Nephro Update Europe 2017

6-7 October, Vienna

Acute Kidney Injury

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AKI Diagnosis & Staging

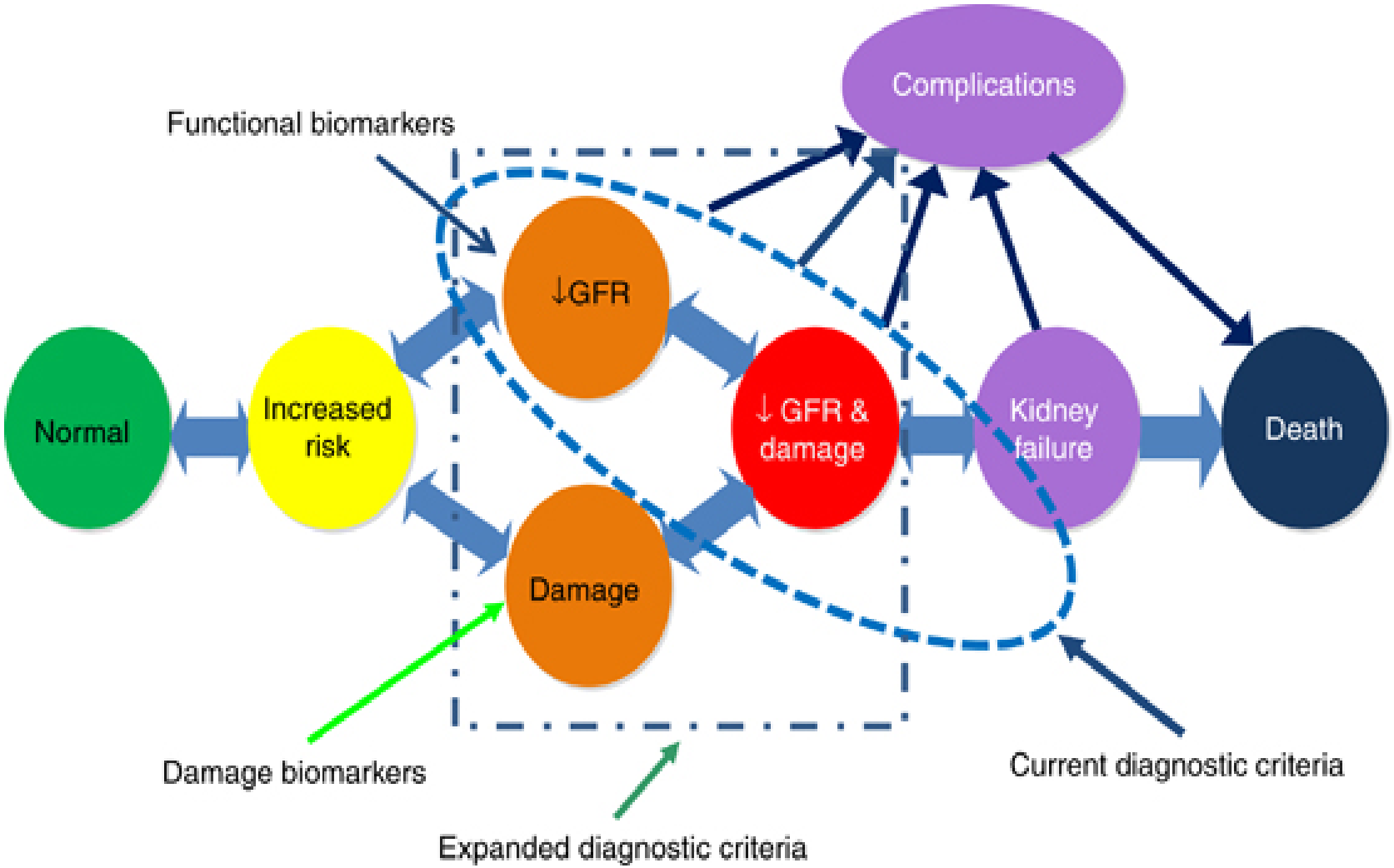
AKI Guidelines: Current Status of Criteria for Diagnosis & Staging

- *Validated Classification Systems*

	Risk/Stage 1	Injury/Stage 2	Failure/Stage 3
RIFLE[1] 2004	• Increased SCr × 1.5 **or** • GFR decrease >25%	• Increased SCr × 2 **or** • GFR decrease >50%	• Increased SCr × 3 or GFR decrease 75% **or** • SCr ≥4 mg/dL (acute rise of ≥0.5 mg/dL)
AKIN[2] 2007	• Increased SCr ≥0.3 mg/dL **or** • >1.5–2.0 × baseline	• Increased SCr >2–3 × baseline	• Increased SCr >3 × baseline **or** • SCr ≥4 mg/dL (acute increase of ≥0.5 mg/dL)
KDIGO[3] 2012	• Increased in SCr by >0.3 mg/dL (≥26.5 µmol/L) within 48 h **or** • 1.5–1.9 × baseline	• Increased in SCr by 2.0–2.9 × baseline	• Increased SCr by ≥4.0 mg/dL (≥353.6 µmol/L) **or** • 3.0 × baseline or initiation of RRT **or** • In patients <18 y, decrease in eGFR to <35 mL/min/1.73 m^2

1. Bellomo R et al. Crit Care. 2004;8:R204-212
2. Mehta RL et al. Crit Care. 2007;11:R31
3. KDIGO Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl. 2012;2:1-138. www.KDIGO.org

