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AKI PATHOGENESIS

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Health-e-Child

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OUTLINE

1. The scenario: AKI in the pediatric setting
2. AKI genesis: causes and mechanisms

Pediatric AKI studies

- ***Pre-2004***: focus on RRT-requiring AKI and technique
- ***Epidemiology***: Rare, HUS, GN, sepsis, cancer
- ***Transition of PD/HD to CRRT***: prospective pediatric CRRT registry largest child Epi study

- **Post 2005:**
- Definitions
- AKI as a contributor to poor outcome
- Interest: understanding disease *patterns* and *prevention*

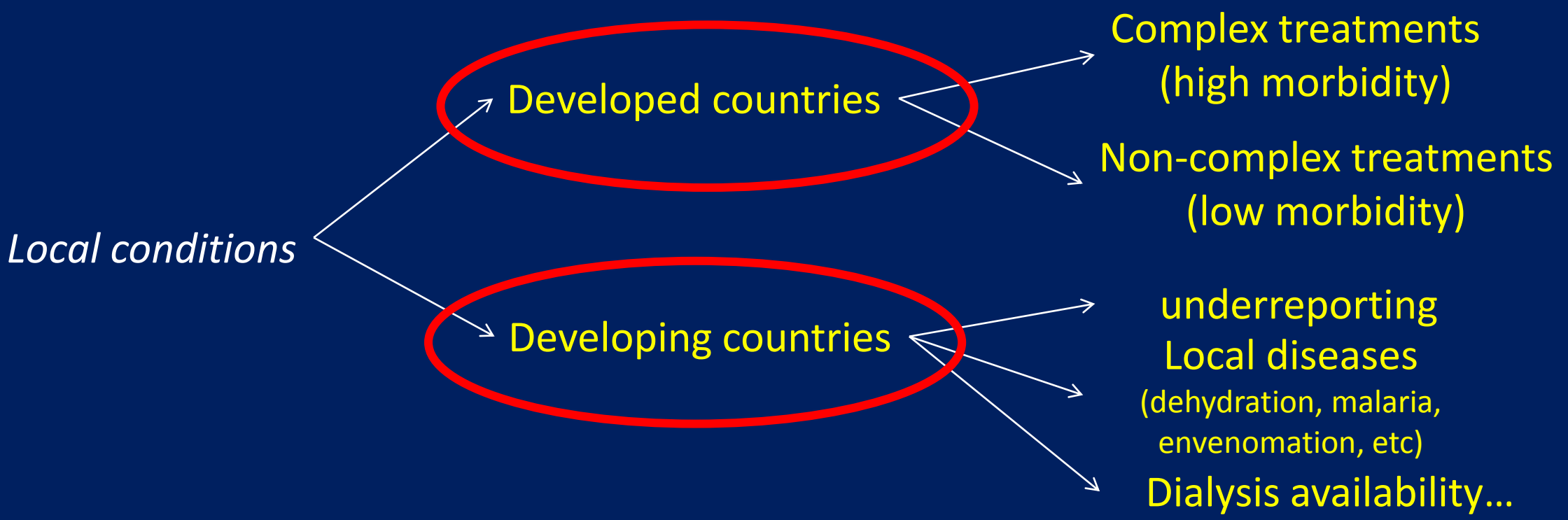
Zappitelli M, 2016

AKI in children: the dimension of the problem

- 10% of all children admitted in PICU suffer from varying degrees of AKI (Schneider, 2010)
- AKI carries a 50% mortality rate in children requiring CRRT (Symons, 2007)
- Pediatric AKI survivors are at risk for progression to CKD (Askenazi, 2006)
- AKI worsens mortality rates, increases duration of mechanical ventilation, prolongs hospital stays in critically ill children (Basu, 2011)
- AKI-associated mortality is not solely secondary to standard sequelae (e.g., hyperkalemia, acidosis, or uremia (cross-talk between the kidney and other vital organs) (Doi, 2011)

FACTORS AFFECTING AKI INCIDENCE

AKI definition: more than 30 definitions until sCreat/UO based classifications…



AKI OR AKI RECOGNITION IS INCREASING

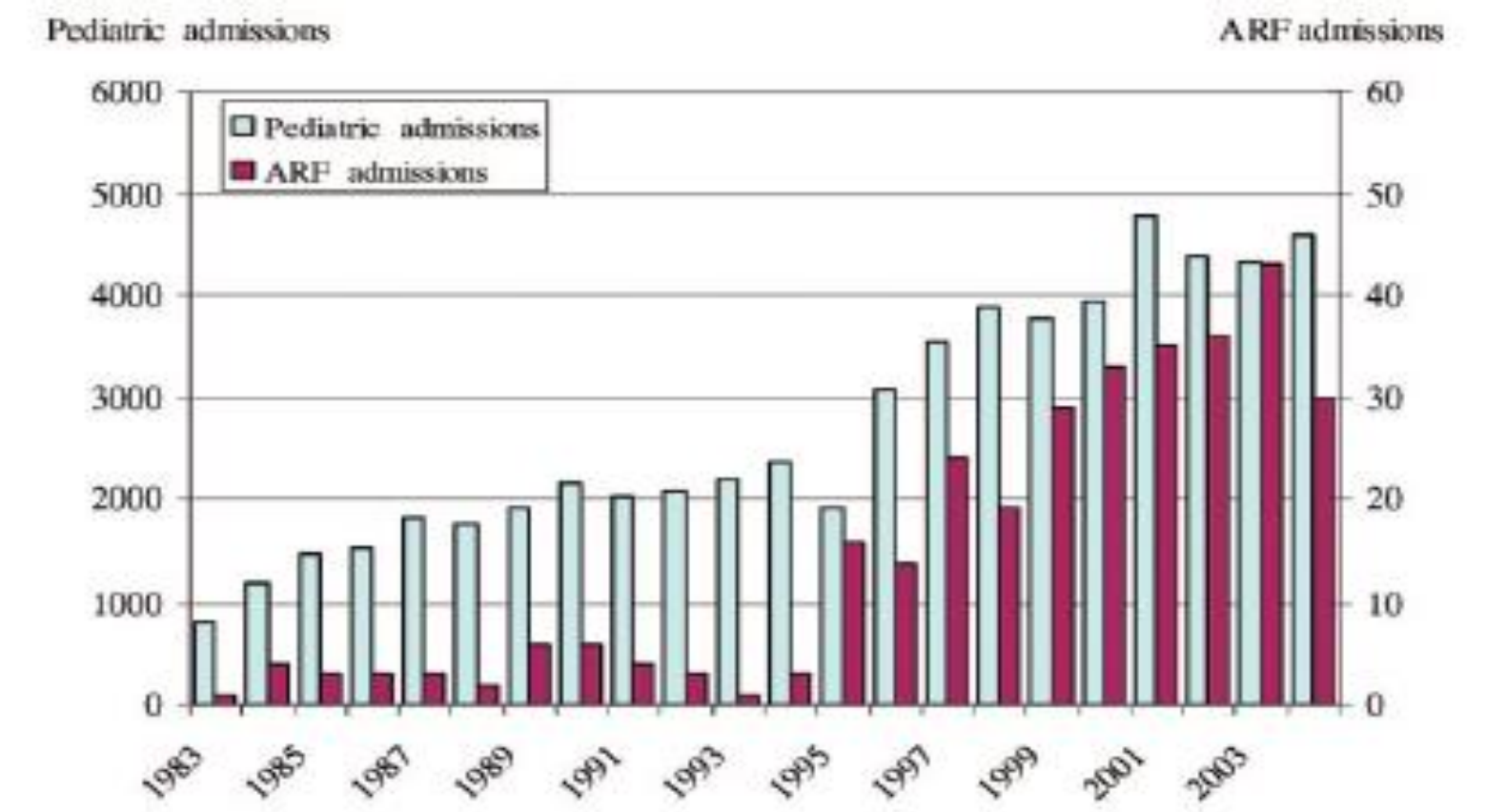


FIGURE 1
Comparison of the incidences of general pediatric admissions and ARF cases according to year.

