Approach to patient with renal dysfunction

Introduction

- Patients with renal disease have a variety of different clinical presentations.
- symptoms or signs that are directly related to the kidney (such as hematuria)
- extrarenal manifestations (edema, hypertension, signs of uremia).
- Many patients are asymptomatic and are incidentally found to have an elevated serum creatinine concentration. Proteinuria or microscopic hematuria.
- Specific disorders generally cause acute, subacute, or chronic kidney injury.

Fatehi P et al Diagnostic approach to adult patients with subacute kidney injury in an outpatient setting. Waltham (MA): UpToDate;2018.

Acute kidney Injury

- Acute kidney injury (AKI) is a complex syndrome characterized by a decrease in renal function, associated with numerous etiologies and pathophysiological mechanisms.
- It is a common diagnosis in hospitalized patients, associated with poorer short- and long-term outcomes.
- It is important to recognize AKI in pediatric and adult patients, ambulatory, hospitalized, and critically ill patients due to its prognostic impact.
- The incidence of AKI is lowest in ambulatory patients and higher in critically ill and patients who need dialysis.

Gameiro J et al. J Clin Med. 2018; 7(10): 307.

Acute kidney Injury

- AKI is most commonly reported in surgical and critical settings, where patients are systematically monitored by assessing hourly urinary output and daily creatinine.
- AKI occurs in up to 40% of acute decompensated heart failure with cardiorenal syndrome type 1.
- AKI is more common in older patients and those with predisposing factors have higher probability of developing severe disease
- Sepsis is the leading cause of AKI in critically ill patients accounting for 50% of cases.

Gameiro J et al. J Clin Med. 2018; 7(10): 307.

AKI definition and staging according to KDIGO criteria

AKI is *defined* as any of the following:		
1	Increase in sCr ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hours; or	
2	Increase in sCr ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or	
3	Urine volume <0.5 mL/kg/h for 6 hours.	
AKI is *staged for severity* according to the following criteria		
Stage 1	1.5–1.9 times baseline OR ≥0.3 mg/dL (≥26.5 μmol/L) absolute increase in sCr	Urine volume <0.5 mL/kg/h for 6–12 hours
Stage 2	sCr ≥2.0–2.9 times baseline	Urine volume <0.5 mL/kg/h for ≥12 hours
Stage 3	sCr ≥3.0 times from baseline OR Increase in sCr to ≥4.0 mg/dL(≥353.6 μmol/L) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 mL/min per 1.73 m^2	Urine volume <0.3 mL/kg/h for ≥24 hours OR Anuria for ≥12 hours

Makris K et al. Clin Biochem Rev.2016; 37:85-98

RIFLE criteria for classification and staging AKI and the modifications proposed by the AKIN network

RIFLE criteria for classification/staging AKI			AKIN criteria for classification/staging AKI		
Stage	GFR criteria	Urine output criteria	Stage	Serum Creatinine criteria	Urine output criteria
Risk	1.5fold increase in sCr or >25% decrease in GFR	UO < 0.5mL/ kg/h for 6h	Stage 1	Absolute increase in sCr ≥ 0.3 mg/dL (≥26.5 **µmol**/L) or ≥ 1.5 to 2.0 fold from baseline	UO < 0.5mL/ kg/h for 6h
Injury	2.0fold increase in sCr or >50% decrease in GFR	UO < 0.5mL/ kg/h for 12h	Stage 2	Increase in sCR> 2.0 to 3.0 fold from baseline	UO < 0.5mL/ kg/h for 12h
Failure	3.0fold increase in sCr or >75% decrease in GFR or sCr>4.0 mg/dL with an acute increase of 0.5 mg/dL	UO < 0.3mL/ kg/h for 24h or anuria for 12 h	Stage 3	Increase in sCr > 3fold from baseline or increase of sCr to ≥4.0 mg/dL (≥ 354 **µmol**/L) with an acute increase of at least 0.5 mg/dL (44 **µmol**/L)	UO < 0.3mL/ kg/h for 24h or anuria for 12h
Loss	Complete loss of kidney function for > 4 weeks				
ESKD	End stage kidney disease for > 3 months				

ESKD=end stage kidney disease, AKI=acute kidney injury, GFR=glomerular filtration rate, sCr= serum creatinine, UO=urinary output

Makris K et al. Clin Biochem Rev.2016; 37:85-98

Comparison of Recent Consensus AKI Definitions

AKI Stage	Urine Output	KDIGO	AKIN	RIFLE
1	<0.5 mL/kg/h for 6-12 h	Scr to 1.5-1.9 × baseline over 7 d or ≥0.3 mg/dL absolute increase over 48 h	Scr to 1.5-2 × baseline or ≥0.3 mg/dL absolute Scr increase within 48 h	*Risk*: Scr to ≥1.5 × increase within 7 d, sustained for ≥24 h
2	<0.5 mL/kg/h for ≥12 h	Scr to 2.0-2.9 × baseline	Scr to >2-3 × baseline	*Injury*: Scr to ≥2 × increase
3	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h	Scr to ≥3.0 × baseline, or Scr increase to ≥4.0 mg/dL or initiation of RRT	Scr to >3.0 × baseline, or Scr increase to ≥4.0 mg/dL (with increase of 0.5 mg/dL) or initiation of RRT	*Failure*: Scr to ≥3.0 × increase or Scr increase to ≥4.0 mg/dL (with increase of 0.5 mg/dL) or initiation of RRT
				Loss: Complete loss of kidney function for >4 wk
				ESKD: ESKD for >3 mo

Moore PK aet al. Am J Kidney Dis.2018; 72(1): 136-148

Recommendations for AKD staging

Stage	Definition
Stage 0*	A: Absence of criteria for B or C. B: Continued evidence of ongoing injury, repair and/or regeneration or indicators of loss of renal glomerular or tubular reserve C: Serum creatinine level <1.5 times baseline but not back to baseline levels B/C: Serum creatinine level <1.5 times baseline but not back to baseline levels, and continued evidence of ongoing injury, repair and/or regeneration
Stage 1	Serum creatinine level 1.5–1.9 times baseline
Stage 2	Serum creatinine level 2.0–2.9 times baseline
Stage 3	Serum creatinine level 3.0 times baseline or increase in serum creatinine to ≥353.6 µmol/l (≥4.0 mg/dl)‡ or ongoing need for renal replacement therapy