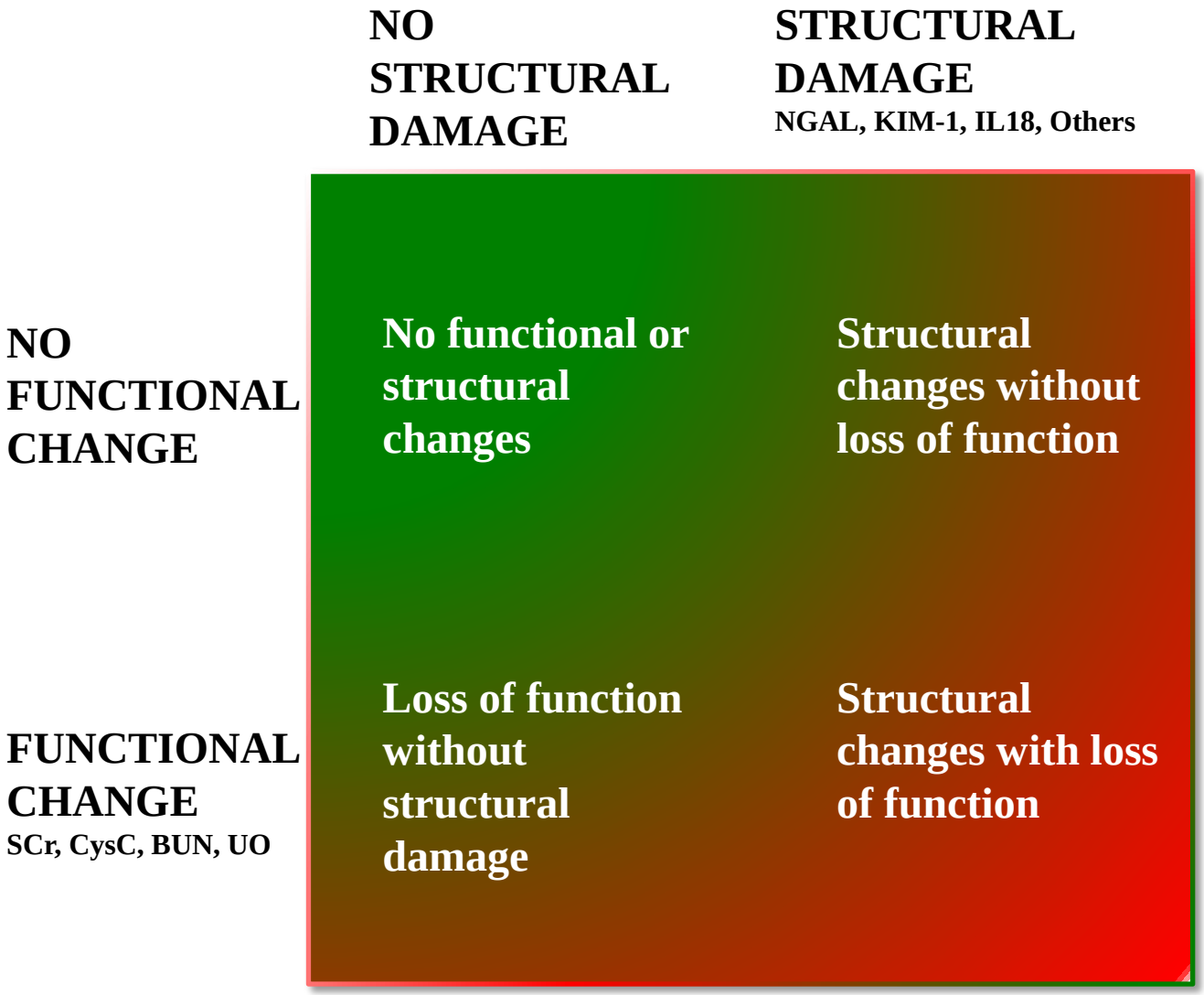
Evolution of AKI Conceptual Framework



www.ADQI.org

Murray PT, et al, for the ADQI Workgroup: 2014;85:513-521

The New Spectrum of AKI Diagnostics



Murray PT, et al for the ADQI Workgroup: Kidney Int 2014;85:513-521

www.ADQI.org

TIMP2.IGFBP7 AKI Biomarker Studies

Discovery & Initial Validation (Kashani- Sapphire Study):

Urinary BM of AKI risk [tissue inhibitor of metalloproteinase-2] × [insulin-like growth factor binding protein-7]; cell cycle arrest markers

Cut-off Derivation & Validation (Hoste et al- Sapphire & Opal studies; Bihorac et al- Topaz study):

Predicts risk of Stage ≥2 AKI within 12 hours (AKI%; RR):

High sensitivity cut-off: ≤ 0.3 (<5%; RR 1)

Intermediate values: >0.3 - ≤ 2.0: (12.6%; RR ≈ 4)

High specificity cut-off: >2.0 (49%; ≥10)

Kashani K, et al: Crit Care 2013;17:R25

Hoste E, et al: Nephrol Dial Transplant

Bihorac A, et al: Am J Respir Crit Care Med 2014;189, 932-939

Furosemide Stress Test (FST) Predicts AKI Severity

2-hour UOP following Furosemide 1-1.5mg/kg: Progression to AKIN Stage 3 (n=77)

Total Urine Output over 2 hours		Sensitivity		Specificity
< 100 ml		90.2%		60.0%
< 200 ml		87.1%		84.1%
< 300 ml		85.3%		88.0%
< 400 ml		66.7%		88.0%
< 500 ml		50.5%		88.0%

AUC 0.87

Chawla LS, et al: Crit Care 2013;17(5):R207

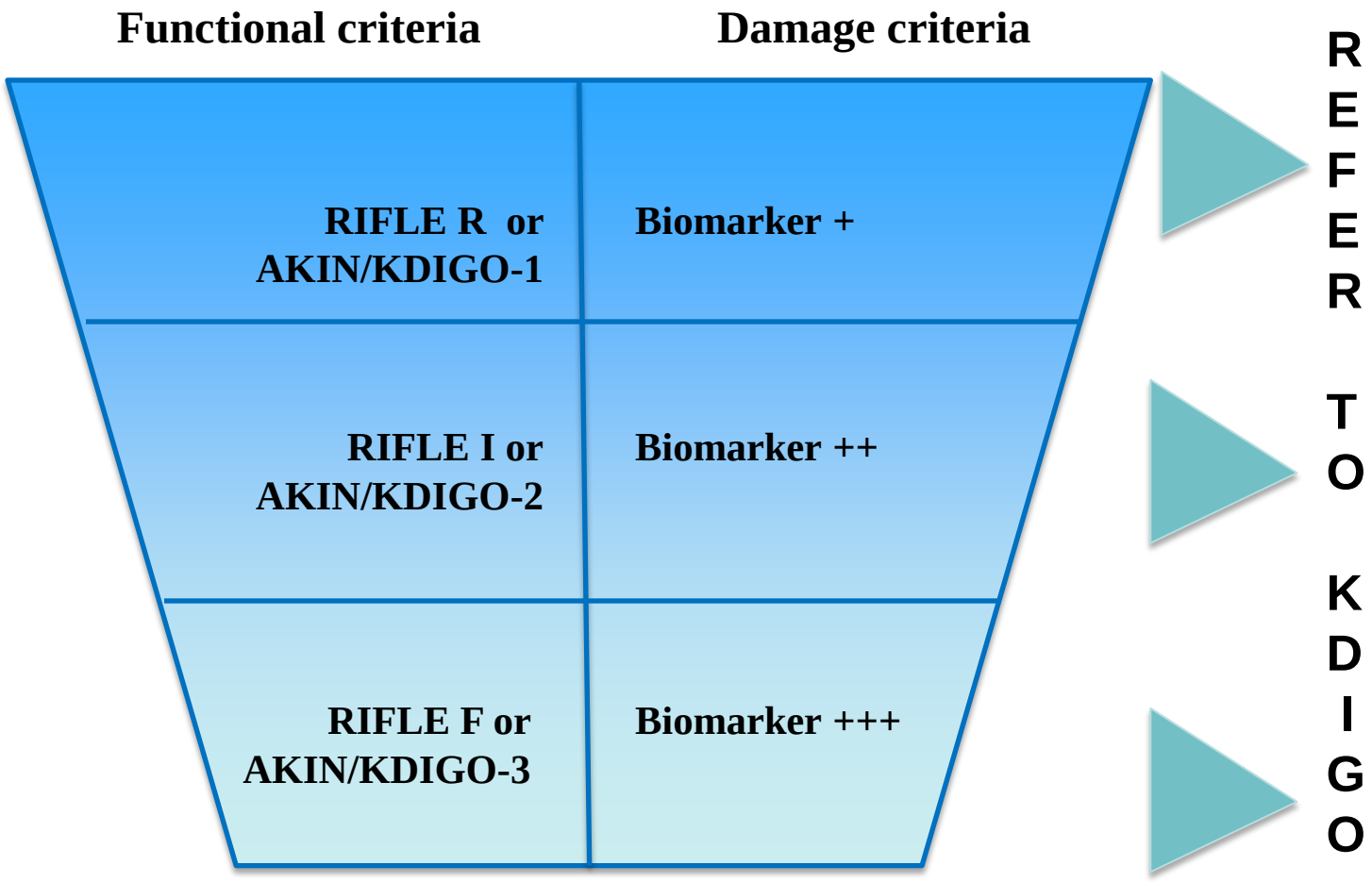
FST plus AKI Biomarkers

Measured BMs in previous FST cohort samples (n=77)

