Netrin-1	Urine	Early	46,47,78

L-FABP, L-type fatty acid–binding protein; NGAL, neutrophil gelatinase-associated lipocalin; KIM-1, kidney injury moleclue-1.

utility of novel biomarkers for early detection , pathogenesis and prognosis of sepsis-induced AKI is very encouraging

Identification of Urinary Activin A as a Novel Biomarker Reflecting the Severity of Acute Kidney Injury

- Activin A was undetectable in the urine of normal mice. but, significantly increased in ischemic mice at 3 h after reperfusion.
- In humans, urinary activin A undetectable in healthy and in pre-renal AKI, but was significantly increased in renal AKI.
- There was no significant correlation between urinary activin A and serum activin A.
- ***Collectively, urinary activin A might be a useful biomarker reflecting the severity of AKI.***

Scientific Reports **volume 8**, Article number: 5176(2018)

Attempts directed at limiting and reversing sepsis induced AKI

- Considering the very high and even growing number of patients with sepsis in the United States and other parts of the world, there is an urgent need for new approaches and treatment
- ***There are certain key gaps in the field of sepsis induced AKI that require further research***
- ***MPs are potential therapeutic targets to prevent or treat sepsis and sepsis-AKI***

Critical Care Medicine: April 2018 - Volume 46 - Issue 4 - p 658–660

Therapeutic Options for the present and future

- Supportive treatment include :
  - Fluid management
  - Antibiotics
  - Vasopressors
  - Diuretics
  - Dialysis
- pharmacologic attempts directed at limiting and reversing sepsis induced AKI

pharmacologic attempts directed at limiting and reversing sepsis induced AKI

- It is imperative to note that sepsis affects several pathways including:
  - injury caused by endotoxin
  - complement cascade
  - Coagulation pathway activation
  - release of arachidonic acid and nitric oxide
  - vascular injury, and others that mediate the development and course of sepsis.
- Such complexity may have been an important contributor to the failure of clinical trials targeting just one of these pathways.

Nature Reviews Nephrology **volume14**, pages217–230(2018)

A potential therapies for sepsis appear promising in animal, but have not yet been adequately studied in humans

- Toll-like receptor antagonists 2
- Neutralizing ntibodies
- Talactoferrin
- Interferon gamma
- Macrophage migration inhibition factor
- Synthetic peptide that inhibits bacterial superantigen-induced expression of certain proinflammatory genes.

Potential therapies for sepsis that studied in humans, but have conflicting results and require additional investigations

- Polyclonal intravenous immune globulin (IVIG)
- Interleukin-1 receptor antagonists
- Hemoperfusion through adsorptive materials or membranes
- Plasma exchange
- Whole blood exchange
- Coupled plasma filtration adsorption
- Granulocyte-macrophage colony stimulating factor (GM-CSF)
- Hemofiltration (remove proinflammatory molecules)
- Anticoagulants
- Naloxone : (lead to hemodynamic improvement)
- Pentoxifylline (increase red cell deformability and decrease erythrocyte aggregation)
- Statins.(antiinflammatory properties, such as suppression of endotoxin-induced up-regulation of TLR- 4 and TLR-2)
- B blocker (attenuate the deleterious effects of the sympathetic adrenergic response that occurs during septic shock

potential therapies for sepsis have been investigated, but either caused harm or failed to improve clinical outcomes

- Recombinant human activated protein C : drotrecogin alfa promotes fibrinolysis and inhibits thrombosis.
- **The Toll-like receptor (TLR)-4 antagonist (Resatorvid)**
- **The human anti-endotoxin monoclonal antibody, HA-1A**
- **The human anti-Enterobacteriaceae common antigen (ECA) monoclonal antibody**
- **Alkaline phosphatase**
- **Granulocyte colony-stimulating factor (filgrastim, G-CSF)**
- **Anti-tumor necrosis factor monoclonal antibody**
- **Tumor necrosis factor receptor antagonist**
- **Interleukin-1 receptor antagonist**
- **Antithrombin (formerly known as antithrombin III)**
- **Recombinant human tissue factor pathway inhibitor (tifacogin)**
- **Ibuprofen**
- **N-acetylcysteine**

Nitric oxide inhibitors

- **The bradykinin antagonist, deltibant**
- **Growth hormone**
- **Intravenous selenium supplementation**
- **Talactoferrin – restores the barrier properties of the gastrointestinal mucosa**
- **Calcitriol**
- **Levosimendan**

pharmacologic attempts directed at limiting and reversing sepsis induced AKI

- MSCs or their microvesicles were effective in various animal models of diseases including AKI.
- Their renoprotective effects are complex but are mainly mediated by:
  - paracrine mechanisms that act on surviving tubular cells by stimulating proliferation, migration, and ultimately differentiation into mature epithelial cells as well as by stimulating expansion and differentiation of resident progenitor stem cells.