Vachvanichsanong et al, Pediatrics, 2006 (THAILAND)

	Children (n=1643)*	Adults (n=993)†
Infection	380 (23%)	274 (28%)
Septicaemia	370	232
HIV	6	0
Tetanus	4	1
Pyelonephritis	0	12
Typhoid	0	7
Cholera	0	22
Glomerular disease	350 (21%)	76 (8%)
Acute glomerulonephritis	183	57
Nephrotic syndrome	115	10
Rapidly progressive acute glomerulonephritis	46	4
Lupus nephritis	5	5
Membranoproliferative acute glomerulonephritis	1	0
Nephrotoxin	270 (16%)	182 (18%)
Haemoglobinuria from:		
Plasmodium falciparum malaria haemolysis	198	34
G6PD deficiency haemolysis	18	0
Infection	0	41
Transfusion reaction	0	2
Autoimmune haemolytic anaemia	2	0
Herbal remedies ingestion	6	8
Holy water	0	7
Henna (para-phenylenediamine)	0	12
Unspecified drugs	0	17
Furosemide	5	0
ACE inhibitors	5	0
Cytotoxic drugs	5	0
Unspecified	31	61
Intravascular volume depletion or hypoperfusion	174 (11%)	50 (5%)
Gastroenteritis	169	42
Inadequate volume replacement before and after surgery	4	0
Severe haemorrhage	1	0
Unspecified	0	8
Obstructive uropathy	146 (9%)	46 (5%)
Renal stone	60	16

(Table 2 continues in next column)

	Children (n=1643)*	Adults (n=993)†

(Continued from previous column)

Congenital anomaly of the kidney and the urinary tract		
Posterior urethral valves	32	0
Renal agenesis	4	0
Prune belly syndrome	1	0
Prostate	0	9
Malignancy	0	2
Schistosoma	0	2
Unspecified	49	17
Vascular disease or haemolysis	116 (7%)	11 (1%)
Haemolytic uraemic syndrome	111	1
Thrombotic thrombocytopenic purpura	2	0
Purpura fulminans	1	0
Renal vein thrombosis	1	1
Sickle cell crisis	1	0
Haemolysis, other	0	9
Medical, other	0	36 (4%)
Liver disease	0	15
Cardiac	0	8
Malignant hypertension	0	13
Malignancy	40 (2%)	19 (2%)
Birth asphyxia	27 (2%)	0
Obstetric or gynaecological	0	157 (16%)
Septic abortion	0	66
Pre-eclampsia or eclampsia	0	43
Pre-partum or post-partum haemorrhage	0	30
Ureter ligation after hysterectomy	0	7
Unspecified	0	11
Surgical	0	54 (5%)
Trauma, burns, or fractures	0	43
Postoperative	0	1
Other	0	10
Unspecified	140 (9%)	88 (9%)

G6PD=glucose-6-phosphate dehydrogenase. ACE=angiotensin converting enzyme.
*17 paediatric studies. †14 adult studies.

Table 2: **Causes of acute kidney injury in children and adults**

kidney injury to be 72·8% and 82·9%.[14,16] In the remaining studies, most cases were probably community-acquired,

Olowu, 2016

Table 1 Etiology of pediatric acute renal failure (ARF)[a]

Cause	*n*	%
Hemolytic-uremic syndrome	108	21.0
Glomerulonephritis	65	12.6
Acute tubular necrosis[b]	120	23.3
"Intrinsic renal disease"[b]	44	8.5
Urinary obstruction	17	3.3
Postoperative	35	6.8
Sepsis	32	6.2
Ischemic/Prerenal	23	4.5
Other[c]	71	13.8
Total	515	100

[a] Compiled from references [15, 16, 17, 18, 20, 22, 26]
[b] Specific causes not specified
[c] Including metabolic disorders, renal venous thrombosis, hepato-renal syndrome, complications of organ transplantation, and other miscellaneous causes

1985-1997

from Flynn JT, 2002

Table 2. ARF Causes for Patients With Underlying Systemic Disease

Underlying Systemic Disease	Most Common Primary ARF Causes
Cardiac (n = 43)	Ischemic (69%)
	Nephrotoxins (7%)
	Sepsis (7%)
Hematology/oncology (n = 33)	Nephrotoxins (33%)
	Malignancy (24%)
	Sepsis (9%)
Gastrointestinal (n = 11)	Ischemic (45%)
	Nephrotoxins (27%)
Any systemic disease (n = 187)	Ischemic (27%)
	Nephrotoxins (18%)
	Sepsis (9%)

…Primary renal diseases accounted for only 17 cases (7%; acute glomerulonephritis [9 patients], pyelonephritis [5 patients], and hemolytic uremic syndrome [3 patients]).

Hui-Stickle S, 2004

AKI: Pediatric Issues

1. *Broadening of pediatric AKI epidemiology*

   due to morbidity deriving from new complex treatments (heart surgery, BMT, liver and heart tx, etc)

More critical children with AKI receiving Intensive Care

2. ***In critical children with AKI:***
   - ***Lack of prospective studies***
   - ***Lack of treatment stratification (medical and dialysis)***
   - ***Inconsistent control of illness severity***

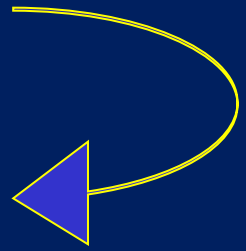
Outcome interpretation is difficult

PEDIATRIC MODS: EARLIER AND WORST

Differently from adult patients:

- Children die less but develop MODS early in ICU course
  - Maximum number of organ failures occurs within 72 hours of ICU admission (87% of patients)
- Children die with MODS very early in ICU course
  - 88.4% of deaths occur within 7 days of MOSF diagnosis

Quick identification of children at risk of AKI is needed in order to initiate early treatment



Proulx F, 1994

- *How “new” pediatric AKI epidemiology affects management*
- Presently, in a typical western world, tertiary care hospital setting pediatric AKI is more often due to systemic diseases or is part of the comorbidities induced by the new treatments than to primary renal diseases.

TAKE HOME MESSAGE:

→ we are more and more engaged in domains different from Pediatric Nephrology

The “classic” approach

Table 1 Etiology of common causes of acute kidney injury

Type	Etiology
Pre-renal injury	Decreased true intravascular volume Decreased effective intravascular volume
Intrinsic renal disease	Acute tubular necrosis (vasomotor nephropathy) Hypoxic/ischemic insults Drug induced Toxin mediated Endogenous toxins—hemoglobin, myoglobin Exogenous toxins—ethylene glycol, methanol Uric acid nephropathy and tumor lysis syndrome Interstitial nephritis Drug induced Idiopathic Glomerulonephritis—RPGN Vascular lesions Renal artery thrombosis Renal vein thrombosis Cortical necrosis Hemolytic uremic syndrome Hypoplasia/dysplasia with or without obstructive uropathy Idiopathic Exposure to nephrotoxic drugs in utero
Obstructive uropathy	Obstruction in a solitary kidney Bilateral ureteral obstruction Urethral obstruction

Andreoli, 2009

The “modern” approach

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.