- Endpoints: 2-hour UOP prediction of.....
  - Stage 3 AKI: n=25 (32.5%); AUC 0.87±0.09
    - Significantly better than any other BM ($p<0.05$)
  - RRT: n=11(14.2%); AUC 0.86±0.08; p=0.001
  - Inpatient Mortality: n=16 (20.7%); AUC 0.7±0.09, p=0.02
- In 33 patients with [TIMP2].[IGFBP7] >0.3, higher AUCs: Stage 3 (0.9), RRT (0.91)

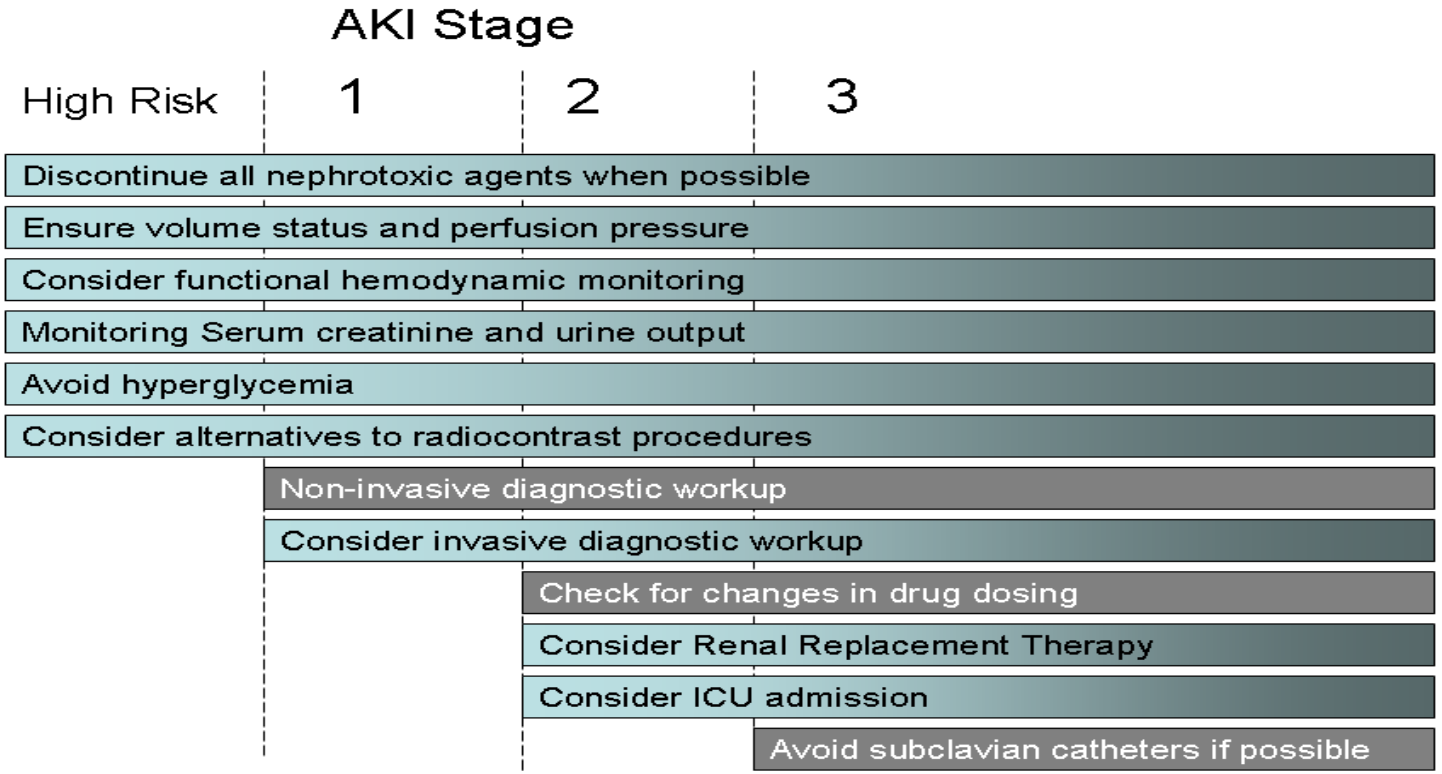
Koyner JL, et al: J Am Soc Nephrol 2015;26:2023-31

The New Spectrum of AKI Diagnostics



Murray PT, et al for the ADQI Workgroup: Kidney Int 2014;85:513-521

Stage-Based AKI Management



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.

KDIGO AKI Work Group: KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int, Suppl,* 2012;2(1):1-138

Take-Home Message

Several AKI Classification Systems have been developed and validated

- Based upon functional criteria (SCr, UOP)
  - FST, real-time GFR, other functional markers will refine these criteria
- Novel biomarkers of kidney damage may also improve the diagnostic evaluation of AKI
- Combination of functional and damage biomarkers, implementation research required