Maresin 1 attenuates mitochondrial dysfunction through the ALX/cAMP/ROS pathway in the cecal ligation and puncture mouse model and sepsis patients

- *Laboratory Investigation* (2018) doi:10.1038/s41374-018-0031-x

pharmacologic attempts directed at limiting and reversing sepsis induced AKI

- VEGF levels are elevated among septic patients
- They are correlated with mortality
- Anti-VEGF antibody (bevacizumab) has been shown to attenuate inflammation and decrease mortality in an experimental model of severe sepsis

Metabolic reprogramming and tolerance during sepsis-induced AKI

- The capacity of the host to decrease its own susceptibility to inflammation- induced tissue damage — termed tolerance — might be as important as resistance in determining the outcome of the infection.
- Metabolic adaptations are central to the function of the cellular immune response.
- Coordinated reprogramming of metabolic signalling enables cells to execute resistance and tolerance pathways, withstand injury, steer tissue repair and promote organ recovery.
- *Nature Reviews Nephrology* **volume13**, pages143–151(2017)

- *J Am Soc Nephrol 22: 999–1006, 2011*
- *Kidney International (2010) 77, 485 – 487.*
- Kidney International (2012) 81, 819–825
- Kidney International (2015) 87, 1100–1108;
- *Scientific Reports* volume 8, Article number: 5176(2018)
- *Nature Reviews Nephrology* volume14, pages217–230(2018
- *Laboratory Investigation* (2018) doi:10.1038/s41374-018-0031-x
- *Nature Reviews Nephrology* volume13, pages143–151(2017)
- Critical Care Medicine:April 2018 - Volume 46 - Issue 4 - p 658–660

The END

pharmacologic attempts directed at limiting and reversing sepsis induced AKI

- Activated drotrecogin alfa, also known as recombinant human activated protein C, improve survival in patients with severe sepsis and septic shock.

pharmacologic attempts directed at limiting and reversing sepsis induced AKI

- In critically ill patients with sepsis-associated AKI, treatment with Alkalin phosphatase (AP) reduced the urinary excretion of tubular injury biomarkers and plasma markers of inflammation, which was associated with improvement of renal function.
- Action of AP in AKI is unknown
- But might be related to detoxification of circulating lipopolysaccharide and other proinflammatory mediators that lose their proinflammatory effects after dephosphorylation.

pharmacologic attempts directed at limiting and reversing sepsis induced AKI

- Anti-TNF monoclonal antibodies have beneficial effects in several animal models of sepsis Nonetheless, these and other cytokine-blocking failed in clinical trials.
- Toll-like receptors (TLRs) are a class of proteins that play an important role in alerting the innate immune system
  - Modulation of TLRs may become a novel therapeutic target especially in the treatment of organ injury in sepsis.

pharmacologic attempts directed at limiting and reversing sepsis induced AKI

- ***Inhibition of platelet-activating factor, endothelin, anti-thrombin, tissue factor pathway, leukocyte adhesion, and administration of natriuretic peptides and growth factors were all promising novel therapeutic approaches that unfortunately either never made it to clinical trials or failed to produce the desired effects in large clinical trials.***

Table 5. Focus areas of interest in sepsis-induced acute kidney injury (AKI) research

1.	Optimization of animal models that closely mimic human sepsis and AKI
2.	Role of immune modulation in sepsis-induced AKI
3.	Identification of specific biomarker profile for sepsis-induced AKI
4.	Appropriate fluid management in sepsis-induced AKI
5.	Retesting therapeutic interventions in sepsis-induced AKI using novel biomarkers rather than creatinine based changes
6.	Key endpoints in clinical trials of sepsis-induced AKI

Biomarkers in Sepsis-induced AKI ?

- A recent study demonstrated that septic AKI have higher plasma and urine NGAL compared with nonseptic
- utility of novel biomarkers ie NGAL ,cystatin C, liver fatty acid– binding protein, and netrin-1 for early detection , pathogenesis and prognosis of sepsis-induced AKI is very encouraging
  - For instance, urinary liver fatty acid– binding protein is significantly higher in AKI than non-AKI in adult ICU patients

Epidemiology ?

- Observations supports the thesis that absolute risk for poor outcomes is more strongly related to acute changes in kidney function than to baseline kidney function.
- Although patients with chronic kidney disease at baseline may carry a greater risk of developing AKI
- The risk for mortality appears to be more strongly associated with the absolute increase in serum creatinine.

sepsis-induced AKI ?

- Major problem to early diagnosis, and appropriate therapeutic modalities in sepsis-induced AKI include:
  - limited histopathologic information
  - Few animal models that closely mimic human sepsis
  - A relative shortage of specific diagnostic tools
  - reliance on creatinine for assessment of kidney function.

