ACUTE KIDNEY INJURY (AKI) IN BURN PATIENTS

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OVERVIEW

- Acute kidney injury (AKI): **common and morbid** complication after severe burn → incidence 30%, mortality 80%.
- Burn-related kidney injury is classified as early (0–3 days after injury) or late (4–14 days after injury).
- Kidney Disease: Improving Global Outcomes (KDIGO) consensus defined stage and severity of AKI based on changes of serum creatinine and urine output across time.
- The reversal of the underlying cause is the first intervention.
- Unfortunately, no beneficial pharmacologic agents have been identified.

Clark A, Neyra JA, Madni T, Imran J, Phelan H, Arnoldo B, et al. Acute kidney injury after burn. Burns. 2017;3:898–908.

DEFINITION

- AKI = an abrupt decrease in kidney function
- Both RIFLE and AKIN have been validated in burn ICUs → increased severity of AKI correlate closely with mortality and adverse renal outcomes

Table 1 – RIFLE, AKIN, and KDIGO criteria for AKI [6].

	RIFLE criteria		AKIN criteria	KDIGO criteria	Urine output
AKI definition	Increase in sCr of >50% baseline developing over <7 days		Increase in sCr of 0.3 mg/dL or >50% developing over <48 h	Increase in sCr of 0.3 mg/dL developing over 48 h or >50% developing over 7 days	UOP <0.5 mg/kg/h for ≥6 h
Staging					
Risk	1.5–1.9 times baseline sCr or GFR decrease >25%	1	1.5–1.9 times initial/baseline sCr or ≥0.3 mg/dL increase in sCr	1.5–1.9 times initial/baseline sCr or ≥0.3 mg/dL increase in sCr	<0.5 mL/kg/h for 6–12 h
Injury	2.0–2.9 times baseline sCr or GFR decrease >50%	2	2.0–2.9 times initial/baseline sCr	2.0–2.9 times initial/baseline sCr	<0.5 mL/kg/h for ≥12 h
Failure	3.0 times baseline sCr or increase in sCr to ≥4.0 mg/dL with an acute increase of >0.5 mg/dL or GFR decrease >75%	3	3.0 times initial/baseline sCr or increase in sCr to ≥4.0 mg/dL with an acute increase of >0.5 mg/dL or initiation of RRT	3.0 times initial/baseline sCr or increase in sCr to ≥4.0 mg/dL or initiation of RRT	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h
Loss	Need for RRT >4 weeks				
End stage	Need for RRT for >3 months				

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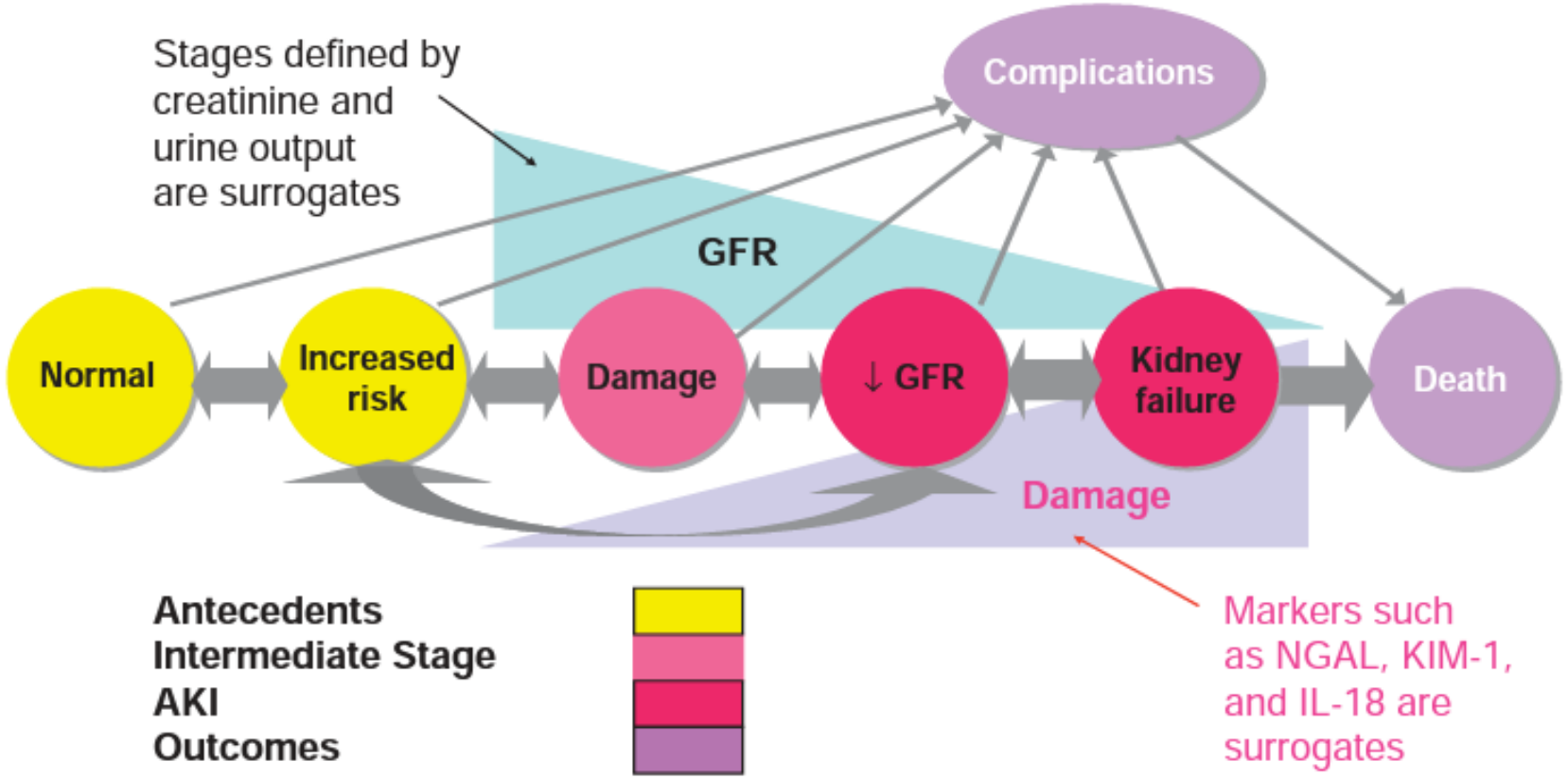


Figure 3 | Conceptual model for AKI. Red circles represent stages of AKI. Yellow circles represent potential antecedents of AKI, and the pink circle represents an intermediate stage (not yet defined). Thick arrows between circles represent risk factors associated with the initiation and progression of disease that can be affected or detected by interventions. Purple circles represent outcomes of AKI. "Complications" refers to all complications of AKI, including efforts at prevention and treatment, and complications in other organ systems. AKI, acute kidney injury; GFR, glomerular filtration rate. Adapted from Murray PT, Devarajan P, Levey AS, *et al*. A framework and key research questions in AKI diagnosis and staging in different environments. Clin J Am Soc Nephrol 2008; 3: 864–868 with permission from American Society of Nephrology[45] conveyed through Copyright Clearance Center, Inc.; accessed http://cjasn.asnjournals.org/content/3/3/864.full

Kidney Disease: Improving Global Outcomes KDIGO Acute Kidney Injury Work Group: KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1–138.