AKI Prevention

KDIGO Conceptual Framework for AKI Risk

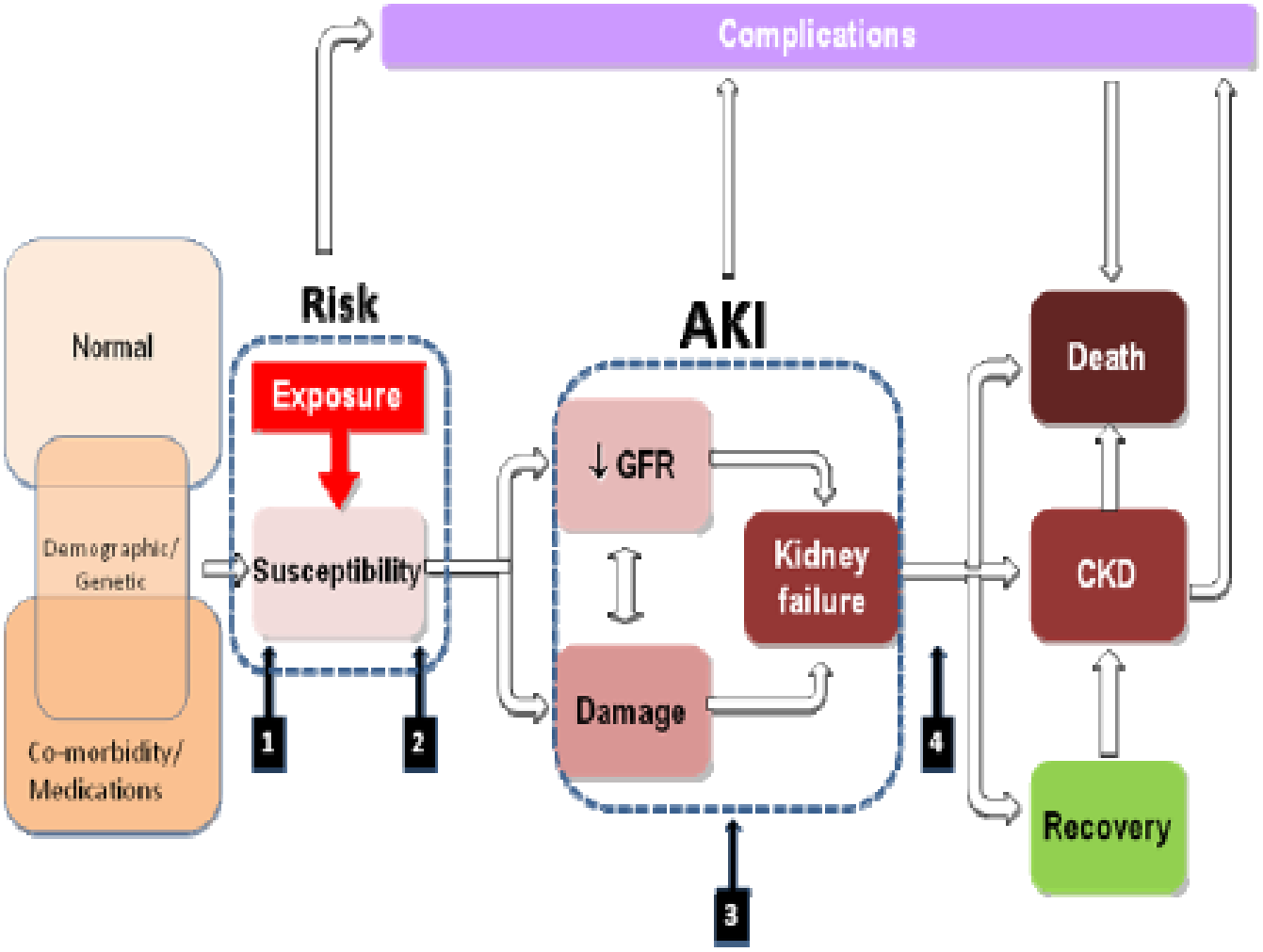


Figure 1: Suggested levels of risk assessment with relevance to AKI

KDIGO AKI Work Group: KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int, Suppl,* 2012;2(1):1-138

Biomarker-Guided Prevention of Cardiac Surgery-Associated AKI

Single-centre, RCT in **high risk** CPB patients

[TIMP2].[IGFBP7] ≥0.3 @ 4h post-CPB

Randomized: standard care vs KDIGO CT Surgery Bundle

Primary Endpoint: AKI ≤ 72h postop:

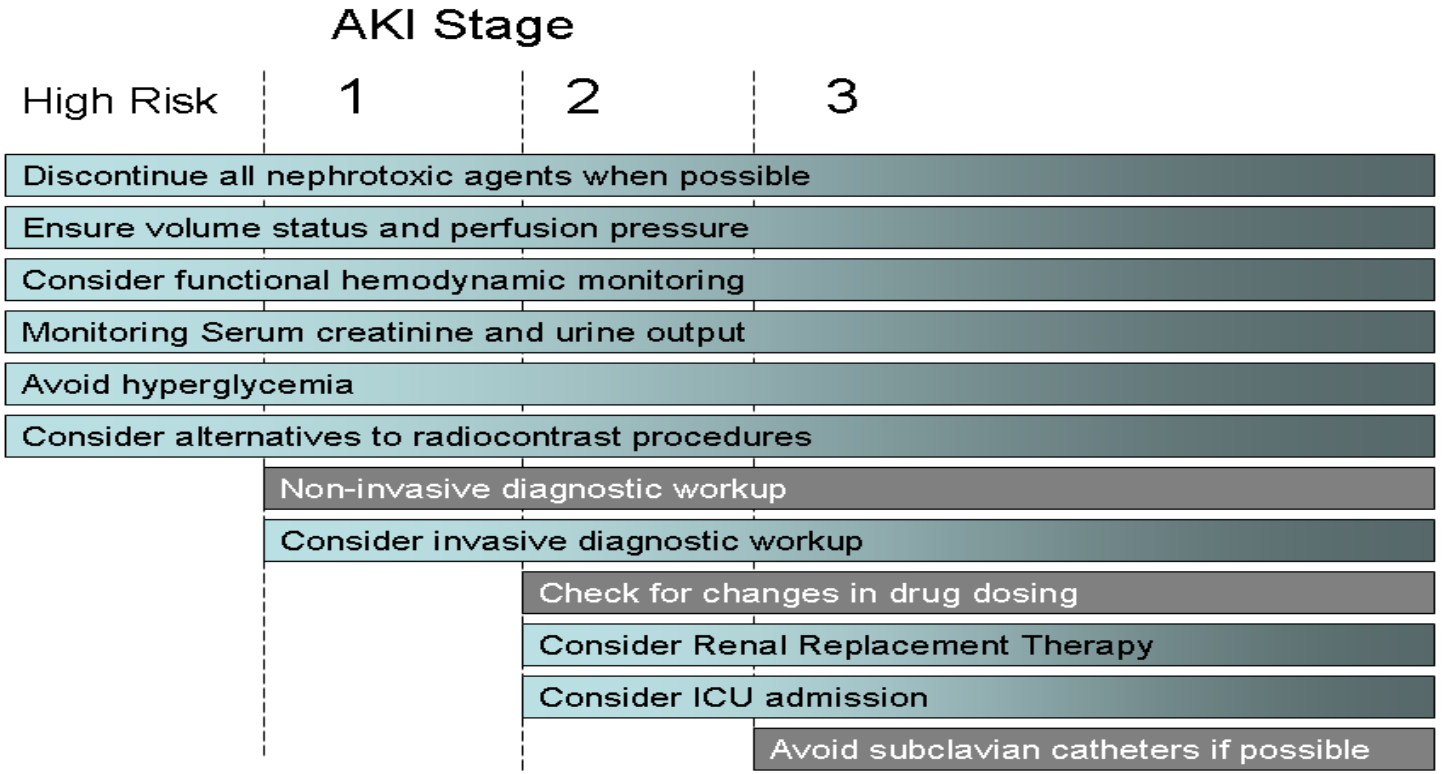
Control (99/138, 71.7%) vs. Intervention (76/138, 55.1%); p=0.004

Stage 2/3 AKI: Control (44.9%) vs. Intervention (29.7%); p=0.009

No difference in RRT, MAKE 30, 60, 90

Meersch M, et al: Intensive Care Med 2017; Jan 21 Epub

Stage-Based AKI Management



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KDIGO AKI Work Group: KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int, Suppl*, 2012;2(1):1-138

Remote Ischemic Pre-conditioning

Short-Term Outcomes

	Control (n=120)	RIPC (n=120)	P value
AKI (72h) %	52.5	37.5	0.02
Stage 1	26.7	25	
Stage 2	11.7	6.7	
Stage 3	14.2	5.8	
RRT	15.8	5.8	

Zarbock A, et al: JAMA 2015;313(21):2133-41

Medium-Term Outcomes

	Control (N=120)	RIPC (n=120)	P value
MAKE (90d) %	20	14.2	0.034
AKI non-recovery (90d) %	23.2	5.3	0.02