Chawla LS et al. Nat Rev Nephrol. 2017;13(4):241-257

GFR/ Serum Creatinine Algorithm

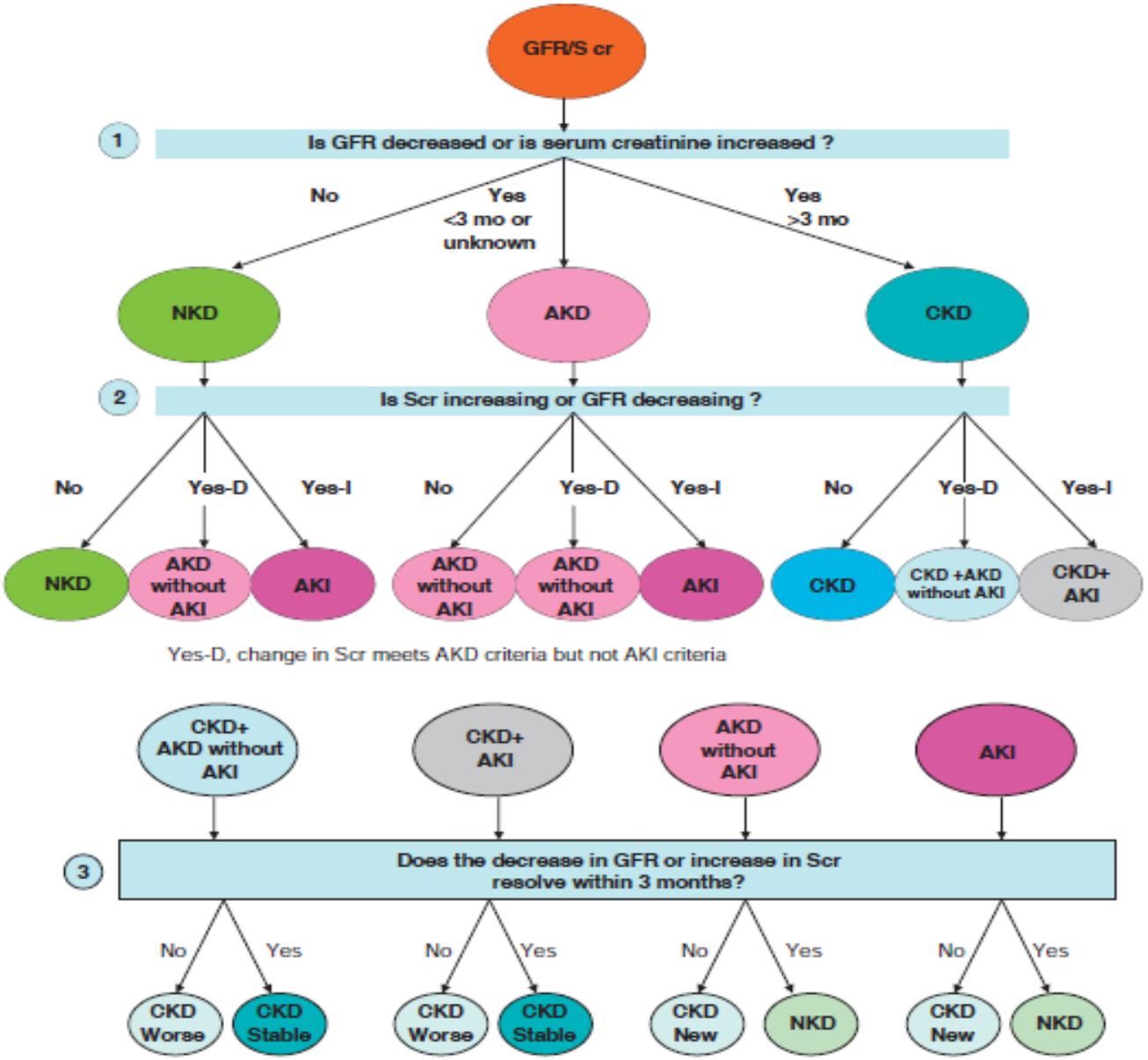
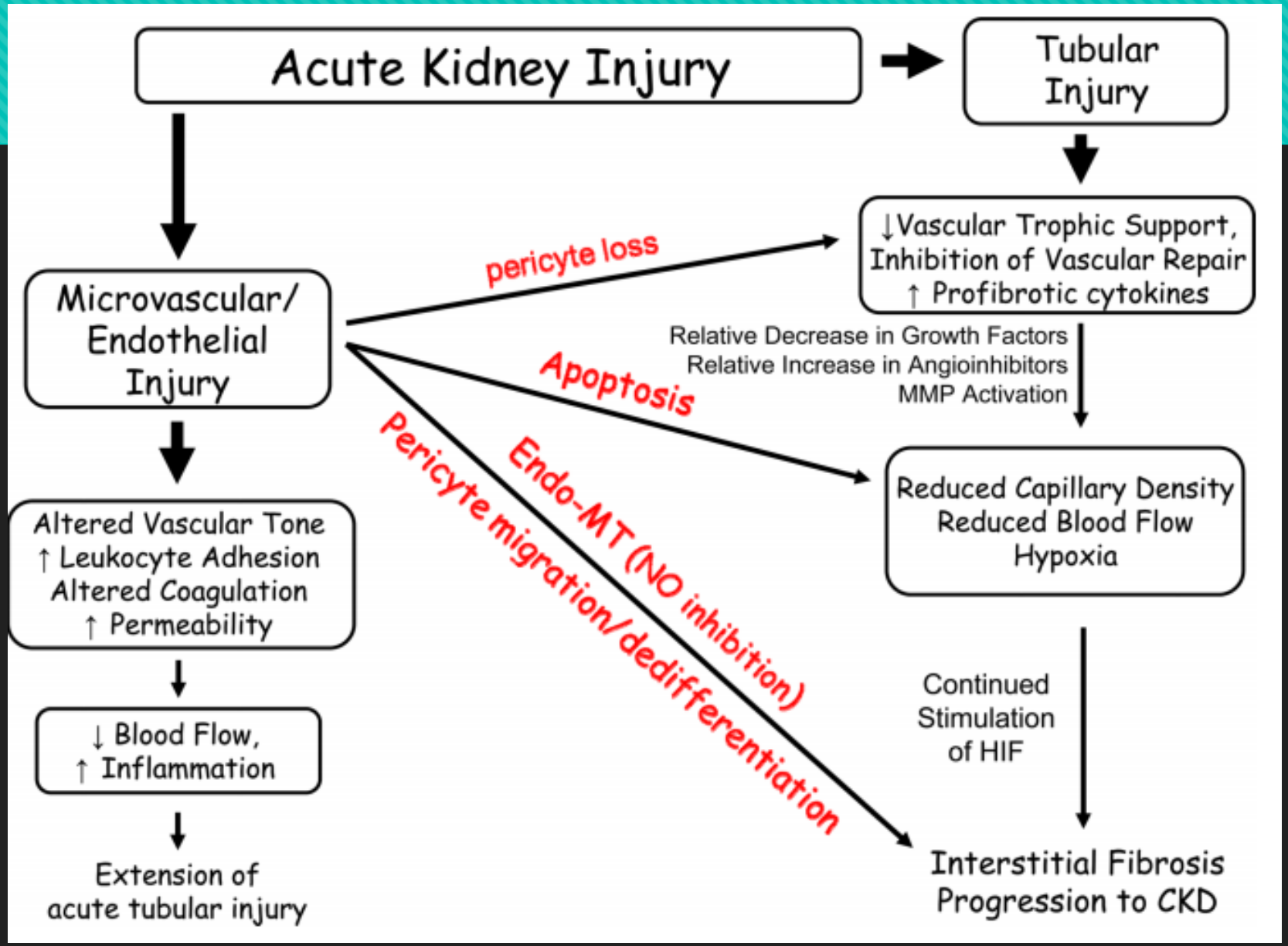