KDIGO 2012

CJASN ePress. Published on July 5, 2013 as doi: 10.2215/CJN.00270113

AKI in Hospitalized Children: Epidemiology and Clinical Associations in a National Cohort

Scott M. Sutherland,* Jun Ji,† Farnoosh H. Sheikhi,‡ Eric Widen,‡ Lu Tian,§ Steven R. Alexander,* and Xuefeng B. Ling†

Table 3. Unadjusted AKI associations

Patients >1 Mo of Age		Patients ≤1 Mo of Age	
Associated Factor	Odds Ratio (95% Confidence Interval)	Associated Factor	Odds Ratio (95% Confidence Interval)
Diagnosis category associations		**Diagnosis category associations**	
Shock	2.15 (1.95 to 2.36)	Condition due to external cause	1.61 (1.39 to 1.87)
Septicemia	1.37 (1.32 to 1.43)	*Severe sepsis*	
Liver diseases	1.24 (1.18 to 1.28)	*Sepsis*	
Coagulation/bleeding disorders	1.23 (1.18 to 1.28)	Liver diseases	1.58 (1.32 to 1.89)
Thrombocytopenia		Circulatory disease	1.47 (1.32 to 1.65)
Disseminated intravascular coagulation		Complication of surgical care	1.42 (1.24 to 1.63)
Coagulation defect not otherwise specified		*Bleeding complicating procedure*	
Respiratory failure	1.21 (1.17 to 1.25)	*Cardiac surgical complication*	
Hypertension	1.2 (1.14 to 1.27)	*Postoperative infection*	
Pulmonary collapse/pleurisy	1.15 (1.11 to 1.19)	Fluid/electrolyte disorders	1.33 (1.25 to 1.42)
Anemia	1.1 (1.07 to 1.12)	Perinatal conditions not otherwise specified	1.2 (1.16 to 1.25)
Fluid/electrolyte disorders	1.09 (1.07 to 1.1)	*Neonatal arrhythmia*	
Nutritional/endocrine/metabolic disorders	1.05 (1.03 to 1.07)	*Neonatal dehydration*	
Disorder phosphorous metabolism		Cardiac congenital anomalies	1.18 (1.13 to 1.23)
Hypocalcemia		Respiratory distress syndrome	1.06 (1.01 to 1.1)
Disorder of magnesium metabolism			
Condition caused by external cause	1.05 (1.02 to 1.07)		
Severe sepsis			
Sepsis			
Hypoxemia			
Procedural category associations		**Procedural category associations**	
Intubation/mechanical ventilation	1.2 (1.16 to 1.25)	Extracorporeal circulatory support	2.58 (2.04 to 3.26)
Vascular catherization	1.18 (1.14 to 1.22)	*Extracorporeal membrane oxygenation*	
Parenteral/enteral nutrition	1.14 (1.09 to 1.19)	*Extracorporeal membrane oxygenation for cardiac surgery*	
Blood transfusion	1.11 (1.08 to 1.15)	Operating room procedure on vessel	2.07 (1.78 to 2.41)
		Occlusion of thoracic vessel	
		Arterial suture	
		Resection of thoracic vessel	
		Blood transfusion	1.42 (1.32 to 1.53)
		Vascular catherization	1.16 (1.11 to 1.21)
		Intubation/mechanical ventilation	1.14 (1.1 to 1.18)
		Parenteral/enteral nutrition	1.1 (1.05 to 1.14)

Electronic Health Record Identification of Nephrotoxin Exposure and Associated Acute Kidney Injury

TABLE 4 Distribution of High NTMx Exposure Admissions and AKI Rates by Specialty Service

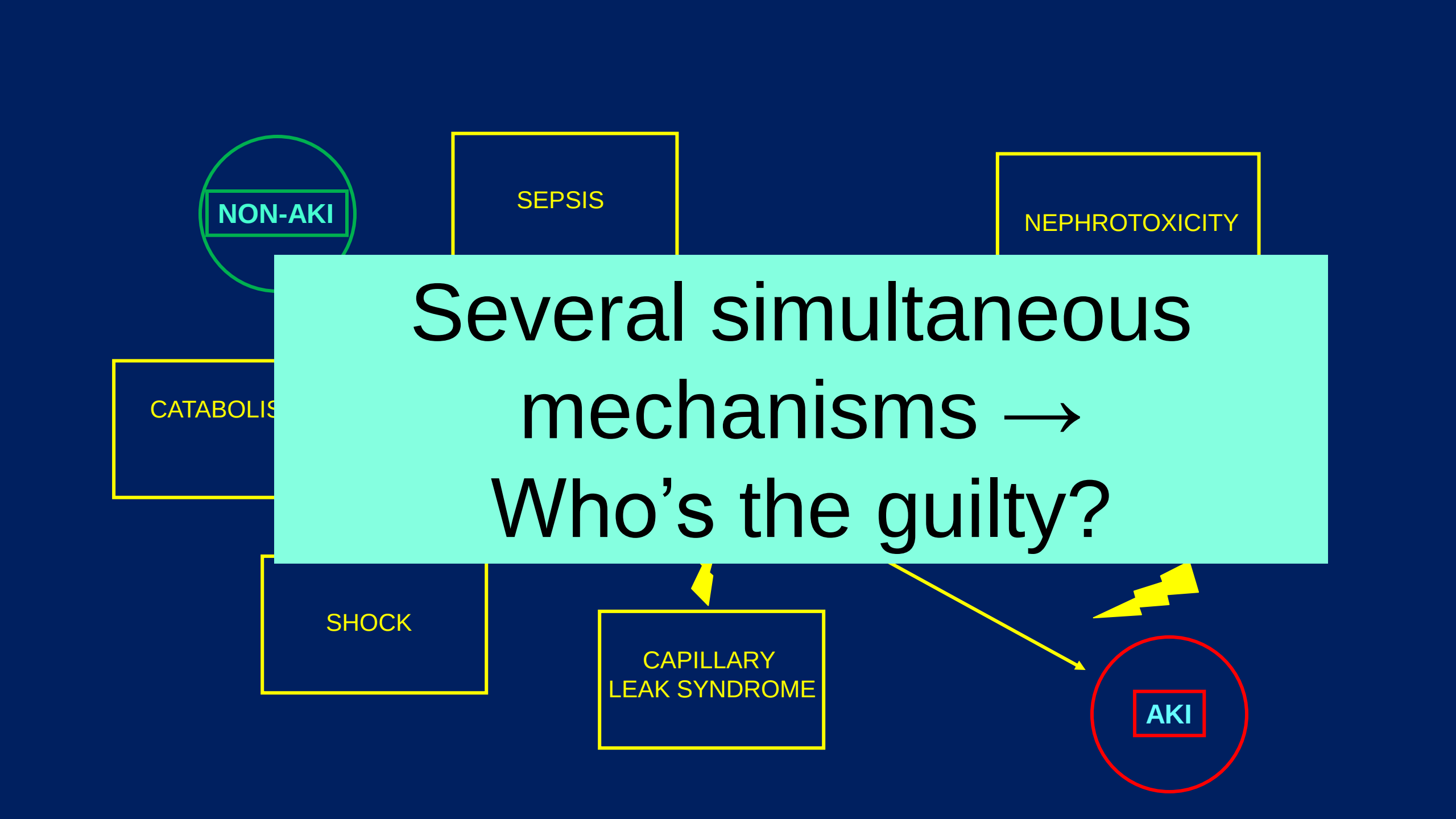
Services	High NTMx Case		AKI Cases			Gender	
	Count	%[a]	No	Yes	%[b]	Female	Male
Bone marrow transplant	263	27.83	142	121	46.01	108	155
Liver transplant	131	13.86	84	47	35.88	81	50
Oncology	105	11.11	68	37	35.24	47	58
Pulmonary (excluding cystic fibrosis)	77	8.15	54	23	29.87	32	45
Cystic fibrosis	71	7.51	65	6	8.45	43	28
General pediatrics	64	6.77	60	4	6.25	35	29
Gastrointestinal surgery, trauma	39	4.13	28	11	28.21	19	20
Orthopedics	30	3.17	25	5	16.67	21	9
Cardiology	27	2.86	18	9	33.33	13	14
Urology	27	2.86	25	2	7.41	12	15
Neurosurgery	26	2.75	22	4	15.38	10	16
Gastroenterology lumen	25	2.65	18	7	28.00	10	15
Otolaryngology	21	2.22	15	6	28.57	9	12
Neurology	20	2.12	18	2	10.00	9	11
Nephrology	11	1.16	6	5	45.45	4	7
Cardiothoracic surgery	2	0.21	2	0	0.00	1	1
Ophthalmology	2	0.21	2	0	0.00	1	1
Physical medicine and rehabilitation	2	0.21	2	0	0.00	2	0
Rheumatology	2	0.21	1	1	50.00	2	0
Total	945		655	290		459	486

NTMx, nephrotoxic medication.