ETIOLOGY

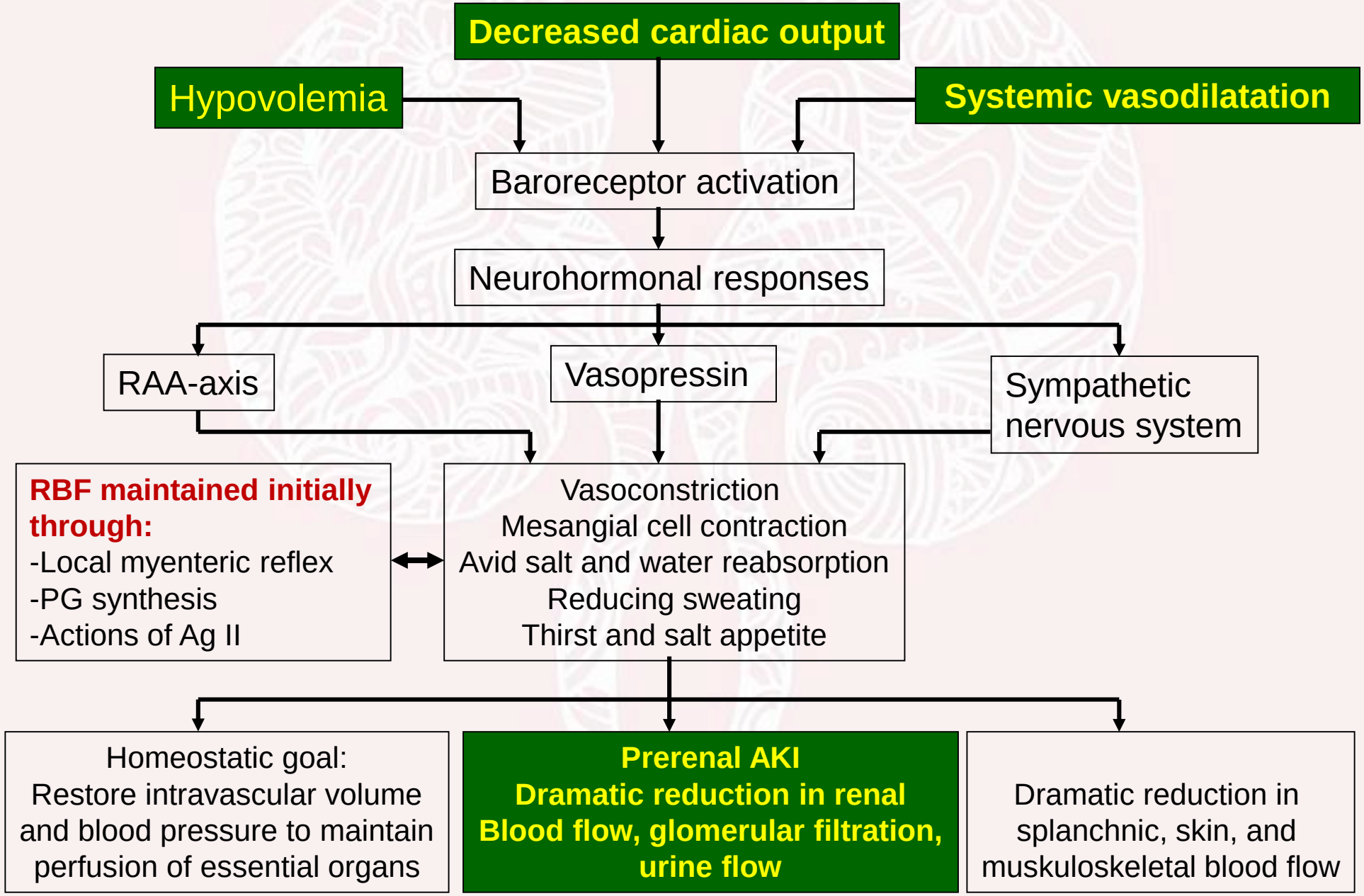
Table 6 | Causes of AKI: exposures and susceptibilities for non-specific AKI

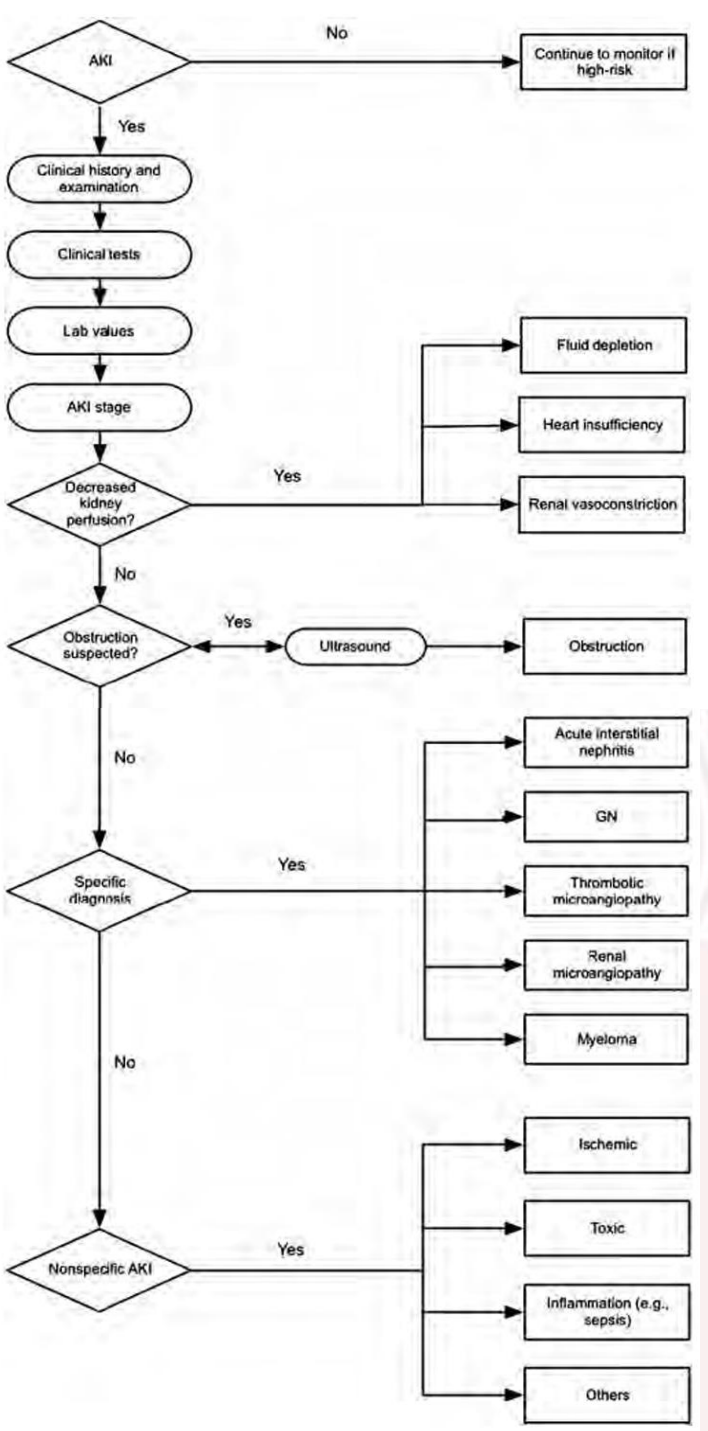
Exposures	Susceptibilities
Sepsis	Dehydration or volume depletion
Critical illness	Advanced age
Circulatory shock	Female gender
Burns	Black race
Trauma	CKD
Cardiac surgery (especially with CPB)	Chronic diseases (heart, lung, liver)
Major noncardiac surgery	Diabetes mellitus
Nephrotoxic drugs	Cancer
Radiocontrast agents	Anemia
Poisonous plants and animals	

CKD, chronic kidney disease; CPB, cardiopulmonary bypass.