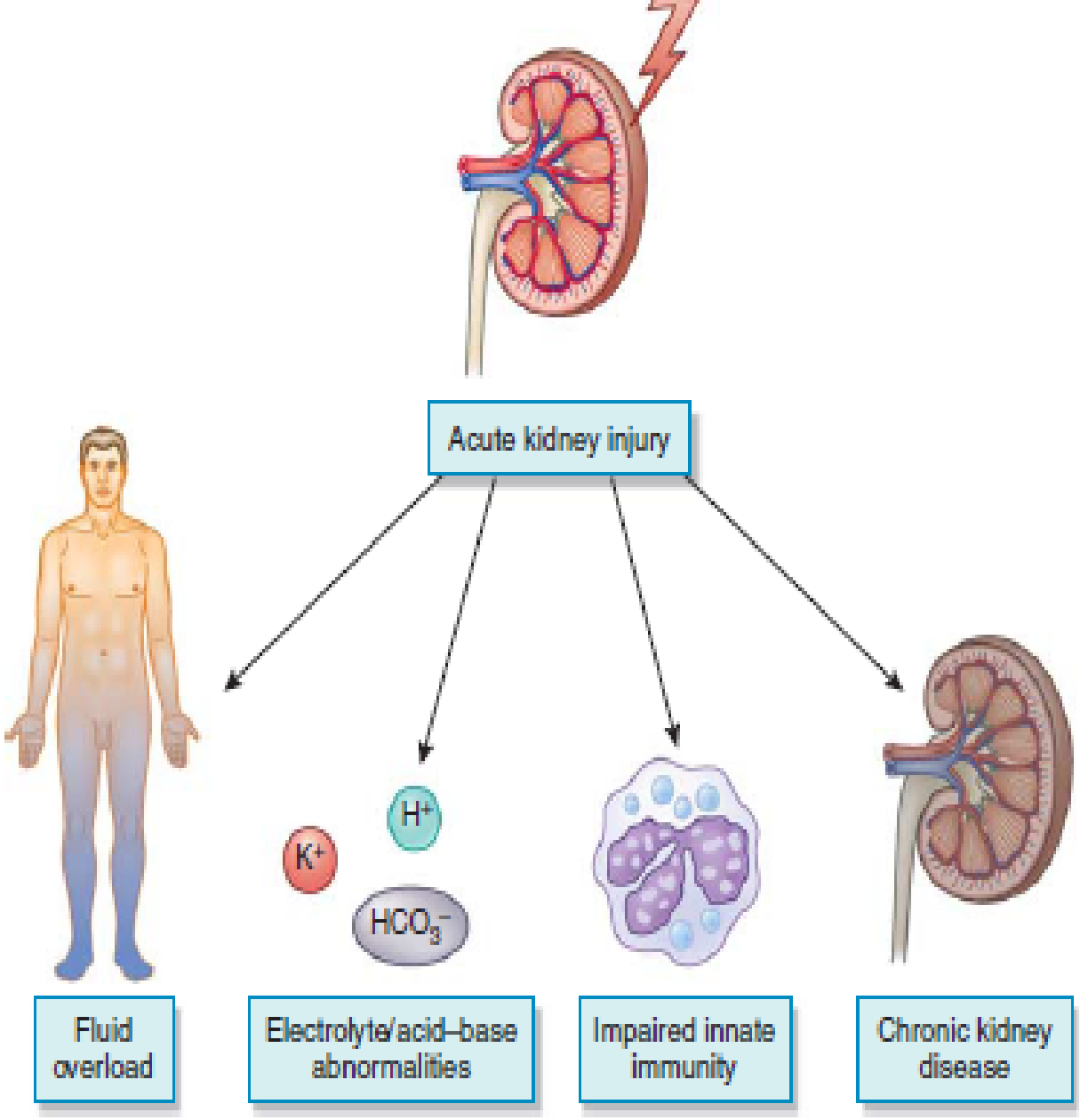
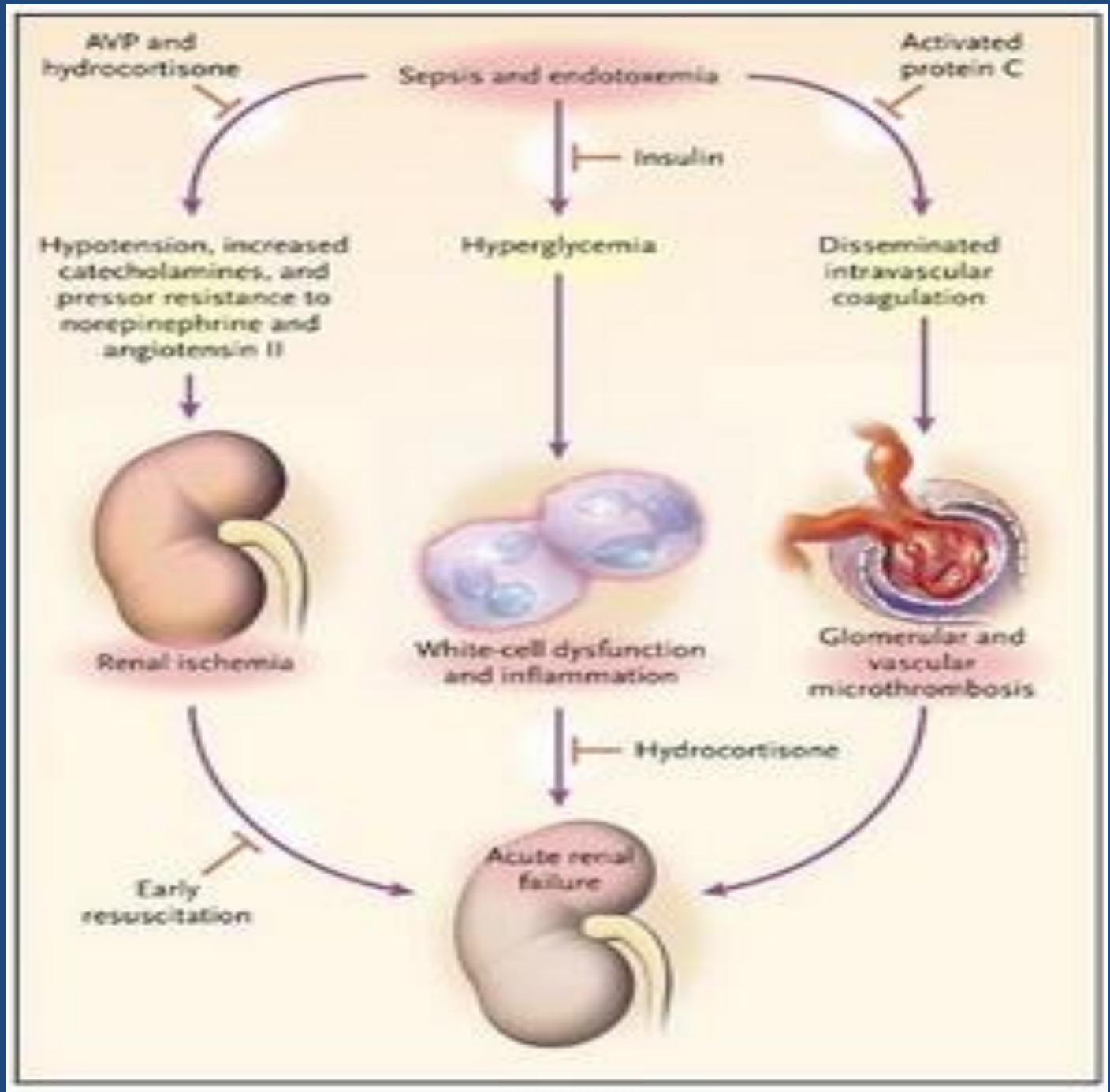