Zarbock A, et al: Anesthesiology 2017;126:787-798

RIPC for Cardiac Surgery: Negative Trials & Meta-analysis

	Control (n=772)	RIPC (n=749)	P value
AKI (??h) %	38	38.3	0.98
Stage 1	29.3	30.7	
Stage 2	5.7	5.1	
Stage 3	3	2.5	
RRT	x	Y	

Hausenloy DJ, et al: NEJM 2015;373:1408-1417

	Control (N=693)	RIPC (n=692)	P value
Stage 2/3 AKI (xd) %	5.1	6.1	0.45
RRT (xd) %	x	y	z

Meybohm, et al: NEJM 2015;373:1397-1407

Meta-analysis: RIPC for renoprotection (RR; 95% CI)

AKI (AKIN): 0.76; 0.57-1.00
AKI (RIFLE): 0.91; 0.75-1.12
RRT: 0.85; 0.37-1.94

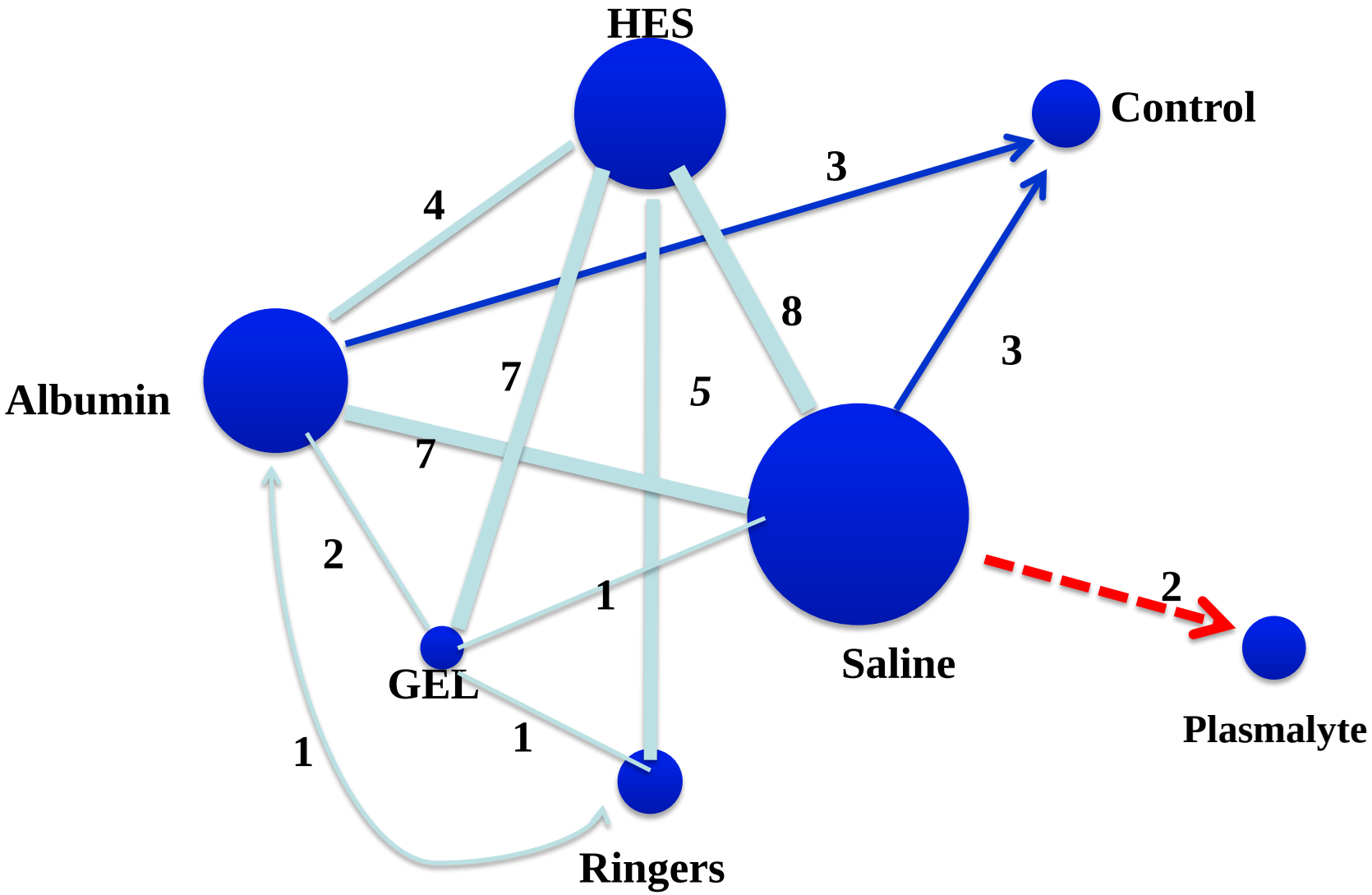
Menting TP, et al: Cochrane Database;2017:1-119

“Adverse Effects”of IV Fluids

Type	AKI	RRT	Coag	ICP	HA	Mort.
HES	●	●	●			●
Alb				●		●
NS	●	●			●	●
BSS						

Raghunathan K, et al; Br. J. Anaesth. 2014;113(5):772-83

Network of Fluid Studies in Critical Care



Raghunathan K, et al; Br. J. Anaesth. 2014;113(5):772-83

Conclusions of Network Meta-Analysis

- No signal of overall superiority of crystalloid vs. colloid
  - No specific type of fluid was clearly superior
- RRT: greatest risk of RRT with a HES, least risk with BSS, and albumin and saline both have similar risk
  - Crystalloid observational trials: more RRT with saline than Plasma-Lyte® (RR 1.6 (95% CI 1.15 to 2.21)
- Mortality in Severe Sepsis: Crystalloids vs. Colloids
  - Sensitivity analysis incl. subgroups from CHEST, SAFE, CRISTAL:
  - No difference in mortality (RR 1.0, 95% CI 0.91-1.1)
    - Limited to trials assessing only HES: still no difference in mortality (RR 0.96, 95% CI 0.86-1.08)

Raghunathan K, et al; Br. J. Anaesth. 2014;113(5):772-83

SPLIT (Saline vs. Plasma-Lyte for ICU Fluid Therapy) Trial: Buffered Crystalloid Solution vs Normal Saline in ICU

- Blinded double-crossover RCT in critically ill patients: BSS (n=1152) vs. 0.9% saline (n=1110)
- AKI (RIFLE): 9.6% vs. 9.2%, p=0.77
- RRT: 3.3% vs. 3.4%, p=0.91
- Mortality: 7.6% vs. 8.6%, p=0.4

Young P, et al, for the SPLIT Investigators & ANZICS CTG, JAMA 2015;314(16):1701-10

Based on Current Evidence…

- There is NO clear evidence of benefit for colloid over crystalloid
- Short-term physiological benefits of colloids may not translate into longer term patient-centered outcomes
- There is RCT evidence of harm for HES in critically ill patients and in severe sepsis
- There is some evidence of benefit for albumin in sepsis
- There is evidence of harm for albumin in TBI
- There are observational data that suggest that hyperchloremia from saline administration may cause harm