Kidney Disease: Improving Global Outcomes KDIGO Acute Kidney Injury Work Group: KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1–138.

Pathophysiology of prerenal AKI (BURN)





Kidney Disease: Improving Global Outcomes KDIGO Acute Kidney Injury Work Group: KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1–138.

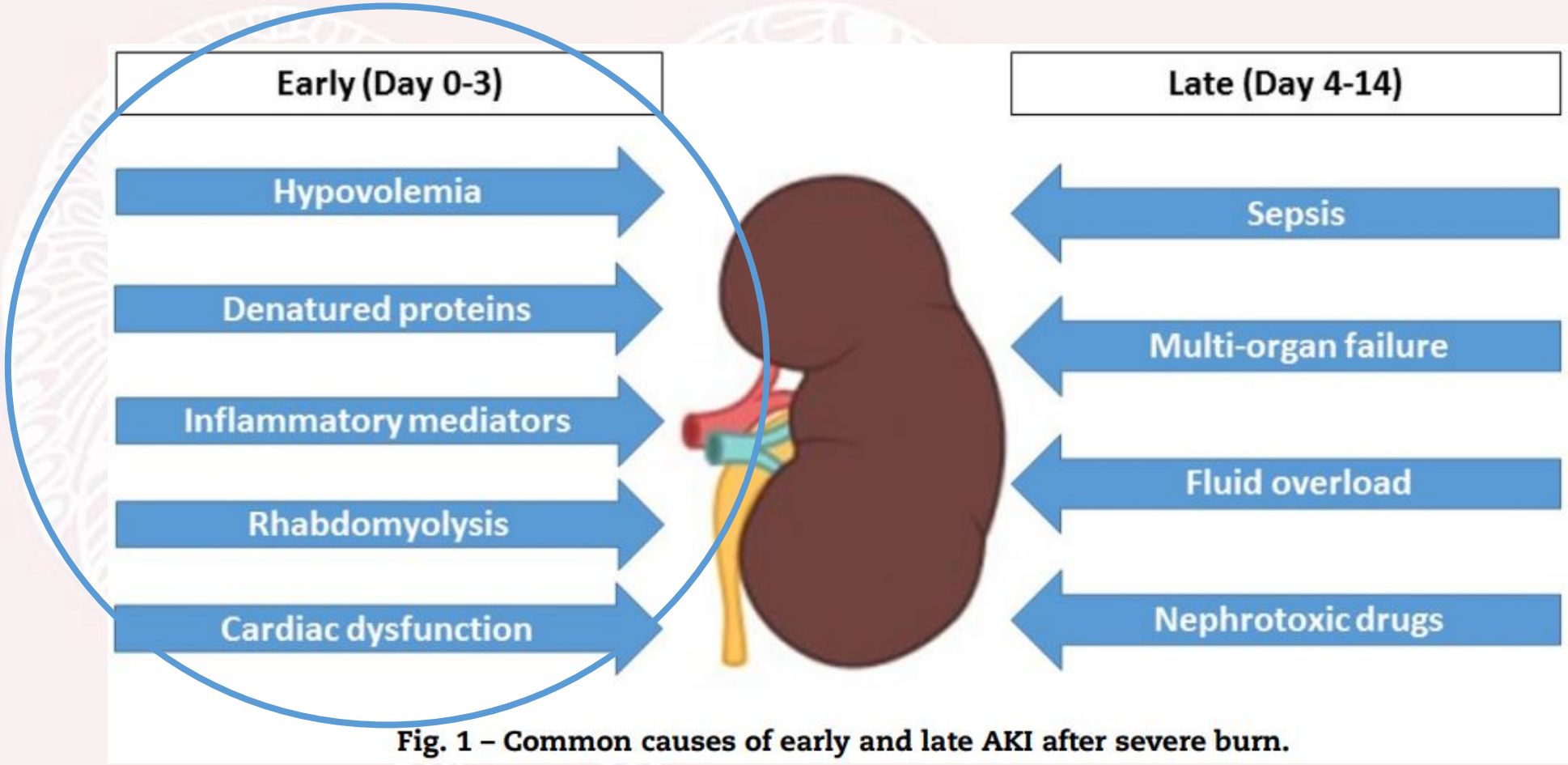


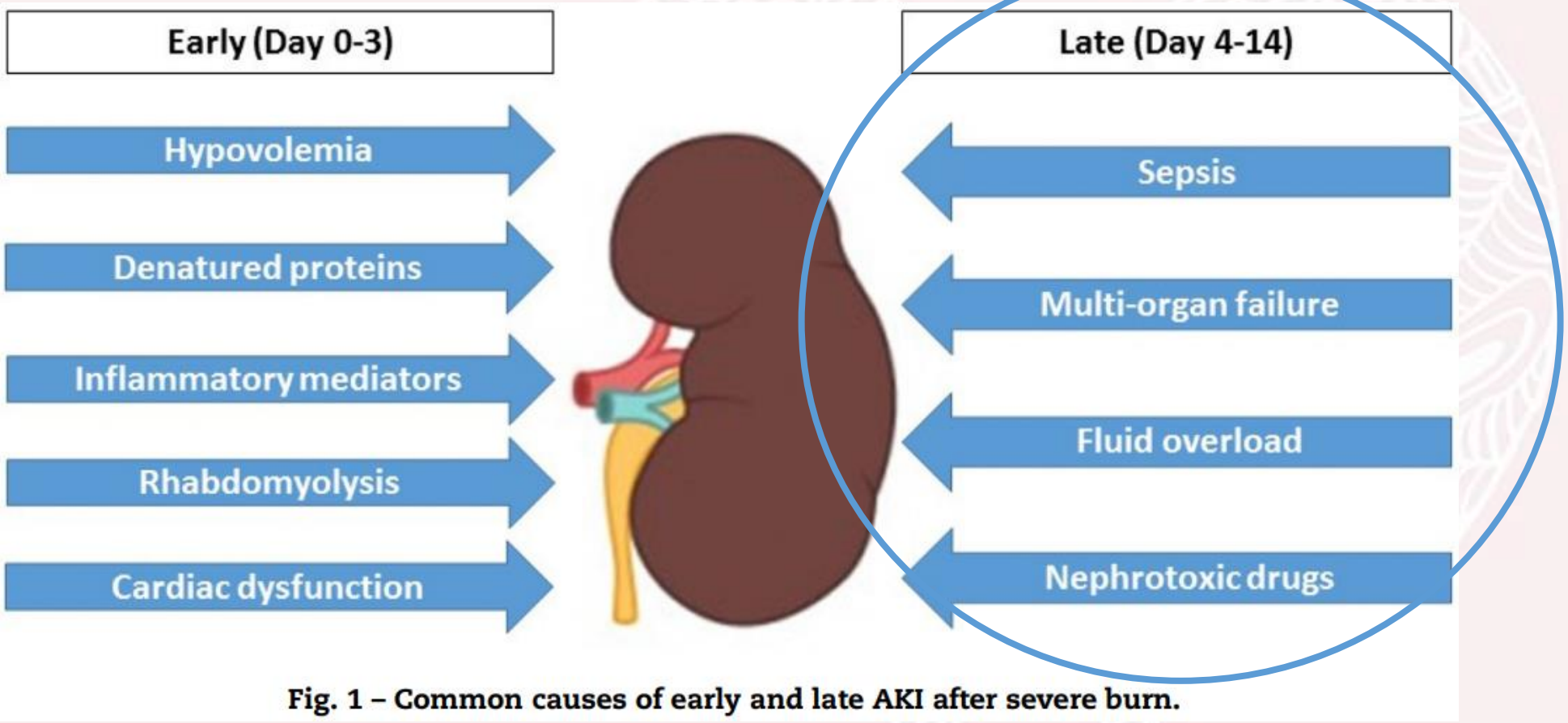
Fig. 1 – Common causes of early and late AKI after severe burn.