Figure **GFR/SCr algorithm.** See text for description. AKD, acute kidney disease/disorder; AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; NKD, no known kidney disease; SCr, serum creatinine.

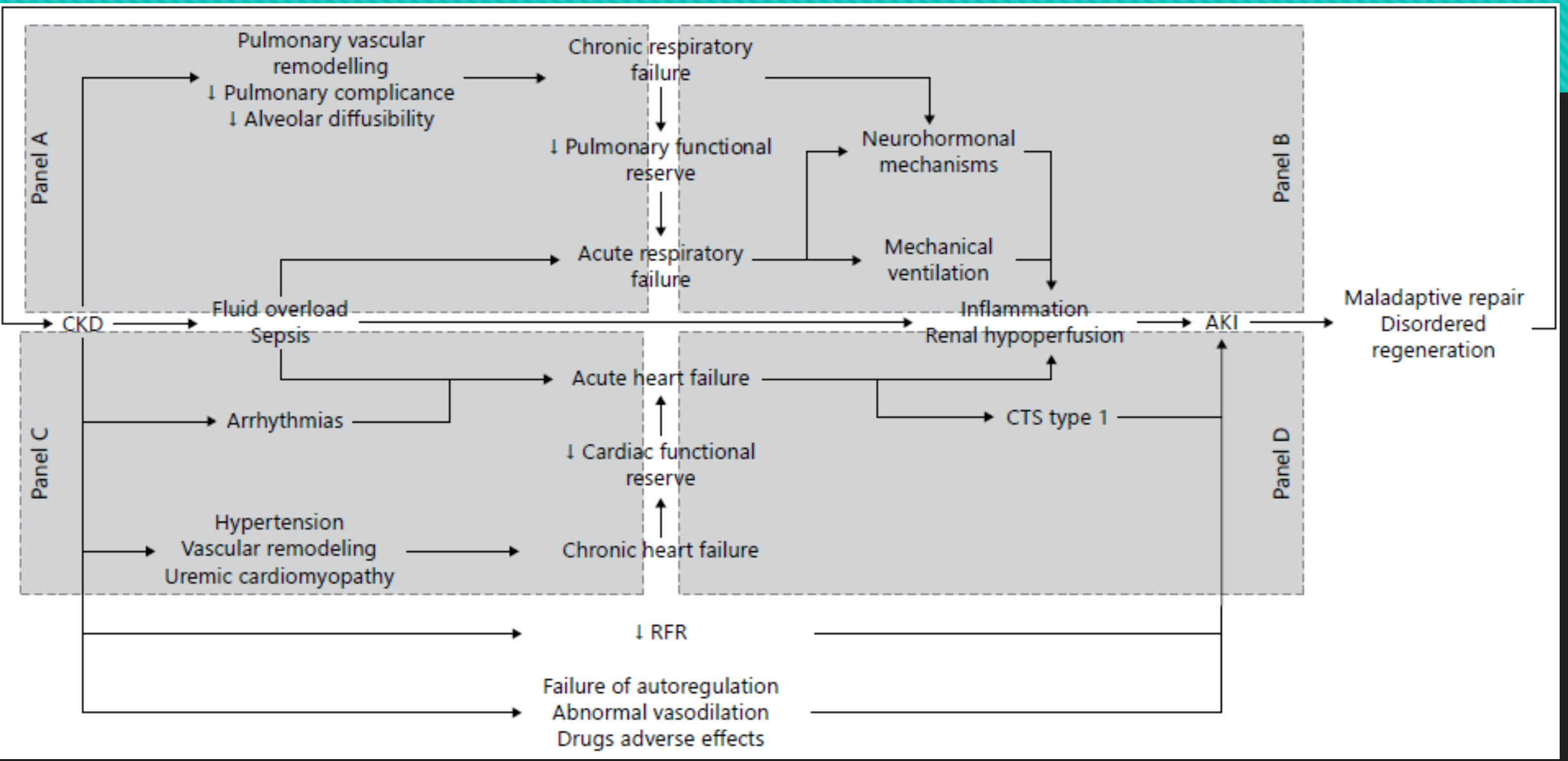
Kellum JA et al. Kidney international supplements. 2012 Jan 1;2(1):1-38.