[a] Represents the percentage of high NTMx cases by each specialty service.

[b] Represents the AKI rates for each specialty service.

Goldstein, 2016


NON-AKI
SEPSIS
NEPHROTOXICITY
CATABOLIS
Several simultaneous mechanisms →
Who's the guilty?
SHOCK
CAPILLARY
LEAK SYNDROME
AKI

Published in final edited form as:
Compr Physiol. 2012 April ; 2(2): 1303–1353. doi:10.1002/cphy.c110041.

Pathophysiology of Acute Kidney Injury

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[1]Department of Cellular & Integrative Physiology, Indiana University School of Medicine, Indianapolis, IN

[2]Department of Medicine, Division of Nephrology, Indiana University School of Medicine, Indianapolis, IN

- Tubular Damage: 1. Ischemic, 2. Nephrotoxic
- Glomerular Damage : glomerulopathies
- Interstitial Damage: acute interstitial nephritis (antibiotics, infections)
- Vascular Damage: hemolytic uremic syndrome (HUS)/thrombotic thrombocytopenia purpura (TTP)

baseline conditions

hemodynamic disturbances

nephrotoxic insults

inflammatory responses

AKI

KIDNEY OXYGENATION

- Even though the kidney is only 0.5% of total bodyweight, it uses approximately 7% of the O2 consumed by the body

- Under pathological conditions the balance of O2 supply compared with demand is disturbed due to the unique arrangement of the renal microvasculature and its diffusive shunting pathways

Hansell 2012

Kidney International, Vol. 62 (2002), pp. 1539–1549

Microvascular endothelial injury and dysfunction during ischemic acute renal failure

TIMOTHY A. SUTTON, CHARLES J. FISHER, and BRUCE A. MOLITORIS

Division of Nephrology, Department of Medicine, and the Indiana Center for Biological Microscopy, Indiana University School of Medicine, Indianapolis, Indiana; Abbott Laboratories, Chicago, Illinois; and the Roudebush VA Medical Center, Indianapolis, Indiana, USA

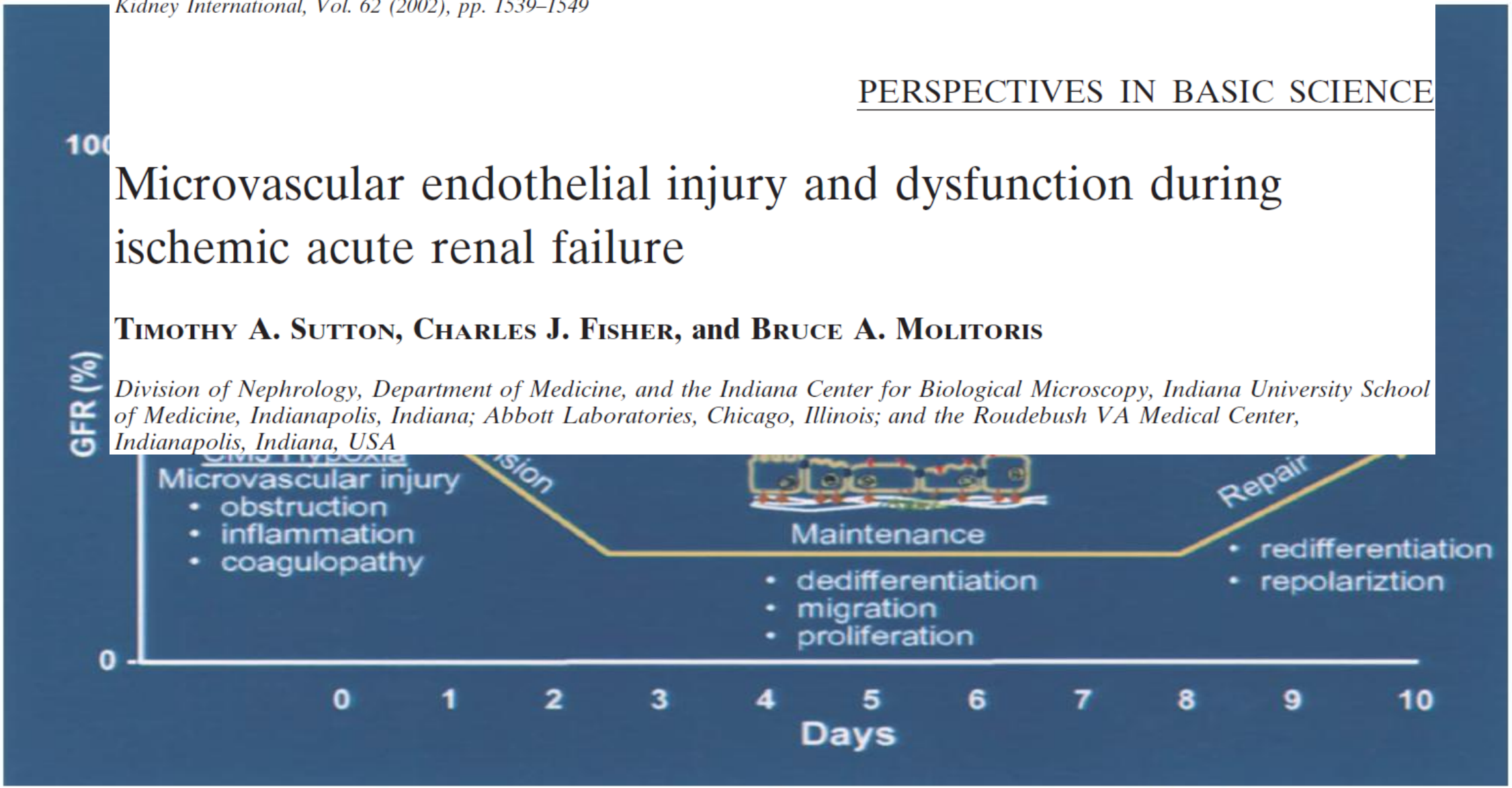

Fig. 1. Relationship between the clinical phases and the cellular phases of ischemic acute renal failure (ARF), and the temporal impact on organ function as represented by the glomerular filtration rate (GFR). Prerenal azotemia exists when a reduction in renal blood flow causes a reduction in GFR. A variety of cellular and vascular adaptations maintain renal epithelial cell integrity during this phase. The initiation phase occurs when a further reduction in renal blood flow results in cellular injury, particularly the renal tubular epithelial cells, and a continued decline in GFR. Vascular and inflammatory processes that contribute to further cell injury and a further decline in GFR usher in the proposed extension phase. During the maintenance phase, GFR reaches a stable nadir as cellular repair processes are initiated in order to maintain and re-establish organ integrity. The recovery phase is marked by a return of normal cell and organ function that results in an improvement in GFR.