AKI in Sepsis: Effects of EGDT

	Mortality 90d n/N (%)		RRT Incidence n/N (%)		RRT Duration Days	Median (IQR)
	Usual	**EGDT**	**Usual**	**EGDT**	**Usual**	**EGDT**
ProCESS	139/412 (33.7%)	129/405 (31.9%)	11/397 (2.8%)	12/382 (3.1%)	8.3±13.7	7.1±10.8
		P=0.66		P=NS	(Mean±SD)	P=0.92
ARISE	150/796 (18.8%)	147/792 (18.6%)	108/798 (13.5%)	106/793 (13.4%)	85.9 (29.3-182.9)	57.8 (25.3-175)
		P=0.9		P=0.94		P=0.4
ProMISE	181/620 (29.2%)	184/623 (29.5%)	81/614 (13.2%)	88/620 (14.2%)	N/A	N/A
		P=0.9		P=0.62		
PL Meta-analysis	475/1871 (25.4%)	462/1852 (24.9%)	198/1874 (10.6%)	204/1852 (11%)	4 (2-7) * RRT grp	3 (2-7) *RRT grp
		P=0.68		P=0.91		P=0.68

Rowan KM, et al, for PRISM Investigators: NEJM 2017;376(23):2223-33

Take-Home Message

Recent Developments in AKI Prevention Literature.....

- Cardiac Surgery:
  - RIPC ineffective
  - BM-guided, protocolised care may be beneficial (requires validation)
- Fluids:
  - Harm in subsets: HES (sepsis), Albumin (TBI); Buffered Crystalloid Solution benefit unproven
- Sepsis: EGDT does not prevent AKI, RRT

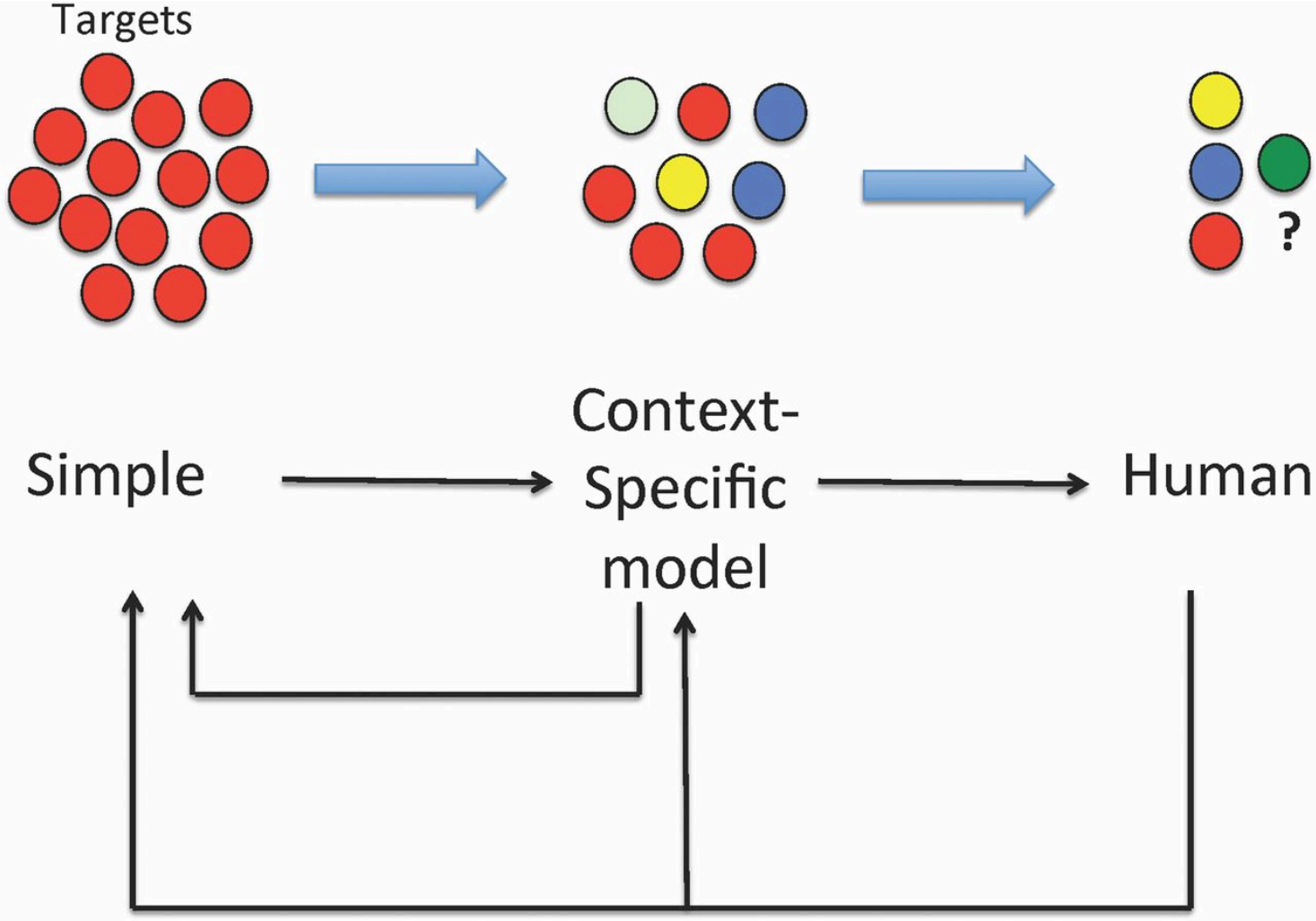
AKI Therapy

State of the Art

No drug has been developed and approved for the prevention or therapy of AKI

- Experimental models may be unrepresentative of clinical AKI
  - Patient comorbities (chronic diseases; multiple acute insults)
    - Solution: greater model complexity
  - Delayed therapy in clinical trials
    - Solution: biomarker-guided trials

Development & Translation of Experimental Models of AKI



Anupam Agarwal et al. JASN 2016;27:1288-1299

www.ADQI.org

Hepatorenal Syndrome Type 1 Rx: ADQI, 2012

- **<u>Fluid Challenge:</u>**
- Optimally Albumin-
  - Initial challenge: 1g/kg/day for 2 days, up to max. 100g/day
  - Followed by: 20-40g/day
- **<u>In Combination with a Vasoconstrictor:</u>**
- Preferably Terlipressin-
  - 0.5-2mg IV q.6h; titrated to SCr and SEs; ≤12mg/d, ≤14d
- Alternatives-
  - Noradrenaline; Vasopressin; Midodrine & Octreotide

Nadim MK, et al; Crit Care 2012;16(1):R23

REVERSE Trial

- Multicentre, randomized, double-blind, placebo-controlled, Phase III trial (CT.gov: NCT01143246)
- Adults with cirrhosis and ascites, and HRS-1 (defined as SCr ≥2.5mg/dl & actual or projected doubling of SCr within 2 weeks)
- Without improvement with 48h diuretic withdrawal, and albumin challenge (1g/kg/d)
- RCT: Terlipressin (1mg IV q.6h) vs. Placebo
- Albumin (20-40g/day) continued in both groups
- Rx for 14d or CHRSR, RRT, Transplant, or Non-Response by Day 4