Pathophysiology

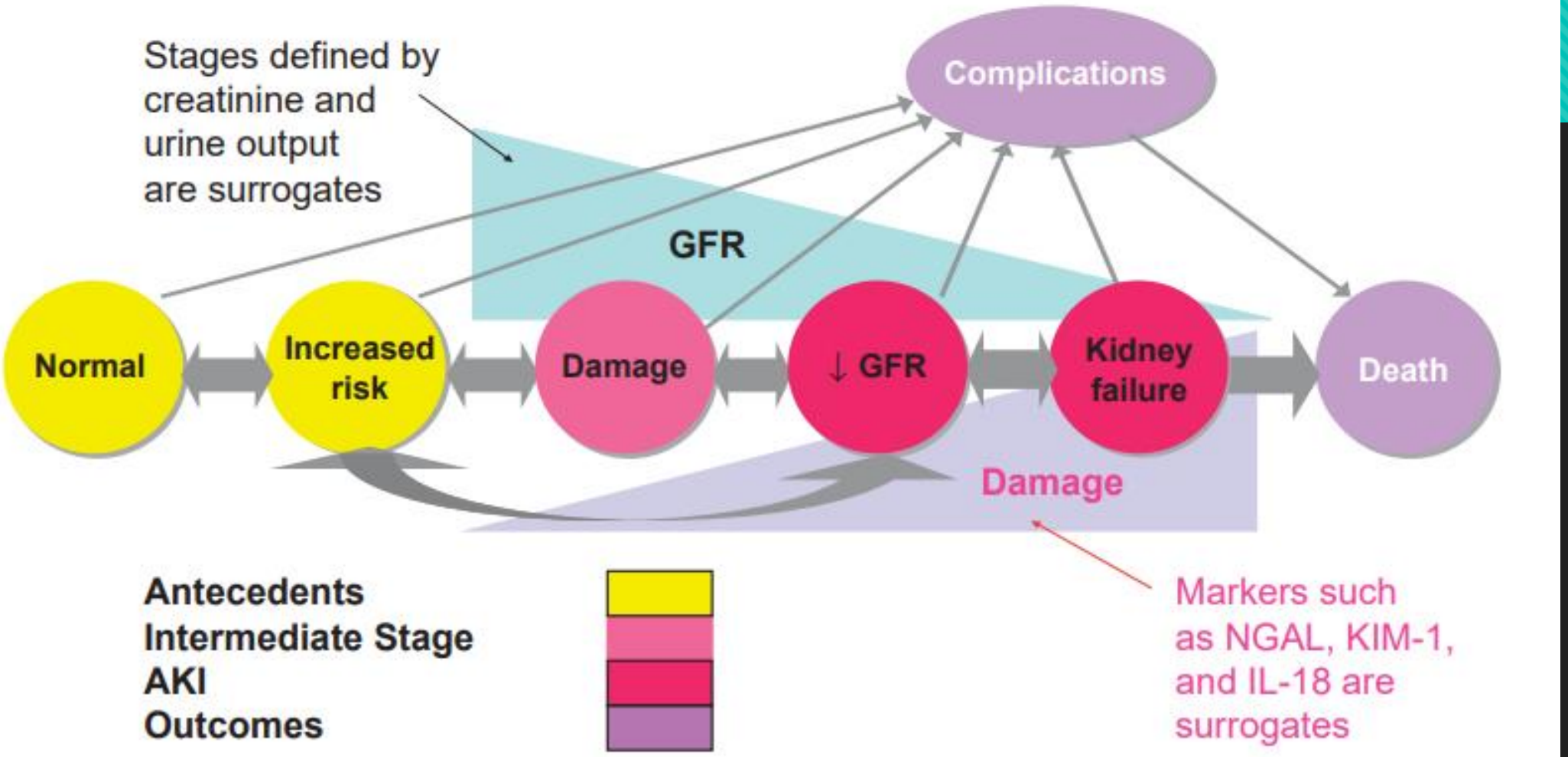


Basile DP et al. Compr Physiol. 2012 ; 2(2): 1303–1353.

Pathophysiological relationship between AKI and CKD



Conceptual model for AKI



AKI- acute kidney injury;
GFR- glomerular filtration rate
NGAL-Neutrophil gelatinase-associated lipocalin
KIM-1 - Kidney Injury Molecule-1

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.

Kellum JA et al. Kidney International Supplements. 2012;2(1):1-38.

Causes of acute kidney injury

Category	Abnormality	Causes
Pre- renal	Hypovolaemia	• Haemorrhage • Volume depletion • Renal fluid loss (over-diuresis) • Third space (burns, peritonitis, muscle trauma)
	Impaired cardiac function	• Congestive heart failure • Acute myocardial infarction • Massive pulmonary embolism
	Systemic vasodilatation	• Anti-hypertensive medications • Gram negative bacteraemia • Cirrhosis • Anaphylaxis
	Increased vascular resistance	• Anaesthesia • Surgery • Hepatorenal syndrome • NSAID medications • Drugs that cause renal vasoconstriction (i.e. cyclosporine)

Makris K et al. Clin Biochem Rev.2016; 37:85-98

Causes of acute kidney injury

Category	Abnormality	Causes
Intrinsic	Tubular	• Renal ischaemia (shock, complications of surgery, haemorrhage, trauma, bacteraemia, pancreatitis, pregnancy) • Nephrotoxic drugs (antibiotics, antineoplastic drugs, contrast media, organic solvents, anaesthetic drugs, heavy metals) • Endogenous toxins (myoglobin, haemoglobin, uric acid)
	Glomerular	• Acute post-infectious glomerulonephritis • Lupus nephritis • IgA glomerulonephritis • Infective endocarditis • Goodpasture syndrome • Wegener disease
	Interstitium	• Infections (bacterial, viral) • Medications (antibiotics, diuretics, NSAIDs, and many more drugs)
	Vascular	• Large vessels (bilateral renal artery stenosis, bilateral renal vein thrombosis) • Small vessels (vasculitis, malignant hypertension, atherosclerotic or thrombotic emboli, haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura)

Makris K et al. Clin Biochem Rev.2016; 37:85-98

Causes of acute kidney injury

Category	Abnormality	Causes
Post renal	Extrarenal obstruction	• Prostate hypertrophy • Improperly placed catheter Bladder, prostate or cervical cancer • Retroperitoneal fibrosis
	Intrarenal obstruction	• Nephrolithiasis Blood clots Papillary necrosis

Makris K et al. Clin Biochem Rev.2016; 37:85-98

Drugs associated with AKI

Pre renal

- ACEIs/ARBs
- Calcineurin inhibitors
- COX-2 inhibitors
- Diuretics
- NSAIDs

Glomerular Injury

- Interferon
- Pamidronate

Crystal Nephropathy

- Acyclovir
- Allopurinol
- Indinavir
- Methotrexate
- Nelfinavir
- Quinolones
- Sulfonamides
- Triamterene

ACEI = angiotensin converting enzyme inhibitors; AIN = acute interstitial nephritis; AKI = acute kidney injury; ARB = angiotensin II receptor blockers; ATN = acute tubular nephritis; COX II = cyclooxygenase 2

Drugs associated with AKI

Acute Interstitial Nephritis

- Allopurinol
- Azathioprine
- Diuretics (thiazides, furosemide)
- NSAIDs
- Phenytoin
- Proton pump inhibitors
- Quinolones
- Rifampin
- Semisynthetic penicillins (ampicillin, nafcillin, oxacillin)
- Sulfonamides
- Vancomycin

Acute Tubular Necrosis

- Aminoglycosides
- Amphotericin B
- Carboplatin
- Cisplatin
- Cyclophosphamide
- Ifosfamide
- Pentamidine
- Radiocontrast media
- Vancomycin