MAIN MECHANISMS OF AKI PHASES

- ***Initiation***: ATP depletion, disruption of cytoskeleton (F-actin damage), up-regulation of IL1, IL6, TNFα,
- ***Extension***: inflammatory cascade of cytokines
- ***Maintenance***: repair, migration, apoptosis and proliferation
- ***Recovery***: cellular differentiation continues, epithelial polarity is re-established and organ function returns

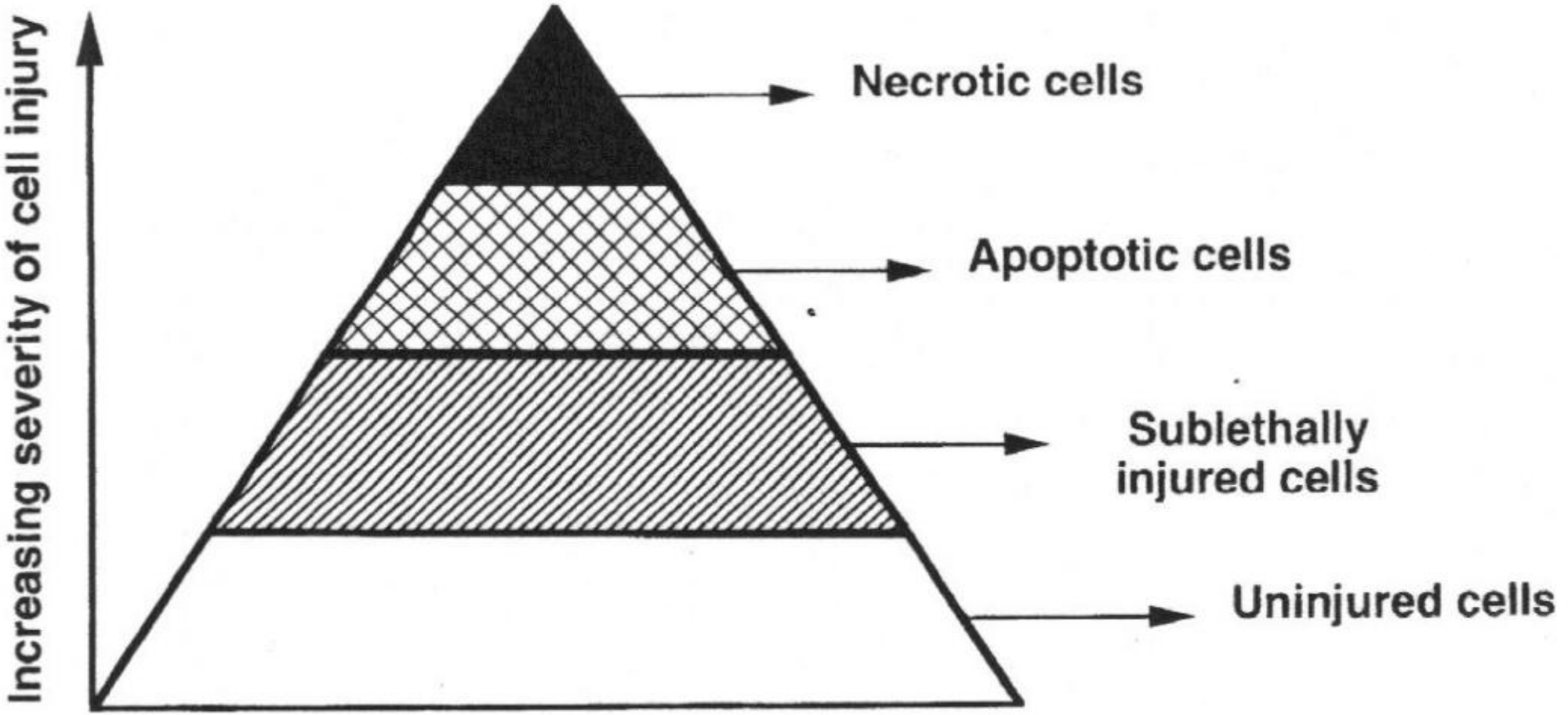

Figure 8. The continuum of renal cell damage
Individual renal tubular cells are likely to respond in different ways to injury depending upon the severity of the noxious stimulus. The majority of cells presumably remain viable, either because they escape injury altogether, or because they are only sublethally injured and able to recover. More severe injury likely results in apoptosis, whereas necrosis only occurs when cells are subjected to extremely severe injury that leads to critical energy depletion and subsequent metabolic collapse. Legend and figure from citation (320).

Basile, 2012

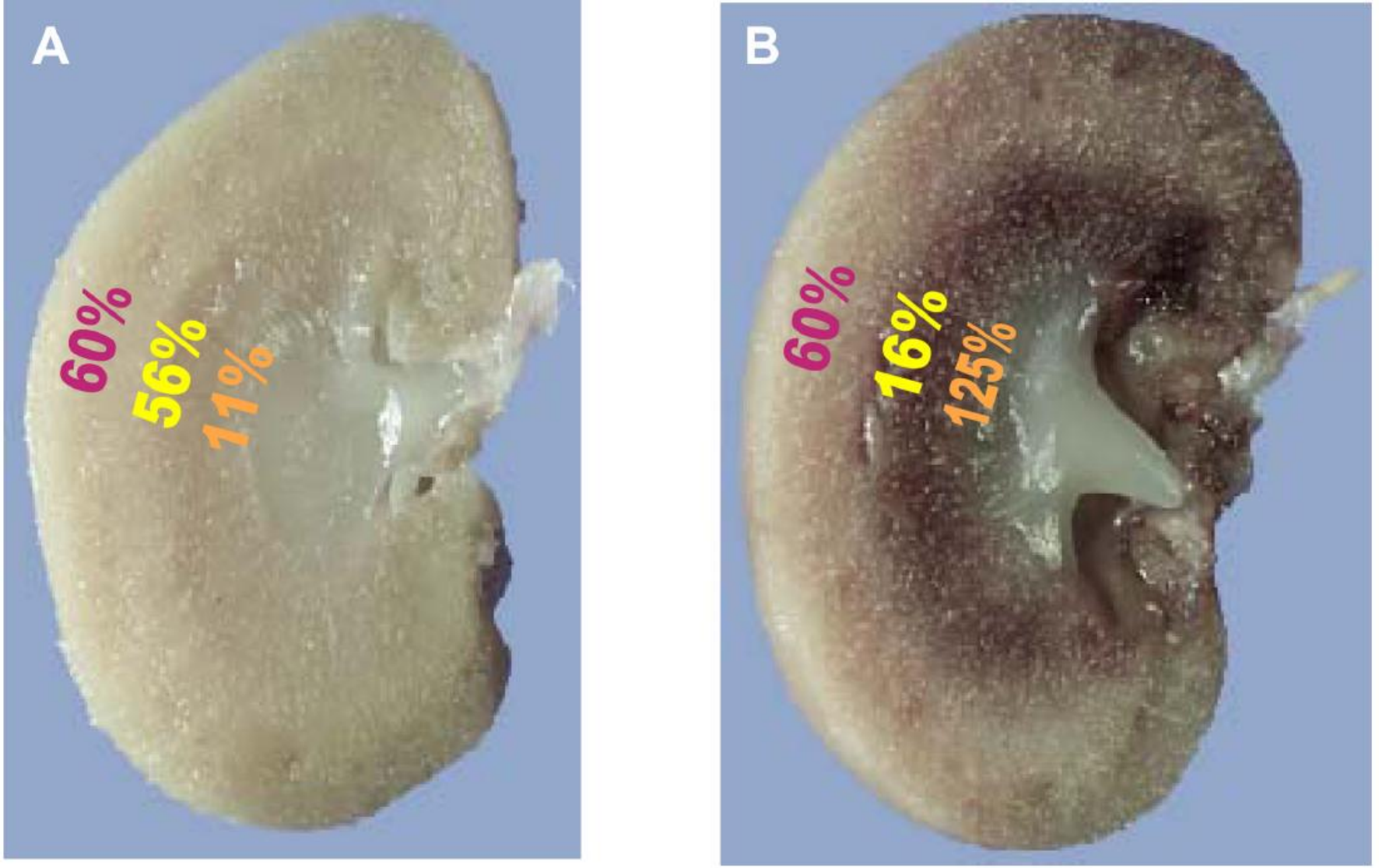

Figure 2. Regional blood flow is altered following injury in ischemic AKI
Immediately following ischemic injury total renal blood flow is reduced but more striking are the regional deficits in blood flow that exist in the cortex, outer stripe of outer medulla and inner stripe of the outer medulla as indicated in panel A (data from (251)). As overall blood flow starts to recover in the ensuing hours after injury, profound regional alterations in blood flow remain with progressive and profound reduction of the blood flow to the outer stripe of the outer medulla as indicated in B (data from (202)).