AKI is not dependent only on the quantity of fluid given,
but also on the degree of shock after severe burn.

Clark A, Neyra JA, Madni T, Imran J, Phelan H, Arnoldo B, et al. Acute kidney injury after burn. Burns. 2017;3:898–908.

Early AKI

- Substantial fluid loss from burn wound + fluid shift from the intravascular to interstitial space → hypovolemia, ↓cardiac output → ↓renal blood flow → ischemia, cellular injury and death.
- Ischemic injury yields oxygen free radicals → tubular damage, disturbance of tight junctions → obstructing cellular casts → urine backflow → ↓GFR
- ↑sympathetic activity + insufficient adrenal response, hypovolemia-induced myocardial ischemia, and direct myocardial suppression by TNF-alpha or some other factor released from myocytes → cardiac dysfunction
- Rhabdomyolysis → muscle fluid sequestration, intrarenal vasoconstriction, release of toxic intracellular components into the systemic circulation → oxidative injury and inflammation → ischemic tubular injury, AKI
- Released myoglobin precipitates in renal tubules → afferent renal arteriolar vasoconstriction + O2 free radicals



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Late AKI

- Nephrotoxic agents (aminoglycosides, some cephalosporins, iv contrast agents) are often given to burn patients.
- Sepsis and septic shock are the leading cause of death in the ICU (up to 87% of AKI cases in the burn ICU). Multifactorial mechanism of sepsis-related AKI:

↓vascular resistance (a high-flow, low pressure state) → systemic arterial vasodilation. Bacteria activate sepsis-associated cytokines → endothelial damage, vasoparalysis, and a procoagulant state → profound hypotension → activates sympathetic nervous system and the renin-angiotensin-aldosterone response → ↑cardiac output state.

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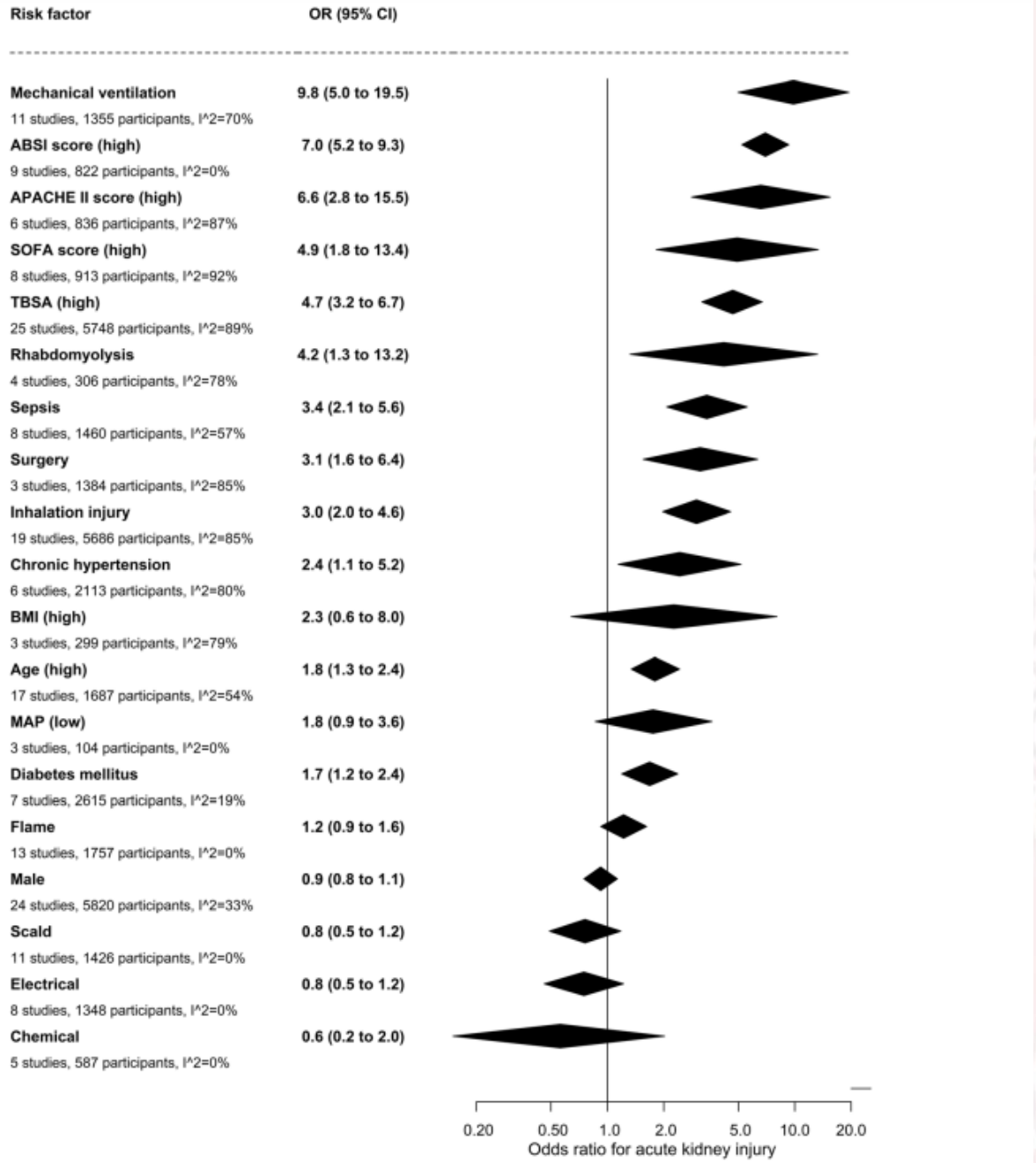


Fig. 3 Risk factors for acute kidney injury in burn patients admitted to the intensive care unit. The contribution from the various risk factors were statistically weighted and adjusted to a single scale. Odds ratios (OR) for continuous risk factors were derived from standardised mean differences. CI, confidence interval; ABSI, Abbreviated Burn Severity Index; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Function Assessment; TBSA, Total Body Surface Area; BMI, body mass index; MAP, mean arterial pressure

RISK FACTORS

- AKI and RRT is common in ICU patients with burn injuries.

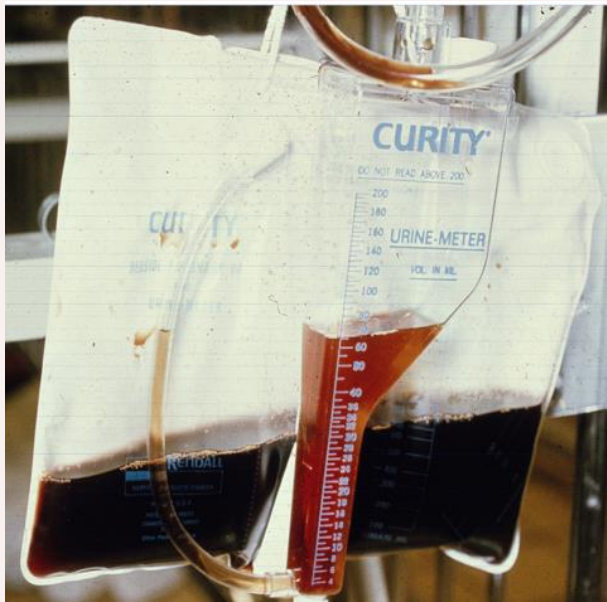
- Patients with old age, chronic hypertension, diabetes mellitus, high TBSA%, high ABSI score, inhalation injury, rhabdomyolysis, surgery, high APACHE II score, high SOFA score, sepsis, and need for mechanical ventilation are at risk for post-burn AKI.