Awdishu L et al. Acute Kidney Injury. CCSAP 2017 Book 2 • Renal/Pulmonar

Causes , clinical settings and findings

Decreased Kidney Perfusion	Obstruction of the Urinary Tract	Parenchymal Kidney Diseases Other Than ATN	ATN
Causes Volume depletion; heart, lung, or liver disease; sepsis; increased intra-abdominal pressure; renal artery stenosis; NSAID toxicity	*Causes* Obstructive nephropathy	*Causes* Acute glomerulonephritis; acute interstitial nephritis; pyelonephritis; thrombotic microangiopathy; cast nephropathy; infarction; atheroembolism	*Causes* Toxic ATN; ischemic ATN
Clinical Setting Signs of volume depletion or overload; SIRS; severe hypertension	*Clinical Setting* Urinary tract symptoms; history of urolithiasis, genitourinary tract neoplasia, or retroperitoneal disease	*Clinical Setting* Systemic diseases; microangiopathic hemolysis	*Clinical Setting* Circulatory shock; sepsis; drug exposure; transient hypotension; hemolysis; rhabdomyolysis; tumor lysis
Urinary Tract Findings Concentrated urine; no RTE cells or casts	*Urinary Tract Findings* Hydronephrosis; relief with urinary catheter	*Urinary Tract Findings* Hematuria with RBC casts; pyuria with WBC casts; RTE cells	*Urinary Tract Findings* Urine not concentrated urine; RTE cells; granular casts

ATN = acute tubular necrosis; CKD = chronic kidney disease; GFR = glomerular filtration rate; NSAID = nonsteroidal anti-inflammatory drug; RBC = red blood cell; RTE = renal tubular epithelial cells; SIRS = systemic inflammatory response syndrome; WBC = white blood cell

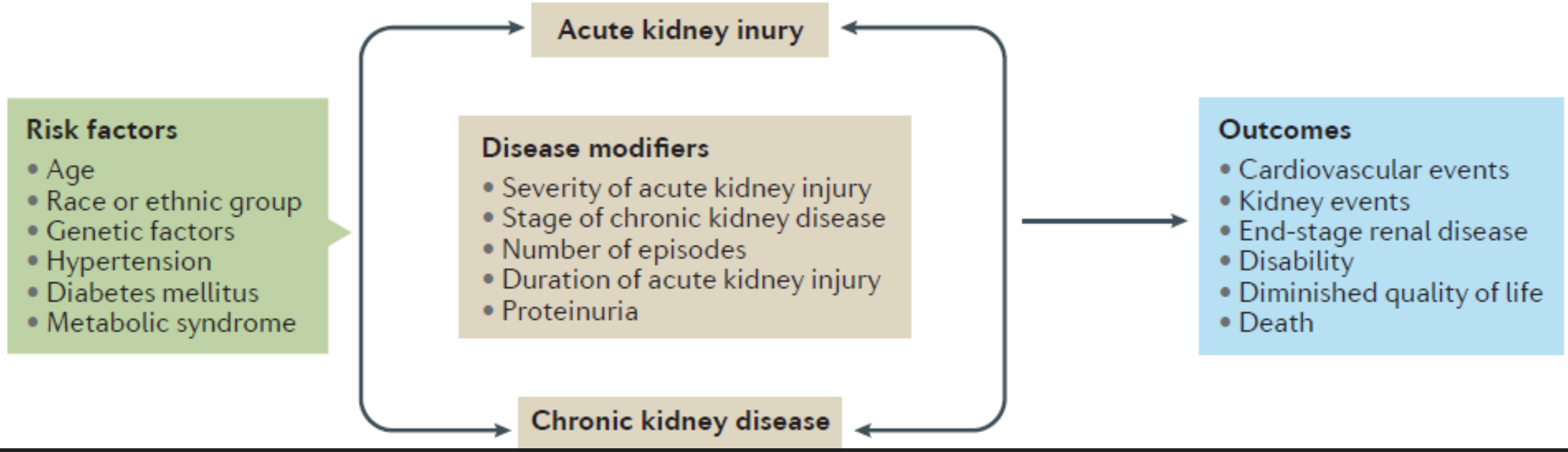
Levey AS et al. *Ann Intern Med*. 2017;167(9): 66-80.

Clinical features

- Patients with subacute kidney injury may present with edema, hypertension, and/or decreased urine output.
- Symptoms and/or signs of prolonged renal failure, including weakness and easy fatigability, anorexia, vomiting, mental status changes, and seizures
- The total absence of urine (anuria) is never observed with subacute injury and always indicates AKI.
- Anuria occurs as a result of shock, bilateral urinary tract obstruction, pregnancy-related cortical necrosis, or any process that causes severe, prolonged loss of renal perfusion.

Fatehi P et al Diagnostic approach to adult patients with subacute kidney injury in an outpatient setting. Waltham (MA): UpToDate;2018.

Acute kidney injury and chronic kidney disease



Chawla LS et al. Nat Rev

Urinary Indices for Differential Diagnosis

Urine Indices	Pre-renal/Hemodynamic	Acute Tubular Necrosis	Postrenal Obstruction
Urine sodium (mEq/L)	< 20	> 40	> 40
FENa (%)	< 1	> 2	> 1
Urine osmolality (mOsm/k)	Up to 1200	< 300	< 300
Urine creatinine/ plasma SCr ratio	> 40:1	< 20:1	< 20:1
Specific gravity	> 1.010	< 1.010	Variable

Awdishu L et al. Acute Kidney Injury. CCSAP 2017 Book 2 • Renal/Pulmonary Critical Care