Basile, 2012

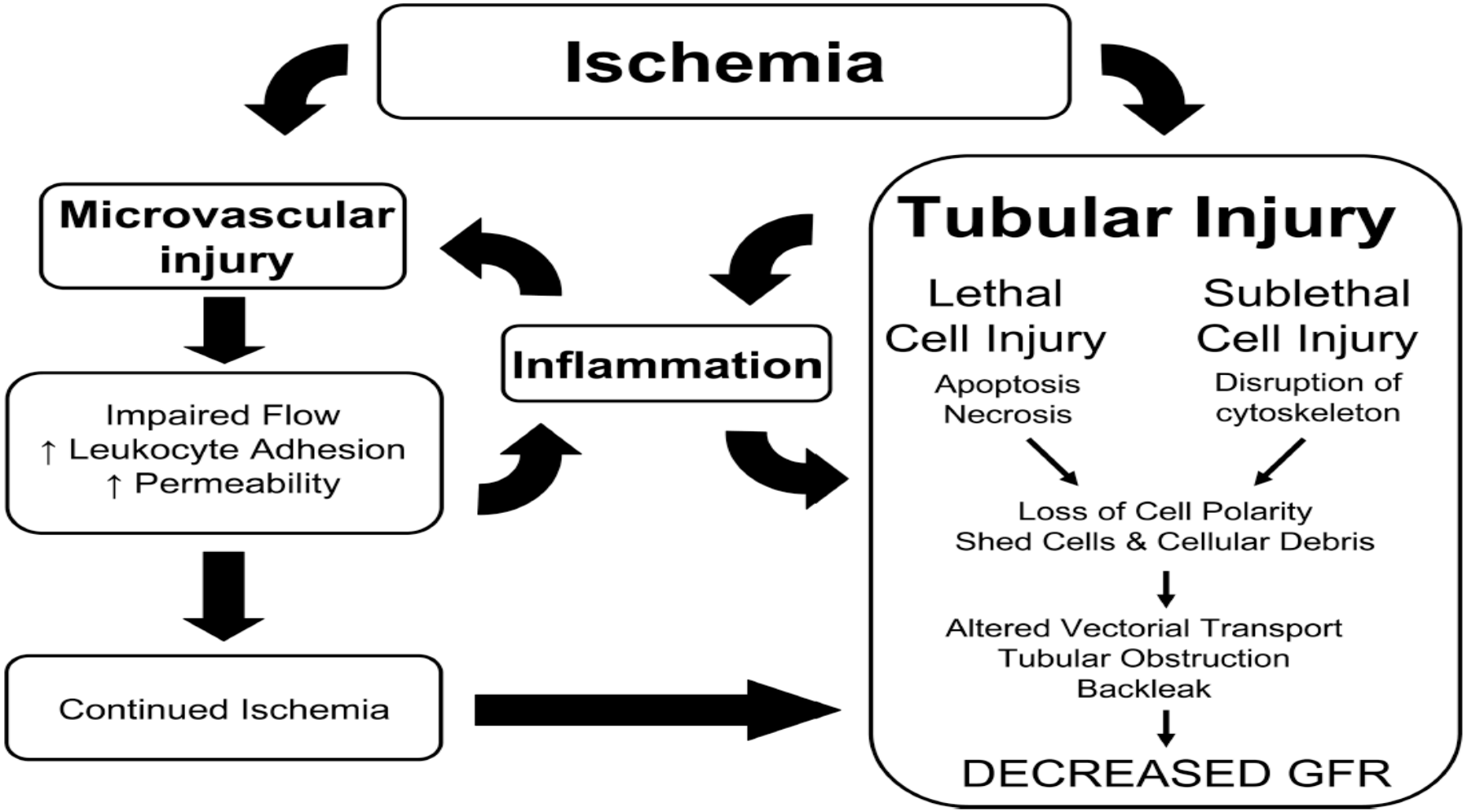

Figure 3. Interplay between tubular and vascular injury leading to sustained reductions of GFR in the extension phase of AKI

Injury induced by ischemia can results in damage to both the tubular as well as the microvascular compartment. Resolution of vasoconstriction appears effective at reducing injury when administered prophylactically, but not following established injury. Resistance may be due to exacerbated inflammation, which may impart reductions in RBF and GFR insensitive to vasodilator therapies. Of central importance in this process is the activation of inflammatory processes which are influenced by factors released by damaged proximal tubules as well as adhesion of damaged microvascular cells. Infiltrating leukocytes may impinge on RBF either by secreting vasoactive factors, or by contributing to the disruption of flow by physical interference. In addition, exacerbated hypoxia leading to tubular obstruction may contribute to reductions in GFR independent of vasodilator therapy. From citation (531)

Basile, 2012

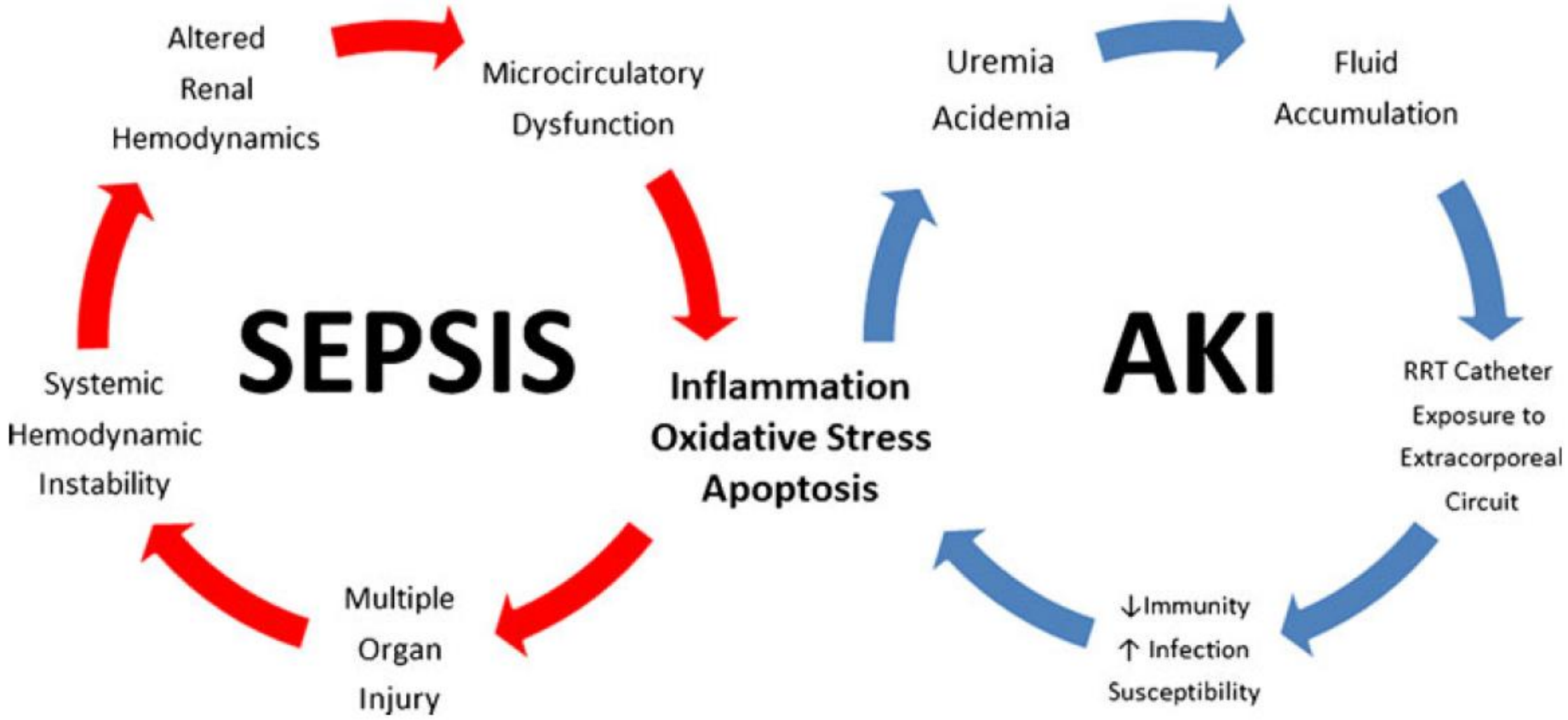

Fig. 1 Summary of the pathophysiologic interaction between sepsis and acute kidney injury (*AKI*). *RRT* Renal replacement therapy