Folkestad T, Brurberg KG, Nordhuus KN, Tveiten CK, Guttormsen AB, Os I, et al. Acute kidney injury in burn patients admitted to the intensive care unit: a systematic review and meta-analysis. Critical Care. 2020; 24(2):1-11

DIAGNOSIS

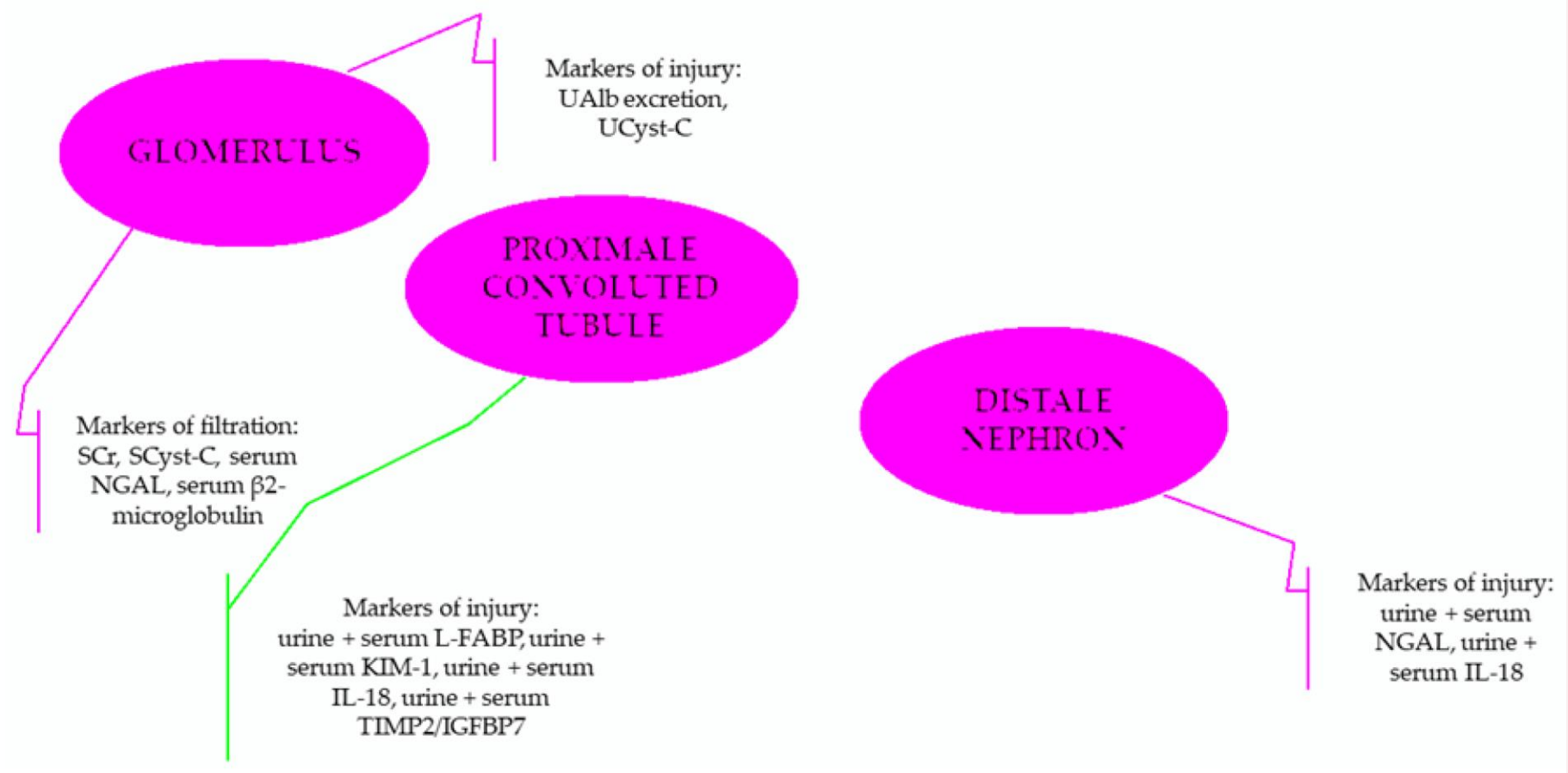
- The diagnosis of AKI after burn can be challenging, as UOP and sCr can be relatively normal even with significant renal injury.
- ↓UOP is often the first physiologic sign of renal injury in burn (very specific, although it is not sensitive)

- Microscopic and biochemical urine sediment analyses :
  - Prerenal condition : normal urinary sediment or hyaline casts, concentrated urine, in oliguric patient.
  - acute tubular necrosis : tubular epithelial cells, granular casts, and epithelial cell casts
  - Rhabdomyolisis → myoglobinuria → pigmented casts on microscopic evaluation and the classic dissociation between positive blood in dipstick urinalysis with absent red blood cells on microscopy



Clark A, Neyra JA, Madni T, Imran J, Phelan H, Arnoldo B, et al. Acute kidney injury after burn. Burns. 2017;3:898–908.

- Particular serum and urinary biomarkers have shown utility in AKI prediction in critically ill patients, including burn injuries.



- Serum and urine NGAL, urinary TIMP-2, and IGFBP7 have superior results.
- Further studies are required to validate & establish cut-off values for cystatin C and urinary KIM-1

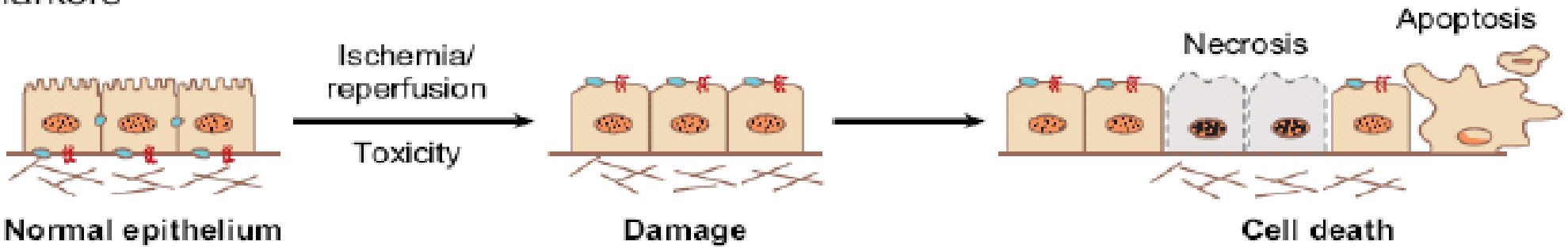
Niculae A, Peride I, Tiglis M, Sharkov E, Neagu TB, Lascar I, et al. Burn-Induced Acute Kidney Injury–Two-Lane Road: From Molecular to Clinical Aspects. *Int. J. Mol. Sci.* 2022, *23*(15), 8712.