Diagnosis

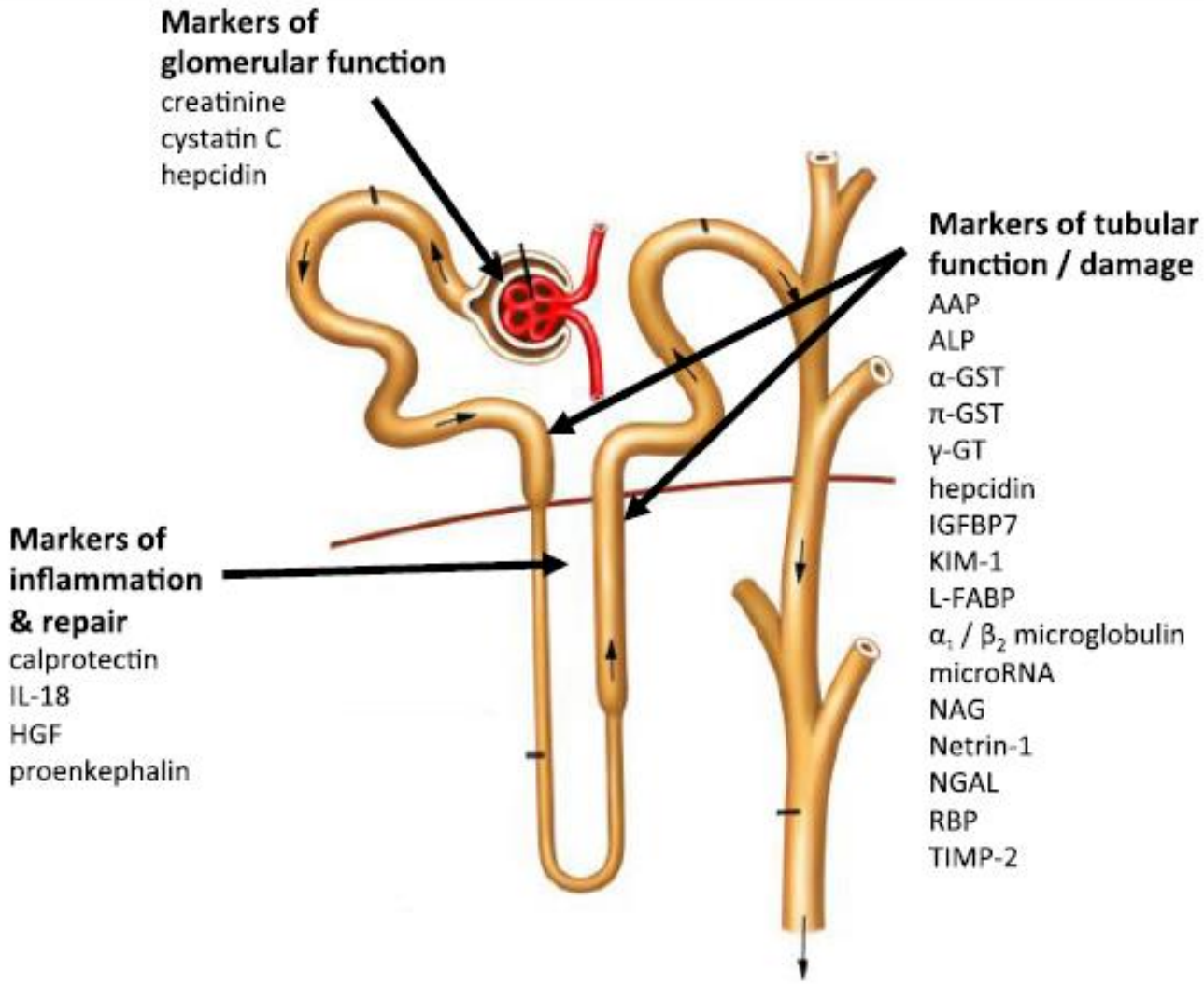
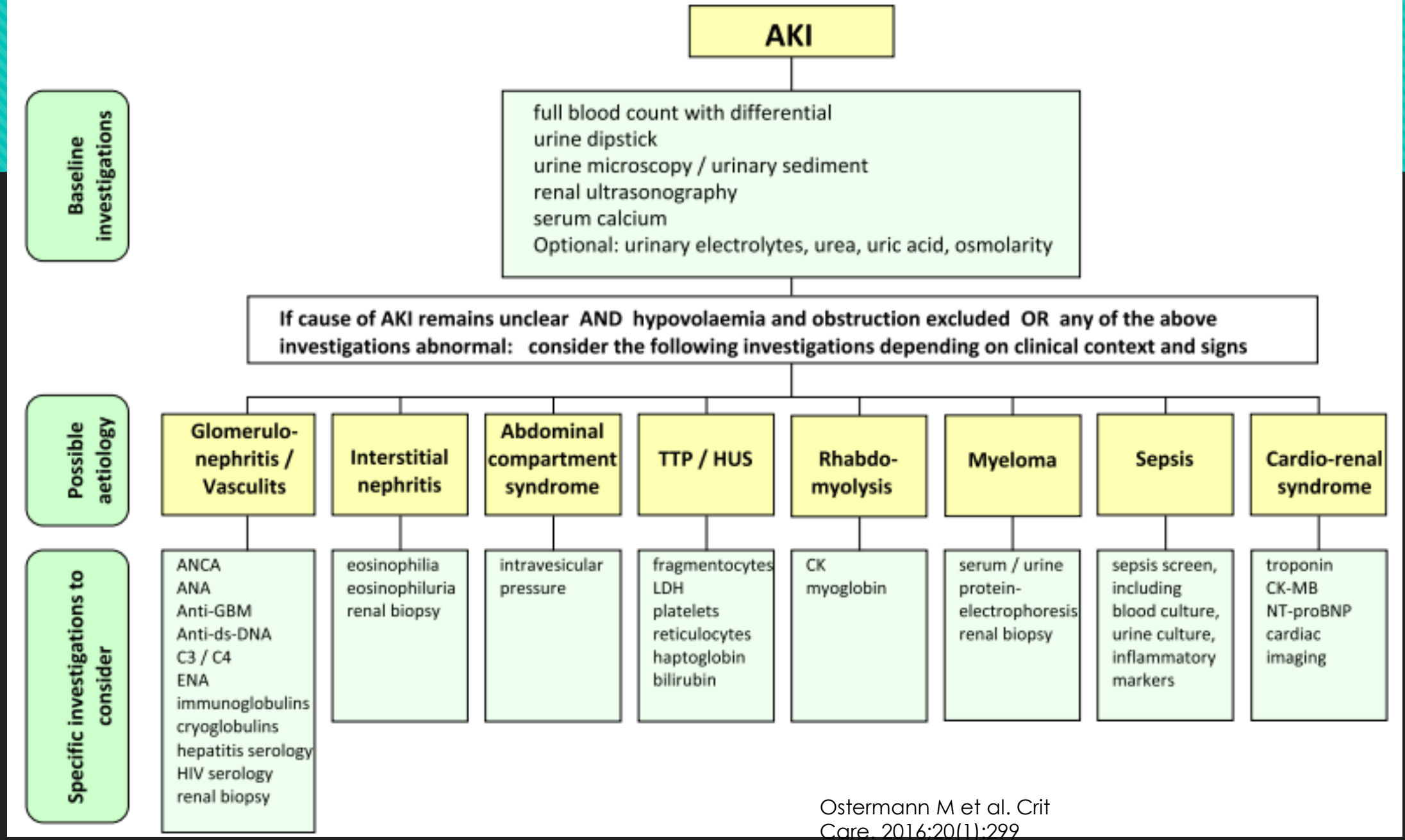