Boyer TD, et al: Gastroenterology 2016;150:1579-89

REVERSE Trial Results

- 196 enrolled: 97 terlipressin, 99 placebo; 65 NAm. sites
- Similar baseline demographics
- Primary Endpoint: CHRSR- Confirmed HRS Reversal- 2 SCr values ≤1.5mg/dl, ≥48 h apart, on Rx, without RRT or liver transplant
  - Terlipressin (19/97, 19.6%) vs. Placebo (13/99, 13.1%), p=0.22
- Secondary endpoints:
  - HRS Reversal: T (23.7%) vs. P (15.2%), p=0.13
  - ΔSCr baseline to end Rx: T (-1.1) vs. P (-0.6) mg/dl, p=0.001
  - No difference in overall or transplant-free survival, or overall AEs (but more ischemic AEs in terlipressin group)

Boyer TD, et al: Gastroenterology 2016;150:1579-89

Earlier Trial of Terlipressin Trials in HRS-1

- 112 subject RCT (2008)
- Similar baseline demographics
- Primary Endpoint: CHRSR- Confirmed HRS Reversal- 2 SCr values ≤1.5mg/dl, ≥48 h apart, on Rx, without RRT or liver transplant in ≤14 days
  - Terlipressin (14/56, 25%) vs. Placebo (7/56, 12.5%), p=0.093
- Secondary endpoints:
  - HRS Reversal: T (33.9%) vs. P (12.5%), p=0.08
  - ΔSCr baseline to day 14: T (-0.7) vs. P (0) mg/dl, p=0.009
  - No difference in overall or transplant-free survival, or overall AEs (but 1 non-fatal MI in terlipressin group)

Sanyal AJ, et al: Gastroenterology 2008;134(5):1360-68

Pooled Analysis of Terlipressin Trials in HRS-1

- 308 subjects (T 153; P 155)
- Similar baseline demographics
- Primary Endpoint: HRS reversal (SCr <133 micromol/L on treatment)
  - Terlipressin (42/153, 27%) vs. Placebo (22/155, 14%), p=0.004
- Secondary endpoints:
  - Mean between-group differences in SCr (-53 micromol/L, p<0.0001) and eGFR (14 ml/min, p<0.0001) reflecting better renal function in Terlipressin group
  - Proportion alive with HRS reversal at day 90:
    - T: 32/142 (76%) vs. P: 12/22 (55%), p=0.094
  - No difference in overall or transplant-free survival, AEs

Sanyal AJ, et al: Alimentary Pharmacology & Therapeutics 2017;45:1390-1402

Take-Home Message

There is a lack of clinical evidence that pharmacotherapy of AKI is effective

- Diagnostic and experimental methods are evolving
- Mounting evidence supports use of vasconstrictor therapy for HRS-1
  - .....a form of functional AKI

Renal Replacement Therapy (RRT)

Indications for RRT: "State of the Art"

- Uraemia
  - Encephalopathy
  - Pericarditis
  - Bleeding diathesis
- Volume Overload
- Hyperkalemia
- Metabolic Acidosis
- Severe hyperphosphatemia
- Intoxications

- Prevention of uremic complications
- Prevention of uncontrolled positive fluid balance
- "Non-renal" indications

RRT Initiation Studies in AKI

Study	Year	Design	# of pts	Early initiation criteria	Late initiation criteria	Recovery of renal function	Survival
Conger [4]	1975	RCT	18	BUN < 70 mg/dl or SCr < 5 mg/dl	BUN ≥ 150 mg/dl or SCr ≥ 10 mg/dl or clinical indication		Early 64% Late 20%
Gillum, et al. [5]	1986	RCT	34	Treatment goal BUN < 60 mg/dl and SCr < 5 mg/dl	Treatment goal BUN < 100 mg/dl and SCr < 9 mg/dl		Early 41% Late 53%
Bouman, et al. [6]	2002	RCT	106	< 12 hrs after meeting definition for AKI requiring RRT	BUN > 112 mg/dl, K > 6.5 mmol/L or severe cardiogenic pulmonary edema		Early High-dose 74.3% Early Low-dose 68.6% Late Low-dose 75%
Gettings, et al. [7]	1999	Retrospective Observational	100	BUN < 60 mg/dl	BUN > 60 mg/dl	Early 100% Late 91.6%	Early 39% Late 20% ***
Demirkilic, et al. [8].	2004	Retrospective Observational	61	Urine output < 100 ml X 8 hours despite diuretic	SCr > 5 mg/dl or K > 5.5 meq/L		Early 76.5% Late 45.5% ***
Elahi, et al. [9]	2004	Retrospective Observational	64	Urine output 100 ml X 8 hours despite diuretic	Urea > 84 mg/dl or SCr > 3.39 mg/dl or K > 6 meq/L		Early 78% Late 57% ****
Wu, et al. [10]	2007	Retrospective Observational	80	BUN < 80 mg/dl	BUN > 80 mg/dl	Early 39.2% Late 12% ***	Early 37% Late 15.4% ***
Liu KD, et al. [11]	2006	Retrospective Observational	243	BUN ≤76mg/dl	BUN > 76 mg/dl		Early 65% Late 59%

Adapted from: Bagshaw S, et el: Crit Care 2016;20:245

RRT Initiation Studies in AKI: Update

Study	Year	Design	# of pts	Early initiation criteria	Late initiation criteria	Recovery of renal function	Mortality
Wald R, et al: STARRT-AKI/Pilot Trial	Kidney International, 2015	RCT, Canada (12 sites)	100	Two of: KDIGO Stage 2 by SCr or UOP, or PNGAL ≥400ng/ml; within 12 hours	Clinical criteria/emergent indications, > 12 hours	Early 100% Late 96%	Early 38% Late 37%
Zarbock A, et al: ELAIN Trial	JAMA, 2016	RCT, Germany (Single site)	231	KDIGO Stage 2 (within 8 hours)	KDIGO Stage 3 (within 12 hours)	Early 86.6% Late 84.9%	Early 39.3% Late 54.7%
Gaudry S, et al: AKIKI Trial	NEJM, 2016	RCT, France (31 sites)	620	KDIGO Stage 3 (within 6 hours)	Clinical criteria/emergent indications	Early 98% Late 95%	Early 48.5% Late 49.7%
Barbar SD, et al: IDEAL-ICU Trial	Trial in Progress	RCT, France (24 sites)	864	KDIGO Stage 3 (within 12 hours)	Clinical criteria (48-60 hours after eligibility, or emergent)	N/A	N/A
Wald R, et al: STARRT-AKI/Main Trial	Trial in Progress	RCT, International (>60 sites)	2866	KDIGO Stage 2 (within 12 hours)	Clinical criteria/emergent indications (>12 hours)	N/A	N/A

Adapted from: Bagshaw S, et el: Crit Care 2016;20:245

KDIGO CHAPTER 5.8: DOSE & PROTOCOLS FOR DIALYSIS

- **5.8.3: We recommend, in addition, delivering at least a Kt/V of 3.9/week when using intermittent or extended RRT in AKI. (*1A*)**
- **5.8.4: We recommend prescribing and achieving at least an effluent volume of 20 to 25 ml//kg/h for CRRT in AKI. (*1A*)**

KDIGO CHAPTER 5.8: DOSE & PROTOCOLS FOR DIALYSIS

- **5.8.5: In defining prescription and delivery consider other parameters to individualize treatment above standard minimum dose when special situations such as sepsis or hypercatabolic states are present. (*2C*)**
- **5.8.6: We suggest considering changing or combining RRT modalities in order to achieve the adequate RRT dose. (*2B*)**