Figure 2 | Acute kidney injury (AKI) can have both immediately recognizable consequences as well as less noticeable or delayed consequences. Fluid overload and electrolyte/acid-base abnormalities represent well known, easily recognized consequences of AKI. Contrary, impaired innate immunity and chronic kidney disease do not manifest themselves immediately.


AVP and hydrocortisone
Sepsis and endotoxemia
Activated protein C
Insulin
Hypotension, increased catecholamines, and pressor resistance to norepinephrine and angiotensin II
Hyperglycemia
Disseminated intravascular coagulation
Renal ischemia
White-cell dysfunction and inflammation
Glomerular and vascular microthrombosis
Hydrocortisone
Early resuscitation
Acute renal failure

Maresin 1 attenuates mitochondrial dysfunction through the ALX/cAMP/ROS pathway in the cecal ligation and puncture mouse model and sepsis patients

- Inflammation always accompanies infection during sepsis. Mitochondrial dysfunction and the role of reactive oxygen species (ROS) produced by mitochondria have been proposed in the pathogenesis of sepsis. Maresins have protective and resolving effects in experimental models of infection. In the present study, we investigated the effects of maresin 1 (MaR1) on mitochondrial function in cecal ligation and puncture (CLP)-induced sepsis and sepsis patients to identify mechanisms underlying maresin 1-mediated stimulation of ROS in mitochondria. We found that treatment with MaR1 significantly inhibited production of cytokines, decreased bacterial load in the peritoneal lavage fluid, reduced the number of neutrophils, decreased lactic acid level and upregulated cyclic AMP (cAMP) concentration, with the outcome of decreased lung injury in CLP-induced sepsis in mice. The effects of MaR1 on downregulation nitric oxide (NOX) activity, improvement CAT and SOD activity to inhibit ROS production in mitochondria was dependent on lipoxin receptor (ALX) and cAMP. Survival rates were significantly increased after the treatment of mice with MaR1. In BMDM stimulated with LPS, MaR1 inhibited the ROS production, downregulated enzyme activity, reduced mtO2 production, increased mitochondrial membrane potential, improved adenosine triphosphate (ATP) content and mitochondrial DNA (mtDNA) copy number. Finally, the effects of MaR1 on ROS production in the blood of healthy volunteers stimulated with LPS or sepsis patients were associated with ALX and cAMP. Taken together, these data suggest that treatment with MaR1 could attenuate mitochondrial dysfunction during sepsis through regulating ROS production.