Fig. Biomarkers of AKI. *α-GST* α glutathione S-transferase, *AAP* alanine aminopeptidase, *ALP* alkaline phosphatase, *γ-GT* γ-glutamyl transpeptidase, *π GST* π glutathione S-transferase, *HGF* hepatocyte growth fator, *IGFBP-7* insulin like growth factor binding protein 7, *IL-18* interleukin 18, *KIM-1* kidney injury molecule-1, *L-FAB* liver fatty acid-binding protein, *NAG* N-acetyl-β-D-glucosaminidase, *NGAL* neutrophil gelatinase-associated lipocalin, *RBP* retinol binding protein, *TIMP2* tissue inhibitor metalloproteinase 2

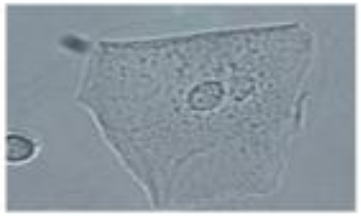
Ostermann M et al. Crit Care. 2016;20(1):299

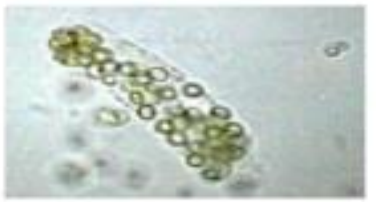
Diagnostic work up of AKI



Ostermann M et al. Crit Care. 2016;20(1):299

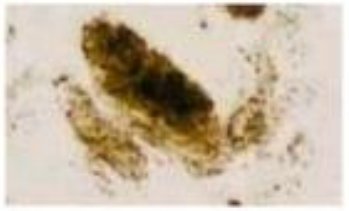
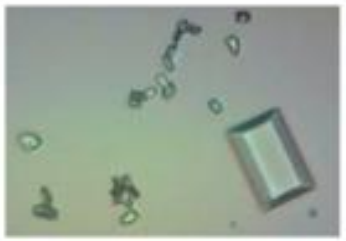
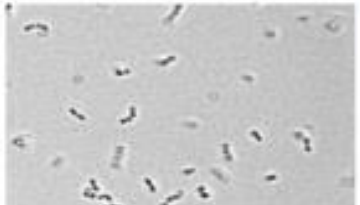
Interpretation of urine microscopy findings

Microscopy finding	Example	Significance
Epithelial cells		Normal
Renal tubular cells		Acute tubular injury
Non-dysmorphic red cells		Non-glomerular bleeding from anywhere in the urinary tract
Dysmorphic red cells		Glomerular disease, but can also be seen if urine sample is not fresh at time of microscopy

Microscopy finding	Example	Significance
Red cell casts		Diagnostic of glomerular disease
Leukocytes		Up to 3 per high-power field = normal; >3 per high-power field = inflammation in urinary tract
White cell casts		Renal infection
Hyaline casts		Any type of renal disease

Ostermann M et al. Crit Care. 2016;20(1):299

Interpretation of urine microscopy findings

Microscopy finding	Example	Significance
Granular casts		More significant renal disease
"Muddy brown cast"		Necrotic tubular cells aggregated with tamm horsfall protein indicating acute tubular injury
Crystals		Some crystals can be found in healthy individuals; "abnormal" crystals may indicate metabolic disorders or excreted medications
Bacteria		Urinary tract infection; contamination

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Potential pitfalls of AKI diagnosis based on creatinine and urine

Clinical scenario	Consequence
Administration of drugs which interfere with tubular secretion of creatinine (i.e. cimetidine, trimethoprim)	Misdiagnosis of AKI (rise in serum creatinine without change in renal function)
Reduced production of creatinine (i.e. muscle wasting, liver disease, sepsis)	Delayed or missed diagnosis of AKI
Ingestion of substances which lead to increased generation of creatinine independent of renal function (i.e. creatin, cooked meat)	Misdiagnosis of AKI
Obesity	Overdiagnosis of AKI if using actual weight when applying urine output criteria
Conditions associated with physiologically increased GFR (i.e. pregnancy)	Delayed diagnosis of AKI
Interference with analytical measurement of creatinine (i.e. 5-fluorocytosine, cefoxitin, bilirubin)	Misdiagnosis and delayed diagnosis of AKI (depending on the substance)
Fluid resuscitation and overload	Delayed diagnosis of AKI (dilution of serum creatinine concentration)
Progressive CKD with gradual rise in serum creatinine	Misdiagnosis of AKI
Extrinsic creatinine administration as a buffer in medications (i.e. in dexamethasone, azasetron)	Pseudo-AKI
Oliguria due to acute temporary release of ADH (i.e. post-operatively, nausea, pain) enhanced by maximal sodium reabsorption in the setting of volume/salt depletion	Misdiagnosis of AKI

ADH anti-diuretic hormone, *AKI* acute kidney injury, *CKD* chronic kidney disease, *GFR* glomerular filtration rate

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New diagnostic biomarkers of AKI

Liver-type fatty acid-binding protein (L-FABP)	14 kDa intracellular lipid chaperone produced in proximal tubular cells and hepatocytes	Freely filtered in glomeruli and reabsorbed in proximal tubular cells; increased urinary excretion after tubular cell damage	CKD Polycystic kidney disease Liver disease Sepsis
α_1 Microglobulin	Low molecular weight protein produced in liver	Freely filtered by glomeruli; reabsorbed and catabolised by proximal tubular cells; urinary excretion after tubular dysfunction	Sepsis
β_2 Microglobulin	12 kDa light chain of major histocompatibility class I expressed on cell surface of every nucleated cell	Freely filtered by glomeruli; reabsorbed and catabolised by proximal tubular cells; urinary excretion after tubular dysfunction	
MicroRNA	Endogenous single-stranded molecules of non-coding nucleotides	Upregulated following tubular injury and detectable in plasma and urine	Sepsis
Monocyte chemoattractant peptide-1 (MCP-1)	Peptide expressed in renal mesangial cells and podocytes	Released into urine	Variety of primary renal diseases
N-acetyl-β-D-glucosaminidase (NAG)	>130 kDa lysosomal enzyme; produced in proximal and distal tubular cells and non-renal cells	Too large to undergo glomerular filtration; released into urine after tubular damage	Diabetic nephropathy