RRT characteristics & AKI Recovery

Table 2 | **RRT characteristics that might affect recovery from AKI**

RRT characteristic	Effect on renal recovery	Effect on patient recovery
Modality (intermittent, prolonged intermittent, continuous, peritoneal)*	Intermittent RRT might delay recovery	No effect
Fluid purity and quality standards	Dialysate purity might affect recovery	No effect
Membrane type‡	Bioincompatible membranes might delay recovery	Bioincompatible membranes might affect recovery
Anticoagulation	No reported effect on recovery	Uncertain effect
Haemodynamic stability§	Hypotension might delay recovery	Uncertain effect
Mode of solute clearance (diffusion or convection)‖	No evidence of effect	No evidence of effect
Ultrafiltration rate	Rapid fluid removal might delay recovery by causing hypotension	No data
Fluid Balance¶	A positive fluid balance during RRT might delay recovery	A positive fluid balance during RRT might delay recovery
Dialysate temperature	A cooler dialysate temperature might minimize hypotension and promote recovery	No data
Dialysate composition	Higher dialysate sodium concentrations might minimize hypotension and thereby promote recovery	No data
Effect of RRT on other care parameters	RRT might affect drug dosing, nutritional support and nephrotoxin accumulation, which might affect recovery	RRT might affect drug dosing, nutritional support and nephrotoxin accumulation, which might affect recovery
RRT components (for example, access, circuit, fluid composition)	Possible adverse effect	Unknown
Dose/intensity (that is, small solute, clearance)#	Level 1 evidence that intensity of solute control does not affect recovery	Level 1 evidence that intensity of solute control does not affect recovery

*Only association studies; one randomized controlled trial (RCT). ‡Bioincompatible membranes are no longer in use. §Based on association. ‖Small underpowered RCTs. ¶Independent association. #No effect of small solute control in two large RCTs. AKI, acute kidney injury; RRT, renal replacement therapy

Chawla LS, et al for ADQI 16 group: Nat Rev Nephrol 2017; Epub doi:10.1038/nrneph.2017.2

Take-Home Message

Unlike Dose and Modality guidelines, RRT initiation criteria in AKI are not evidence-based.....

- Results of early vs. late initiation RCTs are conflicting
- Additional RCTs are ongoing

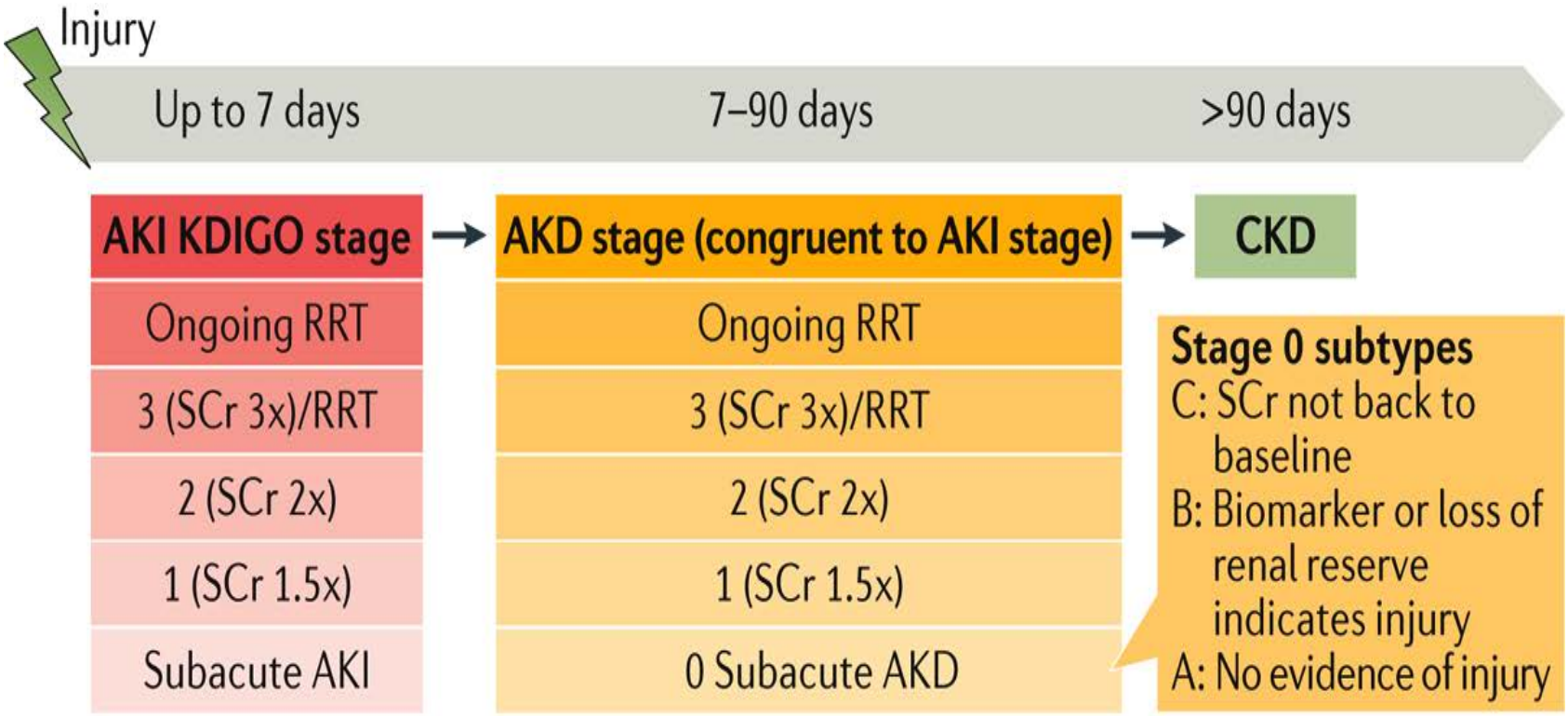
AKI Recovery

CHAPTER 2.3: EVALUATION AND GENERAL MANAGEMENT OF PATIENTS WITH AND AT RISK FOR AKI

- **2.3.4: Evaluate patients 3 months after AKI for resolution, new onset, or worsening of pre-existing CKD. (*Not Graded*)**
  - **If patients have CKD, manage these patients as detailed in the KDOQI CKD Guideline (Guidelines 7-15). (*Not Graded*)**
  - **If patients do not have CKD, consider them to be at increased risk for CKD and care for them as detailed in the KDOQI CKD Guideline 3 for patients at increased risk for CKD. (*Not Graded*)**

KDIGO AKI Work Group: KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int, Suppl,* 2012;2(1):1-138

Acute Kidney Disease (AKD): Next Evolution of AKI and CKD Classification?



Chawla LS, et al for ADQI 16 group: Nat Rev Nephrol 2017; Epub doi:10.1038/nrneph.2017.2

Recommendations for Staging of AKD staging

Table 1 | **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

*Reflects that even when no apparent residual injury is present, the kidney might be vulnerable for some time after an episode of AKI. ‡Assumes the baseline serum creatinine level is <353.6 µmol/l (<4.0 mg/dl), and that an episode of AKI has occurred. AKD, acute kidney disease; AKI, acute kidney injury.

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