Metabolic reprogramming and tolerance during sepsis-induced AKI

- The host defence against infection is an adaptive response in which several mechanisms are deployed to decrease the pathogen load, limit tissue injury and restore homeostasis. In the past few years new evidence has suggested that the ability of the immune system to limit the microbial burden — termed resistance — might not be the only defence mechanism. In fact, the capacity of the host to decrease its own susceptibility to inflammation- induced tissue damage — termed tolerance — might be as important as resistance in determining the outcome of the infection. Metabolic adaptations are central to the function of the cellular immune response. Coordinated reprogramming of metabolic signalling enables cells to execute resistance and tolerance pathways, withstand injury, steer tissue repair and promote organ recovery. During sepsis-induced acute kidney injury, early reprogramming of metabolism can determine the extent of organ dysfunction, progression to fibrosis, and the development of chronic kidney disease. Here we discuss the mechanisms of tolerance that act in the kidney during sepsis, with particular attention to the role of metabolic responses in coordinating these adaptive strategies. We suggest a novel conceptual model of the cellular and organic response to sepsis that might lead to new avenues for targeted, organ-protective therapies.
- *Nature Reviews Nephrology* **volume13**, pages143–151(2017)

Paradigms of acute kidney injury in the intensive care setting

- Acute kidney injury (AKI) is a heterogeneous clinical syndrome that has multiple aetiologies, variable pathogenesis and diverse outcomes. However, these heterogeneities are not reflected in current approaches to the diagnosis and, to some degree, treatment of AKI. For example, congestive heart failure and dehydration can produce identical changes in serum creatinine level and urine output (parameters that are used to define AKI); however, they differ vastly in their physiological contexts and demand completely opposite treatments. AKI is often still considered to be a homogeneous clinical entity, which implies a uniform pathogenesis and a well-defined prognosis. As a consequence, efforts to find effective AKI treatments have been hampered by a lack of clear clinical classifications for various types of AKI. In addition, subclassification of AKI into subclinical phenotypes — for example, on the basis of protein biomarkers and other *in vitro* diagnostics that take into account disease aetiology and underlying pathogenesis — might be necessary to develop therapeutic approaches that effectively target the widely differing pathomechanisms of AKI. In this Review, we discuss the major subtypes of AKI that are associated with sepsis, major surgery, renal hypoperfusion and nephrotoxin exposure —situations that are typically seen in the intensive care setting. We consider differences and similarities in their phenotype, pathogenesis and outcomes and how this information might be used to guide treatment.
- *Nature Reviews Nephrology* **volume14**, pages217–230(2018)

Identification of Urinary Activin A as a Novel Biomarker Reflecting the Severity of Acute Kidney Injury

- Acute kidney injury (AKI) is a common but complex condition that is associated with increased morbidity and mortality. In the present study, we examined whether urinary activin A, a member of the TGF-beta superfamily, is present in mice with ischemia-reperfusion injury and in humans with AKI, as well as its potential as a biomarker for AKI. Expression of activin A was markedly increased in ischemic mouse kidneys. *In situ* hybridization demonstrated that activin mRNA was expressed in tubular cells of ischemic kidneys but not of normal kidneys. Immunoreactive activin A, which was absent in normal kidneys, was detected in the cytoplasm of proximal tubular cells in ischemic kidneys. Activin A was undetectable in the urine of normal mice. In contrast, activin A was significantly increased in the urine of ischemic mice at 3 h after reperfusion. Urinary activin A levels increased according to the period of ischemia. In humans, urinary activin A was almost undetectable in healthy volunteers and in patients with pre-renal AKI, but was significantly increased in patients with renal AKI. There was no significant correlation between urinary activin A and serum activin A. Collectively, urinary activin A might be a useful biomarker reflecting the severity of AKI.
- *Scientific Reports***volume 8**, Article number: 5176(2018)

Sepsis-Induced Renal Failure: Ischemia or Toxemia?*

- Critical Care Medicine:April 2018 - Volume 46 - Issue 4 - p 658–660
- **Abstract**
- **BACKGROUND:**
- Worldwide, both acute kidney injury (AKI) and sepsis are significant clinical complications, particularly in critical care patients. Sepsis is an important cause of AKI, and AKI is a common complication of sepsis.
- **METHODS:**
- We reviewed the literature, including current practice guidelines, on sepsis-associated AKI.
- **RESULTS:**
- We assessed causes of renal failure, potential mechanisms of sepsis-associated acute kidney injury, current practice guidelines, diagnostic criteria and methods, prevention strategies, treatment options, and outcomes.
- **CONCLUSION:**
- In patients with sepsis-associated AKI, appropriate fluid resuscitation and maintenance of blood pressure are important to prevent further kidney damage. Despite multiple clinical trials, the mechanisms of sepsis-associated AKI and the best treatment options remain unclear.