Ostermann M et al. Crit

New diagnostic biomarkers of AKI

Neutrophil gelatinase-associated lipocalin (NGAL)	At least three different types: • Monomeric 25 kDa glycoprotein produced by neutrophils and epithelial tissues, including renal tubular cells • Homodimeric 45 kDa protein produced by neutrophils • Heterodimeric 135 kDa protein produced by renal tubular cells	25 kDa and 45 kDa NGAL undergo glomerular filtration and reabsorption in healthy tubular cells 25 kDa and 135 kDa NGAL are released into urine following tubular damage	Sepsis Malignancy CKD Urinary tract infection Pancreatitis COPD Endometrial hyperplasia
Netrin-1	50–75 kDa laminin-related molecule, minimally expressed in proximal tubular epithelial cells of normal kidneys	Highly expressed in injured proximal tubules and released into urine	
Proenkephalin	Endogenous polypeptide hormone in adrenal medulla, nervous system, immune system and renal tissue	Cleared by glomerular filtration	Systemic inflammation Pain
Retinol binding protein (RBP)	21 kDa single-chain glycoprotein; synthesized by liver	Totally filtered by the glomeruli and reabsorbed but not secreted by proximal tubules; released into urine following tubular injury	Diabetes Obesity Acute critical illness
Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1)	Member of the immunoglobulin superfamily of receptors expressed on granulocytes and monocytes, also possibly produced by endothelial cells and tubular epithelial cells	Detectable in urine following glomerular filtration and possibly local production	Sepsis Systemic inflammation

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Other laboratory tests

- Serum creatine kinase and myoglobin -suspected rhabdomyolysis
- Serum lactate dehydrogenase (LDH) –suspected thrombotic thrombocytopenic purpura (TTP))
- Fragmentocytes – Thrombotic Thrombocytopaenic Purpura/haemolytic uraemic syndrome (HUS))
- N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin – suspected cardio-renal syndrome
- serum/urine protein electrophoresis - suspected myeloma of kidney

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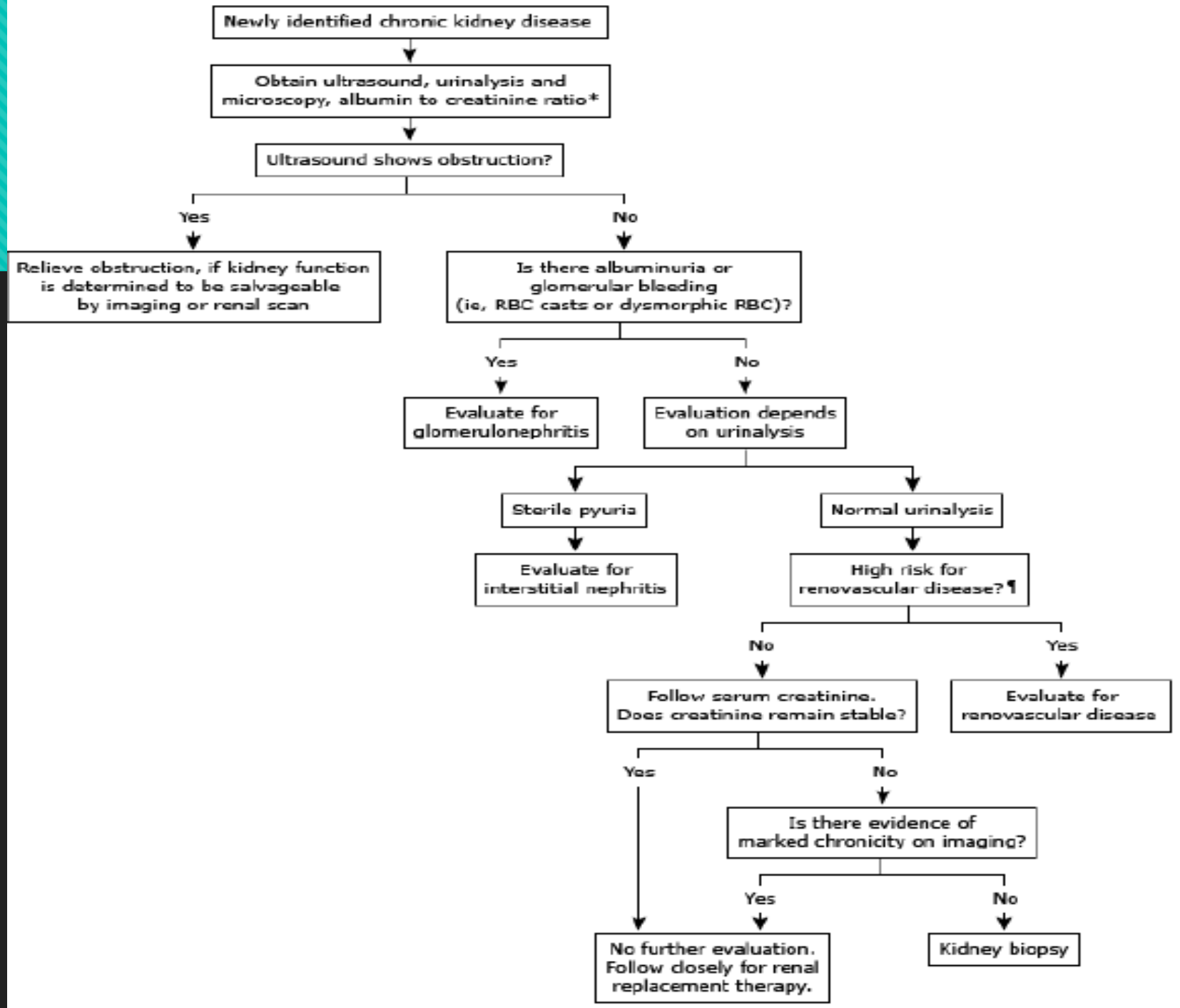
Evaluation of newly identified chronic kidney disease



Fatehi P et al Diagnostic approach to adult patients with subacute kidney injury in an outpatient setting. Waltham (MA): UpToDate;2018.

Referral to nephrologist

- GFR <30 mL/min/1.73 m2 (GFR categories G4-G5)
- A 25% drop in eGFR
- Progression of CKD with a sustained decline in eGFR of more than 5 per year
- A consistent finding of significant albuminuria
- Persistent unexplained hematuria
- Secondary hyperparathyroidism, persistent anion gap acidosis, non-iron deficiency anemia
- CKD and hypertension refractory to treatment with 4 or more antihypertensive agents
- Persistent abnormalities of serum potassium
- Recurrent or extensive nephrolithiasis
- Hereditary kidney disease or unknown cause of CKD

Vassalotti JA et al. Am J Med. 2016;129(2):153-162

Summary

- Acute kidney injury is a clinical syndrome defined by a rise in serum creatinine and/or fall in urine output.
- AKI is an important clinical syndrome associated with poor clinical outcomes for hospitalised patients .
- Prevention early detection, and prompt treatment are important to minimize the associated morbidity and mortality.
- Early diagnosis and appropriate diagnostic work-up are essential to determine the underlying aetiology and to identify cases of AKI that require specific and timely therapeutic interventions.
- The exact diagnostic investigations depend on the clinical context and should include routine baseline tests as well as more specific and novel tests