Pediatr Nephrol (2014) 29:1–12
DOI 10.1007/s00467-013-2427-6

REVIEW

Pathophysiology and management of septic acute kidney injury

Adam Romanovsky · Catherine Morgan · Sean M. Bagshaw

CONCLUSIONS

- AKI genesis is a challenging process
- AKI causes definition has been and is changing in last years due both to improved recognition (emerging countries) and to changes in AKI exposure mainly as a consequence of new treatments (developed countries)
- AKI genesis constantly depends on and may interact with the genesis of underlying disease
- Better comprehension of AKI genesis mechanisms is a clue issue to its prevention , provided that AKI recognition is made in time.

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KIDNEY OXYGENATION

- Renal oxygenation: balance between oxygen (O2) supply and consumption (QO2)
- Under physiological steady state conditions , O2 supply to the renal tissues is well in excess of the O2 demand :
- Renal O2 extraction in the healthy kidney is only 10–15% (in most other organs it is closer to 45%)
- Under pathological conditions the balance of O2 supply compared with demand is disturbed due to the unique arrangement of the renal microvasculature and its diffusive shunting pathways
- High O2 demand is associated with the tubular QO2 necessary for solute exchange and the high rate of aerobic glycolysis
- Even though the kidney is only 0.5% of total bodyweight, it uses approximately 7% of the O2 consumed by the body
- The vast majority of QO2 is due to reabsorption of approximately 99.5% of filtered sodium (Na+)

Hansell 2012

Causes

- **AKI due to other causes >>> primary renal disease**
  - Developing countries:
    - More importance of primary renal disease, Malaria, HUS
    - However, now secondary causes emerging
  - "TOP HITS" around room:
    - "ATN"
    - "Hypovolemia"
    - Sepsis
    - Nephrotoxic medication – almost always significant when looked at!!
    - Heme-Onc
    - Cardiac surgery

Zappitelli M, 2016

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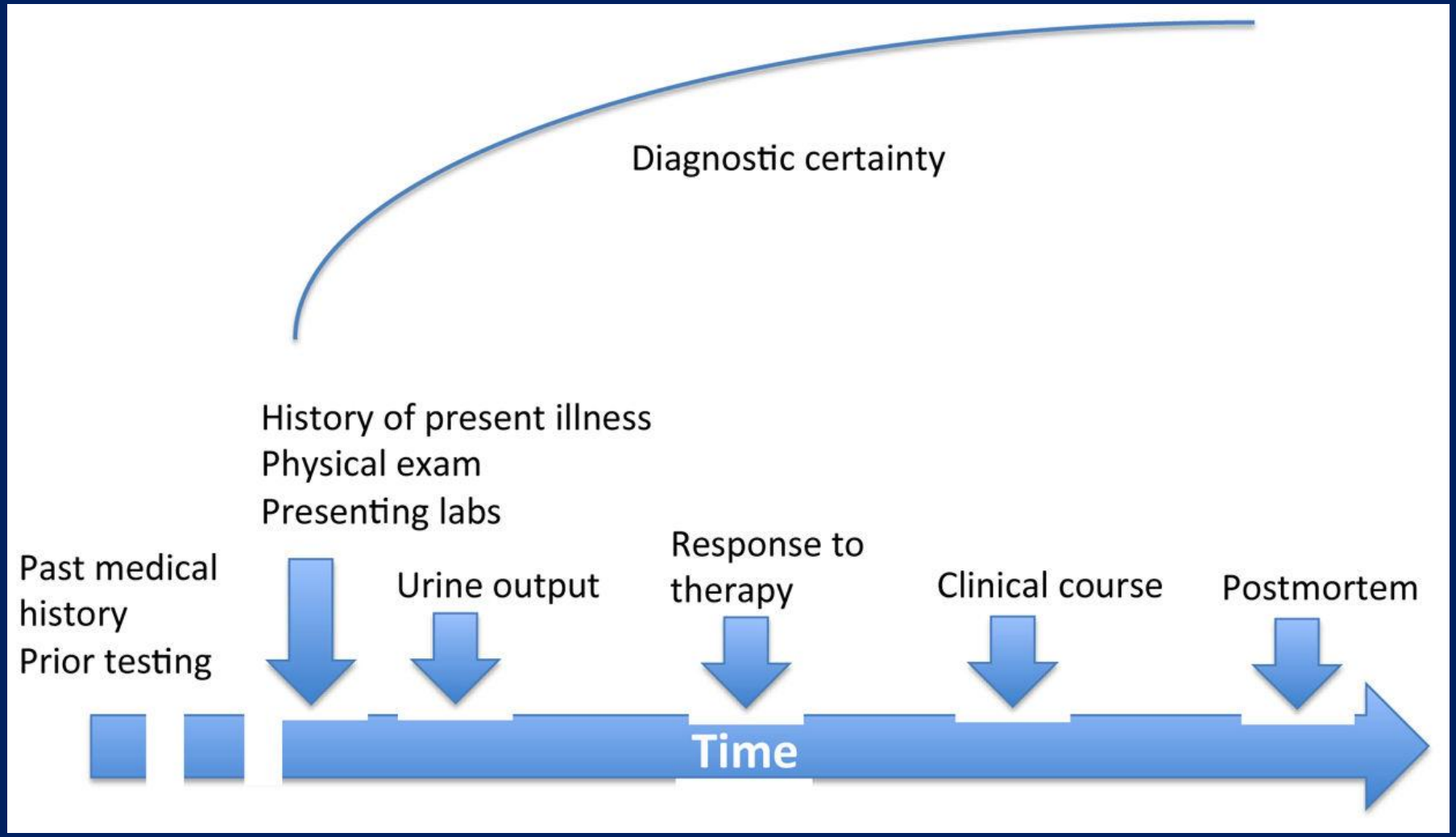

Diagnostic certainty
History of present illness
Physical exam
Presenting labs
Past medical history
Prior testing
Urine output
Response to therapy
Clinical course
Postmortem
Time

Table 5 | Causes of AKI and diagnostic tests

Selected causes of AKI requiring immediate diagnosis and specific therapies	Recommended diagnostic tests
Decreased kidney perfusion	Volume status and urinary diagnostic indices
Acute glomerulonephritis, vasculitis, interstitial nephritis, thrombotic microangiopathy	Urine sediment examination, serologic testing and hematologic testing
Urinary tract obstruction	Kidney ultrasound

AKI, acute kidney injury.