- **Acute Kidney Injury in Sepsis**
- **ICM ARTICLE REVIEW**
- *Septic acute kidney injury (AKI) is a syndrome of acute loss of renal function and organ damage, defined by the simultaneous presence of both Sepsis-3 and KDIGO criteria. AKI is a common complication of sepsis: up to 65 percent of patients with septic shock develop AKI and their mortality is as high as 20-60 percent.*
- Bellomo et al. reviewed the key aspects of the definition, pathogenesis, prevention and treatment of this frequent but still poorly understood syndrome. AKI is a clinical diagnosis, based on serum creatinine and urinary output. Because of the late increase in serum creatinine during the course of AKI and the non-specificity of urinary output as a marker of renal function, novel biomarkers have been evaluated for their ability to detect renal damage before functional change is evident (preclinical AKI) or even in the absence of functional change (subclinical AKI) and predict the need for RRT.
- Septic AKI pathogenesis knowledge is mostly based on animal models. It may develop in the presence of preserved or increased renal blood flow, with a reduction of the glomerular filtration rate due to changes in the intrarenal haemodynamic. Septic AKI may be characterised by a redistribution of flow away from the renal medulla to the renal cortex with a degree of medullary deoxygenation and activation of intrarenal shunting pathways. Tubular injury may be caused by a direct toxic effect on tubular cells of ultra-filtrated inflammatory molecules together with a local response to pathogen associated molecular patterns. The lack of histological changes confirms that, at least initially, septic AKI may be a functional phenomenon.
- Prevention of septic AKI, based on the identification of patients at increased risk of AKI and the treatment of sepsis, is critical to improve outcomes. Earlier and appropriate antimicrobial therapy, along with septic source control, has been associated with lower risk of AKI. Early goal directed therapy failed to show benefit in terms of incidence of AKI, utilisation of RRT, kidney recovery and mortality in recent trails. Aggressive fluid administration, combined with oliguria, may lead to renal oedema with congestion and ischaemia. Both chloride-rich crystalloids (saline) and artificial colloids (hydroxyethyl starch and gelatins) have been related to AKI and mortality. Vasoactive drugs remain the cornerstone of hypotension management, with patients having a history of hypertension requiring a target mean arterial pressure above 80 mmHg. At this time, norepinephrine is the dominant agent, despite no vasopressor has shown better renal protection compared to the others. For septic patients requiring RRT, the optimal timing and cessation remains uncertain. Continuous RRT modalities are more frequently used and recommended for haemodynamically unstable patients. A delivered dose of 20-25 ml/kg/h is the current standard of practice.
- **Conclusion**
- This paper raises awareness of septic AKI within the critical care community, providing clinicians with several reference points which can be easily applied in the clinical practice. Because of the limited understanding of AKI physiopathology and given that there are no effective therapies for the treatment of established AKI, early detection of AKI and optimisation of preventive measures are of pivotal importance. The identification of a “renal troponin”, with a high sensitivity and specificity, may lead to a new definition of septic AKI.

- May 30, 2017
- **Intensive Care Medicine journal**

Sepsis-induced AKI

- Sepsis is the most common cause of AKI.
- Evidence now suggests that the pathogenic mechanisms of sepsis-induced AKI are different from those seen in other etiologies

Curr Opin Crit Care. 2014 December ; 20(6): 588–595.

Sepsis-induced AKI

- The traditional paradigm :
  - Sepsis-induced AKI arises from ischemia
- Recent evidence :
  - total RBF is not universally impaired during sepsis, and AKI can develop in the presence of normal or even increased RBF.
  - Animal and human studies suggest that adaptive responses of tubular epithelial cells to injurious signals and
  - Simultaneously occurring renal inflammation and microcirculatory dysfunction further amplify this

Sepsis-induced AKI

- *In vitro experiments have revealed that incubating human epithelial cells with plasma from septic patients resulted in decreased cell function and shortened the survival of tubular cells and podocytes, suggesting that the plasma from septic patients can induce renal cell injury and dysfunction absent any vasculature or circulating immune effector cells.* [10**, 11].

Sepsis-induced AKI

- A consistent finding in septic humans, independent of the severity of AKI, is the presence of three pathologic findings:
  - ***Microcirculatory dysfunction***
  - ***Inflammation***
  - ***Bio-energetic adaptive response to injury.***

Pathophysiology of sepsis-induced AKI

- **Renal microcirculation during sepsis-induced AKI:**
  - Sepsis causes a profound alteration of the macro- and microcirculation and is characterized by:
    - a decreased peripheral vascular resistance
    - maldistribution of tissue blood flow
    - derangement of microcirculatory perfusion
  - These alterations cause :
    - decrease in functional capillary density
    - an increment in the heterogeneity of regional blood flow distribution

BMC anesthesiology. 2013; 13:25.
Lancet. 2002; 360:1395–6.