Biomarkers for Early Prediction of Acute Kidney Injury

Acute Kidney Injury Biomarkers

Vaidya VS, Ferguson MA, Bonventre JV. Biomarkers of Acute Kidney Injury.
Annu Rev Pharmacol Toxicol 2008;48:463-493

Biomarkers



Biomarkers

Sensitive (early appearance)
Easy to detect
Specific (typical of organ injury)
Correlate with severity (prognosis)
Quantitatively describing the level of injury even in the absence of typical clinical signs
Capable to indicate treatment initiation (theragnostics)

Potential urinary biomarkers for early diagnosis of AKI

NAG
β_2M
α_1M
RBP
Cystatin C
KIM-1
Clusterin
Microalbumin
NGAL
CYR-61
IL-18
OPN
FABP
NHE3
Fetuin A

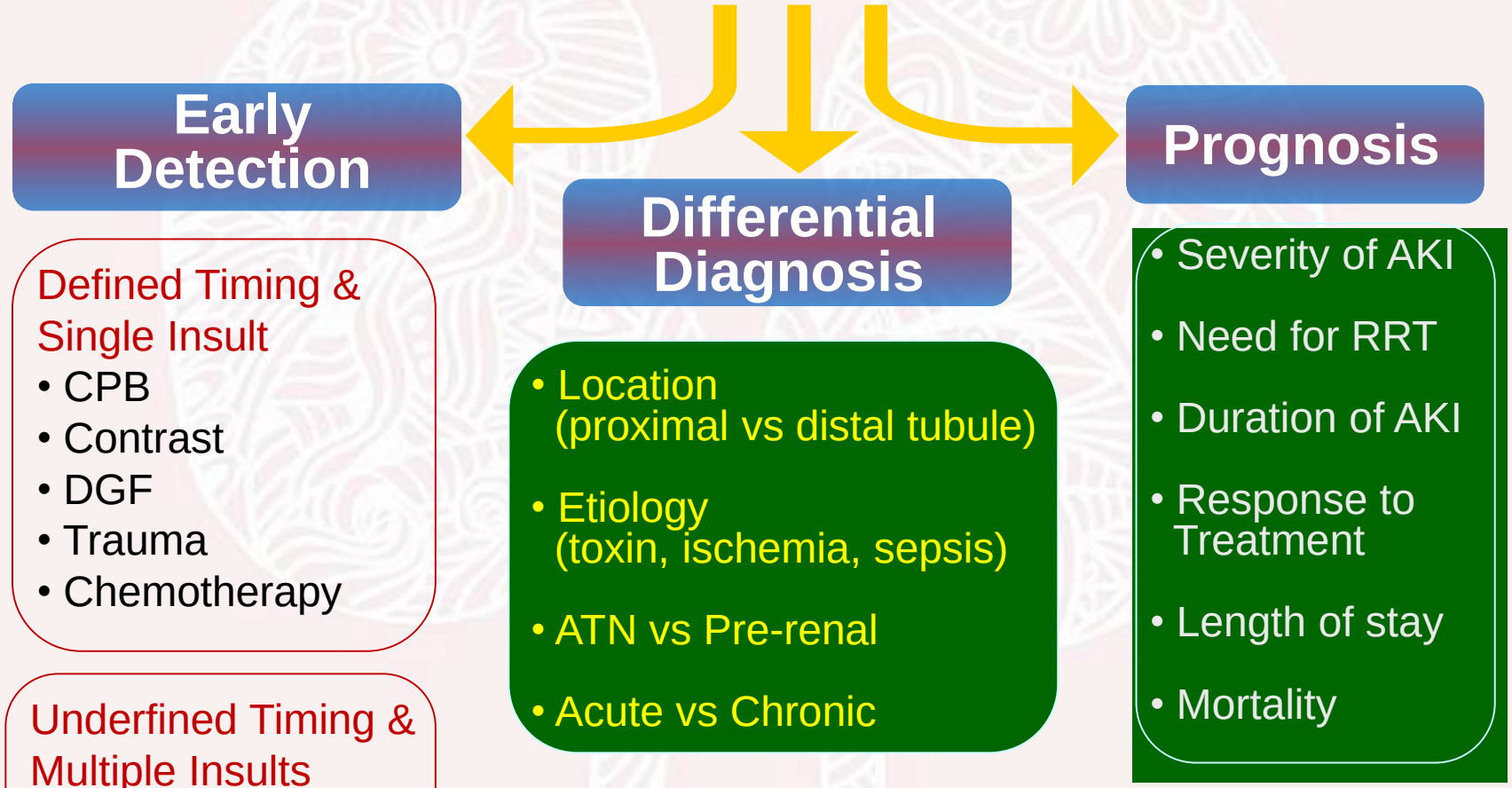
↓GFR

Delayed biomarkers for kidney injury

↑ Serum creatinine
↑ Blood urea nitrogen

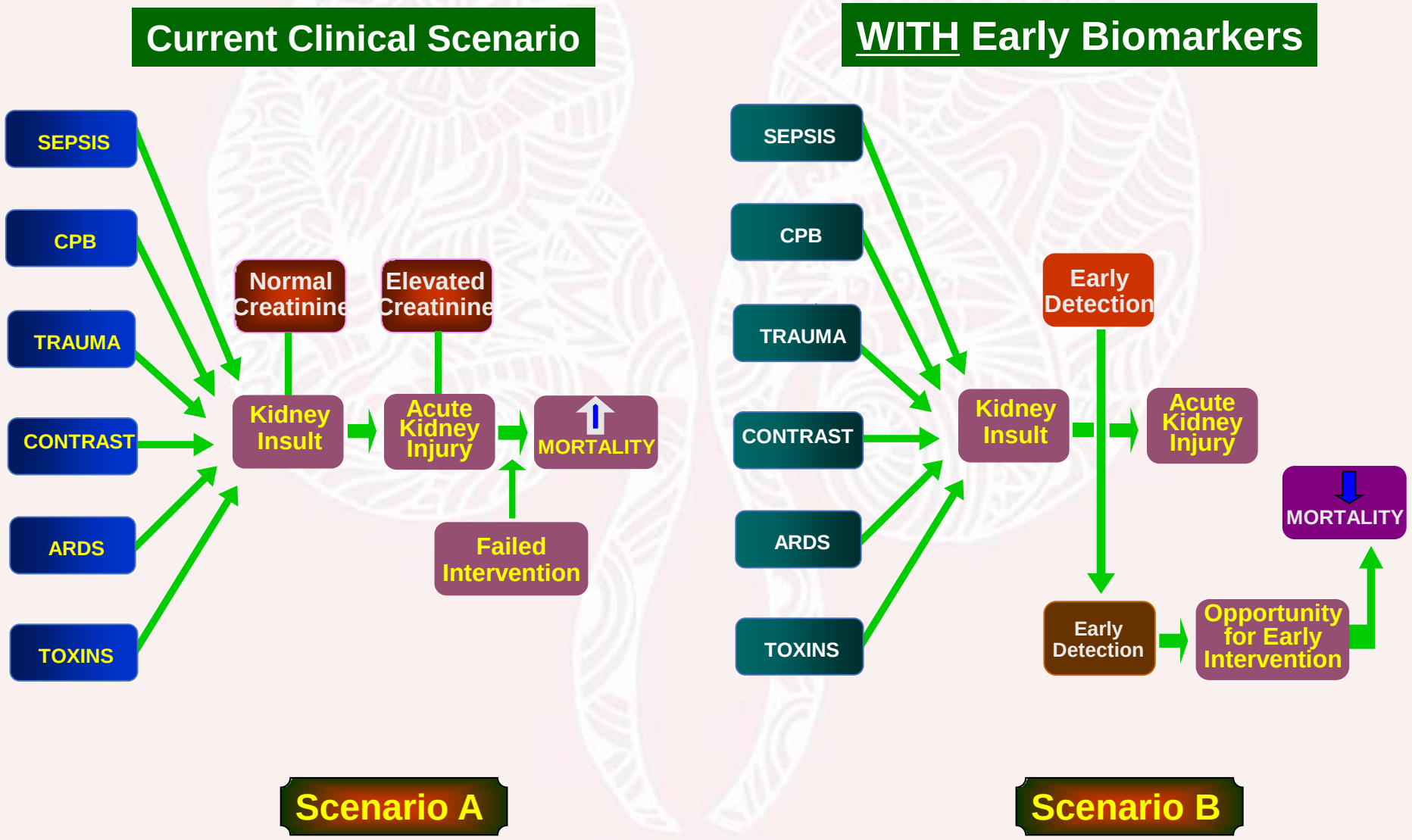
Late detections

Potential Roles of Biomarkers in AKI