CHANGE IN THE EPIDEMIOLOGY OF AKI

Single organ failure

Primary renal disease

+

MODS

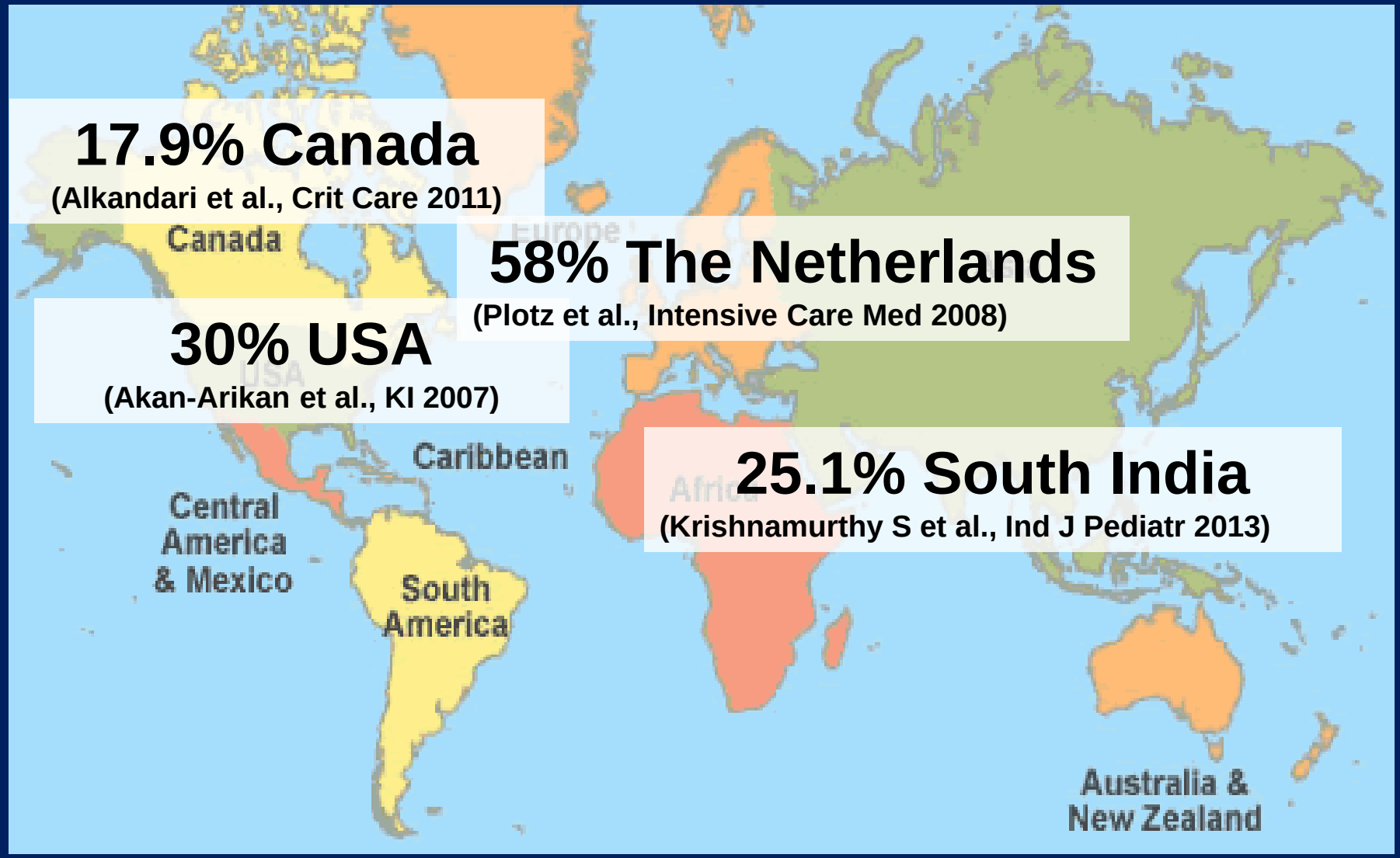
AKI as complication of systemic diseases

Renal ward/ Dialysis Unit

ICU

Courtesy of E. Vidal, modified

AKI Incidence: PICU

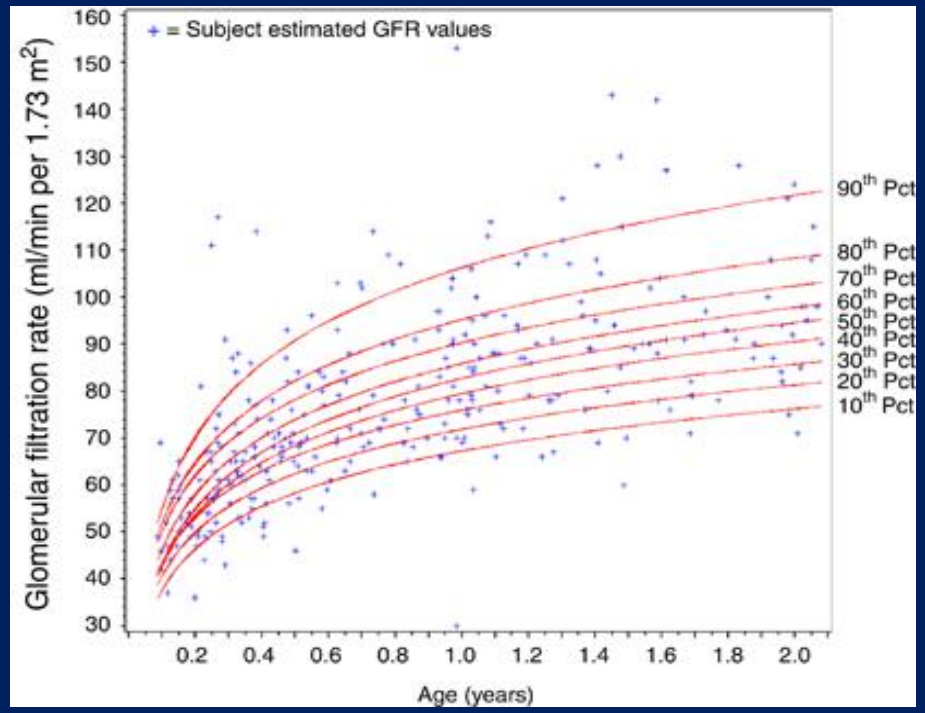


Courtesy of E. Vidal

IN NEONATES

“Immature” newborn kidney

Low GFR



High Urine Output

To accomplish the physiologic extracellular post-natal fluid reduction (10% weight loss)

To manage the large water load coming from breast feeding

Torres de Melo Bezerra, NDT 2013

nRIFLE

Table 1. Synoptic view of adult, paediatric and neonatal RIFLE

	Creatinine criteria			Urine output criteria		
	RIFLE	*pRIFLE*	*nRIFLE*	*RIFLE*	*pRIFLE*	*nRIFLE*
Risk	Increased creatinine × 1.5 or GFR decreases >25%	eCCl decrease by 25%	?	UO ≤ 0.5 mL/kg/h × 6 h	UO < 0.5 mL/kg/h for 8 h	UO < 1.5 mL/kg/h for 24 h
Injury	Increased creatinine × 2 or GFR decreases >50%	eCCl decrease by 50%	?	UO ≤ 0.5 mL/kg/h × 12 h	UO < 0.5 mL/kg/h for 16 h	UO < 1.0 mL/kg/h for 24 h
Failure	Increased creatinine × 3 or GFR decreases >75% or creatinine ≥4 mg/dL (acute rise of ≥4 mg/dL)	eCCl decrease by 75% or eCCl <35 mL/min/1.73 m^2	?	UO ≤ 0.3 mL/kg/h × 24 h or anuria × 12 h	UO < 0.3 mL/kg/h for 24 h or anuric for 12 h	UO < 0.7 mL/kg/h for 24 h or anuric for 12 h
Loss	Persistent failure >4 weeks					
End stage	Persistent failure >3 months					

Question mark ('?') is intended to mean uncertain thresholds.
GFR, glomerular filtration rate; Ecl, estimated creatinine clearance; UO, urine output.

Ricci, Ronco, adapted from Torres de Melo Bezerra, NDT 2013

DISEASE AND SURVIVAL

Diagnosis	N	Survival	Diagnosis	N	%Survival
BMT	26	42%	HUS	16	94%
TLS/Malig	17	58%	ATN	46	67%
CHD	47	39%	Liver Tx	22	17%
Heart Tx	13	67%	Sepsis	39	33%

- Pts on Vasopressors survival = 35%
- Pts not on Vasopressors survival = 89% ($p < 0.01$)

Bunchman TE et al: Ped Neph 16:1067-1071, 2001
Slide courtesy of T.E.B.