- Platelets, fibrin, stiff red blood cells and leukocytes together with endothelial cell swelling are responsible for capillary occlusion [21]. Increased vascular permeability is a common feature in sepsis and leads to interstitial edema and fluid retention

- Endothelial cells are important determinants of vascular tone, leukocyte recruitment and function, and alter the responsiveness of smooth muscles [28]. Injured endothelial cells produce less vasodilators (e.g. nitric oxide) resulting in a more pronounced response to vasoconstrictors with a redistribution of blood flow

- The imbalance between vasoconstrictors, vasodilators and oxidative stress at the endothelial level is receiving considerable attention as a major contributor to the development of AKI

- Nitric oxide (NO) plays a pivotal and multifaceted role in the complex pathophysiology of sepsis [30] and sepsis-induced AKI [31]. During sepsis, global NO production increases, whereas the producing enzyme, inducible NO synthase (iNOS), has a heterogeneous expression pattern, resulting in different regional concentrations of NO [30]. The uneven distribution of NO production may contribute to the heterogeneous perfusion pattern. However, elevated NO also influences renal hemodynamics and causes peroxynitrite-related tubular injury through the local generation of reactive nitrogen species during sepsis [32]. Evidence suggests that this may play an important role as up-regulation of iNOS has been associated with proximal tubular injury during systemic inflammation, and its selective inhibition, with amelioration of the functional impairment caused by cecal ligation and puncture [33]. Therefore, the selective inhibition of renal iNOS might have an implication for the treatment of sepsis-induced AKI.
- **Inflammation propagates renal damage during**

Inflammation propagates renal damage during sepsis

- There is a strong association between cytokine levels (interleukin (IL)-6, IL-10, and macrophage migration inhibitory factor) and the development of sepsis-induced AKI

- During sepsis, infection triggers a host response, in which inflammatory mechanisms contribute to clearance of infection and tissue recovery on the one hand, and organ injury on the other

Adaptive responses of tubular cells to changes in the local environment

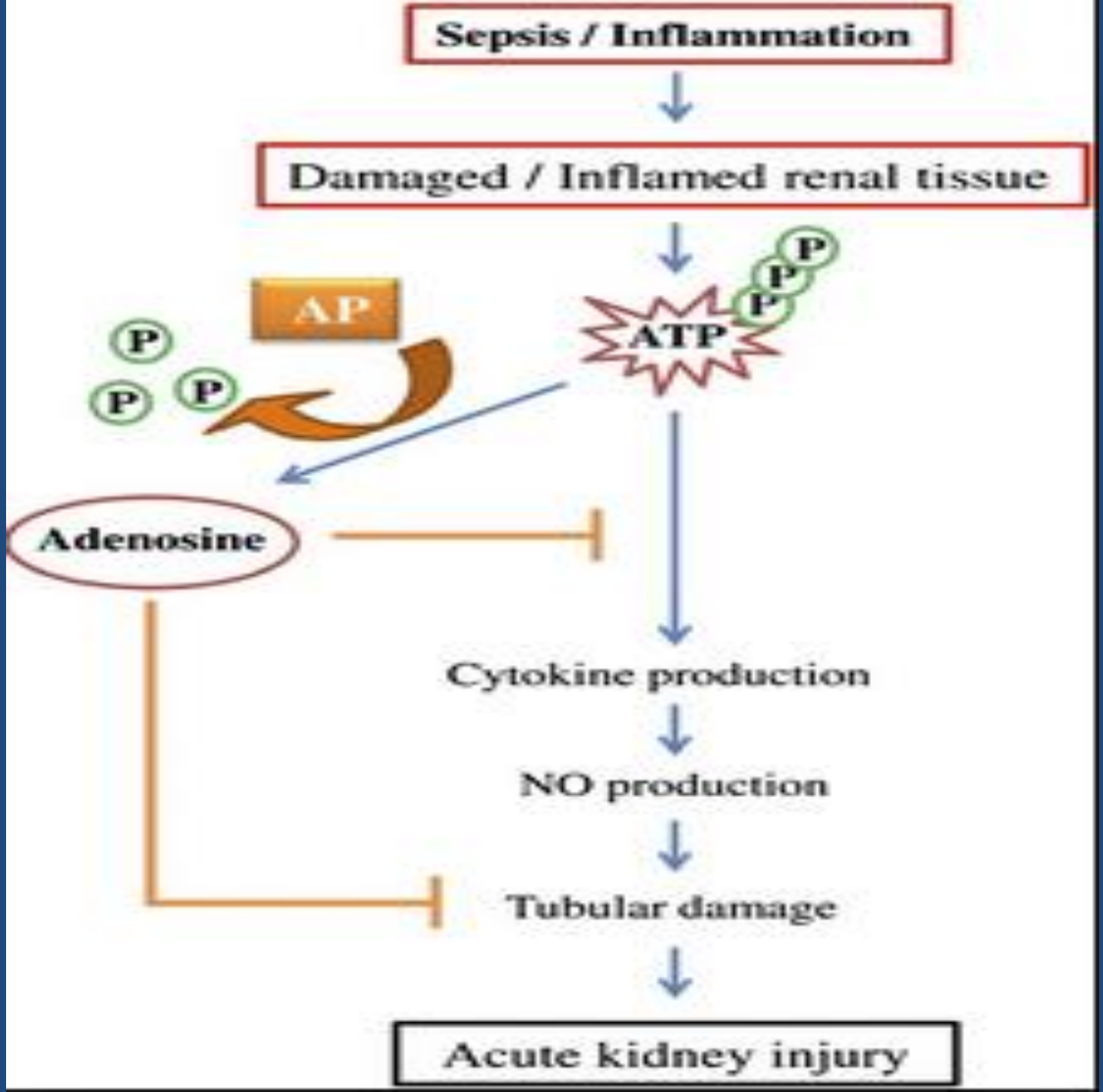
- Tubular cells exposed to inflammation and the consequences of microcirculatory dysfunction act as primary targets and respond by adaptation to the altered tubular environment. They may also spread this signal and shutdown other tubular cells in a paracrine fashion
- Oxidative stress is a hallmark of sepsis-induced AKI.
- Oxidative stress is also linked to tubular dysfunction

Lancet. 2004; 364:545–8.