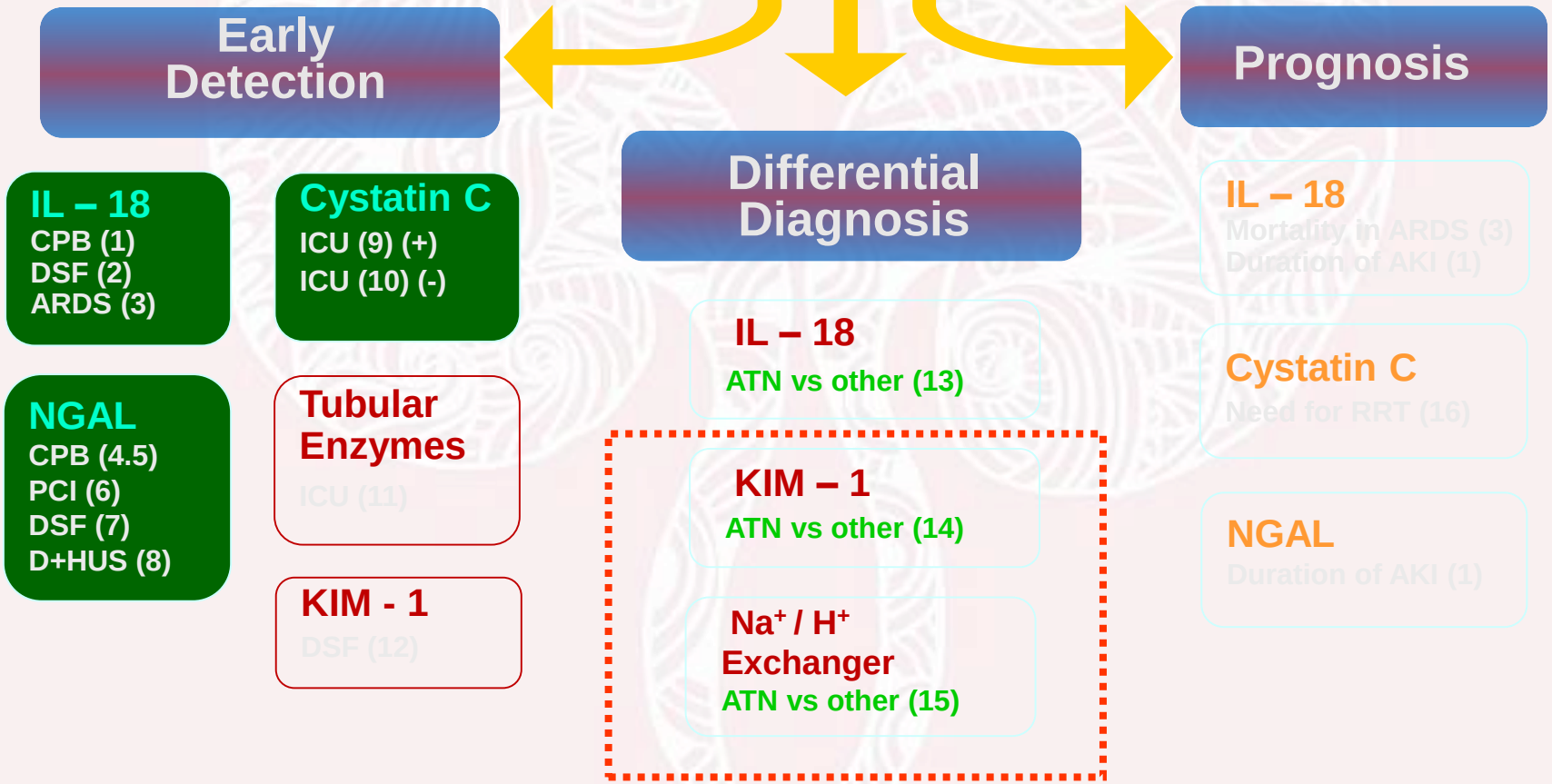
Parikh CR. AKI: better biomarkers and beyond. Kidney I 2008; 73:801-803

Scenario to decrease mortality with early diagnosis



Parikh CR. AKI: better biomarkers and beyond. Kidney I 2008; 73:801-803

Potential Biomarkers in AKI *(Human Data)*



Parikh CR. AKI: better biomarkers and beyond. Kidney I 2008; 73:801-803

Promising Biomarkers for AKI

Marker	Sample	Timing	Commercial test?
NGAL	**Plasma**	**Early**	**Biosite**
Cystatin C	Plasma	Intermediate	Dade- Behring
NGAL	**Urine**	**Early**	**Abott**
IL-18	Urine	Intermediate	None
KIM-1	Urine	Intermediate	None

Nguyen and Devarajan, Pediatric Nephrol, 2007

TREATMENT

- The most important: identification, reversal of underlying cause, correction of electrolyte and fluid derangements.
- If the injury continues to progress despite conventional therapy → RRT should be judiciously initiated to prevent complications.