- To date no therapeutic measures are available to prevent or treat sepsis-induced AKI. A potential reason for this may be that often therapy is started too late in the disease process.

- As increased levels of pro-inflammatory mediators (e.g. IL-6) are associated with the development of AKI [34], it is tempting to speculate that eliminating these mediators or endotoxin can prevent sepsis-induced AKI. Indeed, elimination of cytokines and endotoxin is feasible by hemoadsorption [61, 62] and experimentally it has been shown that hemoadsorption completely protects against AKI in a CLP-model of sepsis [63].

- Alkaline phosphatase (AP) is an endogenous enzyme that exerts detoxifying effects through dephosphorylation of endotoxins and pro-inflammatory extracellular ATP and is reduced during systemic inflammation. Heemskerk and colleagues [64] demonstrated that AP application was associated with a decreased expression of iNOS synthase in proximal tubule cells isolated from urine related to an attenuated urinary excretion of an proximal tubule injury marker. In a small, randomized trial, Pickkers et al. showed that the administration of exogenous AP in septic patients improved endogenous creatinine clearance and reduced the requirement and duration of renal replacement therapy [65].


Sepsis / Inflammation
Damaged / Inflamed renal tissue
ATP
P
P
P
AP
P
P
P
Adenosine
Cytokine production
NO production
Tubular damage
Acute kidney injury

- Modulating TNF-α signaling might be another therapy option, because a polymorphism in the promoter region of the TNFA gene is associated with markers of kidney disease severity and distant organ dysfunction [66].

Nephron Clinical practice. 2013; 123:67–73.

- Microcirculatory dysfunction during AKI initiates hypoxia and inflammation. To improve the microcirculatory perfusion, vasodilators in the setting of sepsis are currently under investigation including nitroglycerin [14, 67], NO administration, and modulation of NO production [30, 32]. Furthermore, drugs with pleiotropic effects on the vasculature, such as statins [68] and erythropoietin [69], have the potential to prevent kidney injury by enhancing eNOS expression and decreasing vascular permeability.

Critical care medicine. 2010; 38:93–100.

European heart journal. 2008; 29:1548–59.

- the old paradigm that sepsis-induced AKI is initiated by renal ischemia as a result of macrovascular dysfunction has been called into question, because AKI can also develop in the presence of normal or increased renal blood flow. Furthermore, in contrast to renal-ischemia reperfusion injury, which is characterized by apoptosis or necrosis of tubular epithelial cells, sepsis-induced AKI is characterized by healthy or reversible injured renal tubular epithelial cells. New evidence suggests that the inflammatory response during sepsis causes an adaptive response of the tubular epithelial cells. These alterations induce a downregulation of the cell function in order to minimize energy demand and to ensure cell survival. The result is reduced kidney function. The simultaneous occurrence of renal inflammation and microvascular dysfunction exacerbates the adaptive response of tubular epithelial cells to injurious signals. In addition, the endothelial cell injury is also of importance in the initiation and development of sepsis-induced AKI through the nitric oxide pathway, leukocyte adhesion, ROS, and inflammation. Targeting tubular epithelial cells and components of the microcirculation may be an effective strategy in preventing and/or treating sepsis-induced AKI.

pharmacologic attempts directed at limiting and reversing sepsis induced AKI

- Heme -oxygenase-1 (HO-1) enzyme system and the products of heme catabolism, including carbon monoxide, biliverdin, and bilirubin have important antioxidant, anti-inflammatory, and anti apoptotic properties.
- These findings have led to clinical trials that are examining the beneficial effects of carbon monoxide in AKI in the setting of delayed graft function in kidney transplantation (clinicaltrials. gov, NCT 00531856) and bilirubin in endotoxemia (clinical trials.gov, NCT 00916448)

Sepsis induced AKI

- When compared with AKI of non septic origin, septic AKI is characterized by a distinct pathophysiology and therefore requires a different approach.
- Despite impressive advances in several fields of medicine, the pathophysiology, diagnostic procedures, and appropriate therapeutic interventions in sepsis are still highly debatable.

Acute kidney injury in sepsis

- **Is a serious complication of sepsis in the ICU that increases :**
  - **Risk of death and morbidity**
  - **Risk of multiple organ failure**
  - **prolonged hospital stay**
  - **Costs of care**
  - **Risk of ESRD**

Kidney International (2010) ***77, 485 – 487.***