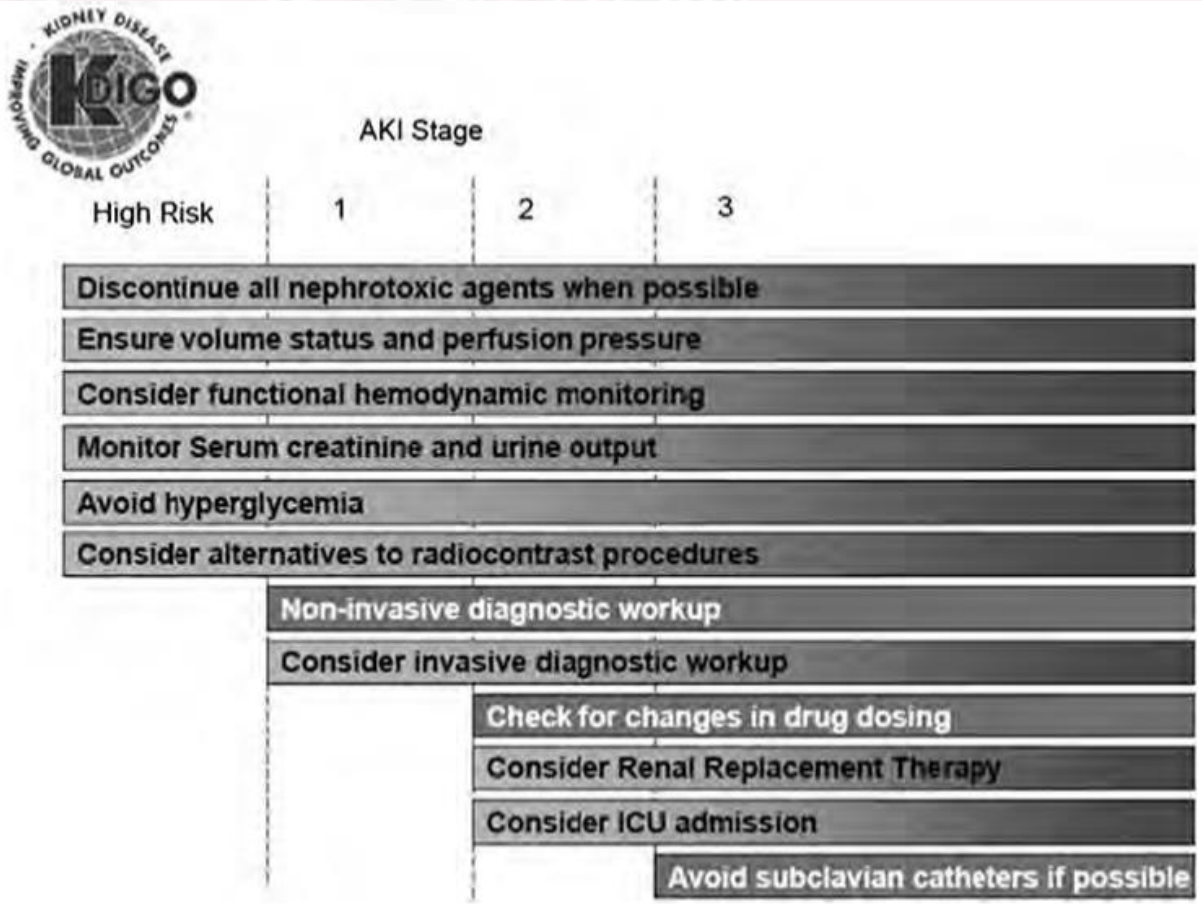


Figure 4 | Stage-based management of AKI. Shading of boxes indicates priority of action—solid shading indicates actions that are equally appropriate at all stages whereas graded shading indicates increasing priority as intensity increases. AKI, acute kidney injury; ICU, intensive-care unit.

Kidney Disease: Improving Global Outcomes KDIGO Acute Kidney Injury Work Group: KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1–138.
Clark A, Neyra JA, Madni T, Imran J, Phelan H, Arnoldo B, et al. Acute kidney injury after burn. Burns. 2017;3:898–908.

TREATMENT

- Early AKI (poor renal perfusion) → early & aggressive crystalloid resuscitation utilizing Parkland formula. Adjust rates & solutions based on the individual's physiologic status to optimize renal perfusion without over-resuscitation.
- Colloids (albumin/ fresh frozen plasma) improve intravascular osmotic pressure, expand intravascular volume, and limit edema in unburned tissue → can be used either early in resuscitation or later if crystalloid being used is excessive
- if initial maneuvers do not maintain a mean arterial pressure over 60mm Hg → norepinephrine to support blood pressure and renal perfusion.
- Vitamin C is a possible adjunct because of its antioxidant effects.

Clark A, Neyra JA, Madni T, Imran J, Phelan H, Arnoldo B, et al. Acute kidney injury after burn. Burns. 2017;3:898–908.

TREATMENT

- Late AKI is often multifactorial and associated with sepsis and multi-organ failure.
- Early recognition of sepsis : increasing insulin resistance, feeding intolerance, or elevation of acute phase reactants → Intervention: goal-directed therapy
- When infectious organism is identified → antibiotics, dose accordingly to renal function status → goal : treat a local infection and gain source control before it spreads systemically and causes septic shock and end-organ damage.
- Nephrotoxic drugs (e.g., aminoglycosides, IV contrast, NSAIDs) should be avoided / discontinued.

Clark A, Neyra JA, Madni T, Imran J, Phelan H, Arnoldo B, et al. Acute kidney injury after burn. Burns. 2017;3:898–908.

TREATMENT -- RRT

- About 12% of AKI patients in burn ICU received RRT
- RRT is not of benefit in most cases of AKI in burn patients, but if renal function continues to worsen despite initial interventions, RRT should be utilized early to prevent complications (severe metabolic derangements or fluid overload).

Table 3 – Modalities of renal replacement therapy.

	IHD	SLED	CRRT
Name	Intermittent hemodialysis	Sustained low efficiency dialysis	Continuous renal replacement therapy
Blood flow	300-400 mL/min	200-300 mL/min	50-200 mL/min
Dialysate flow	500-800 mL/min	1-2 L/h	2-3 L/h
Hemodynamic stability	Poor (hypotension common)	Good	Good
Duration	3-4 h, 3x/week	6-12 h daily	Continuous
Access	Fistula or vascath	Fistula or vascath	Vascath only
Anticoagulation use	None	Rare	Always

Abbreviations: CRRT (continuous renal replacement therapy), IHD (intermittent hemodialysis), SLED (sustained low-efficiency dialysis).

Folkestad T, Brurberg KG, Nordhuus KN, Tveiten CK, Guttormsen AB, Os I, et al. Acute kidney injury in burn patients admitted to the intensive care unit: a systematic review and meta-analysis. Critical Care. 2020; 24(2):1-11
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AKI RECOVERY AND COMPLICATIONS

- Patients with severe burn who develop AKI ↑↑mortality.
- Diagnosis is challenging → measure UOP & SCr
- Factors increasing mortality: severity of AKI , older age, larger % total body surface area, and higher incidence of inhalational injury.
- AKI may lead to more than just adverse renal outcome → risk of stroke, coronary events, and all-cause mortality → observation 1-3 months after discharge is necessary in severe AKI cases, to prevent recurrent AKI or transition to CKD.

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A retrospective study in burn patients admitted to Dr. Soetomo Hospital Burn Center (2018-2020):

Complications of burn patients with AKI:

Complications	n (%)
Sepsis	9 (50)
Inhalation Injury	11 (61)
Hypoalbuminemia	16 (89)
Anemia	7 (39)
Thrombocytopenia	2 (11)
Metabolic acidosis	3 (17)
Hyperkalemia	2 (11)
Pneumonia	3 (17)

Risk factors for mortality in burn patients with AKI:

Variables	OR	P value	CI 95%
Inhalation trauma	1.60	0.034	0.935-2.737
Sepsis	1.50	0.058	0.945-2.381
Hypoalbuminemia	5.50	0.180	0.385-78.573
TBSA	28.0	0.011	1.208-648.809
Age	0.57	0.017	0.301-1.08

Putra ON, Saputro ID, Diana D. RIFLE Criteria For Acute Kidney Injury In Burn Patients: Prevalence And Risk Factors. Annals of Burns and Fire Disaster. 2021;34:252-258

TAKE HOME MESSAGES

- AKI is a common and morbid complication of severe burn.
- The most important aspects of therapy are timely identification, the reversal of the underlying cause, the mitigation of nephrotoxicity, and the correction of electrolyte and fluid derangements.
- An episode of AKI may have lasting effects and increase the risk for CKD, ESRD, cardiac events, stroke, and long-term mortality → further research is needed regarding possible long-term consequences.

Kidney Disease: Improving Global Outcomes KDIGO Acute Kidney Injury Work Group: KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1–138.
Clark A, Neyra JA, Madni T, Imran J, Phelan H, Arnoldo B, et al. Acute kidney injury after burn. Burns. 2017;3:898–908.

THANK YOU