Nephro Update Europe 2019
20 – 21 September, Prague

Acute Kidney Injury

Patrick Murray, Ireland

AKI Diagnosis & Staging

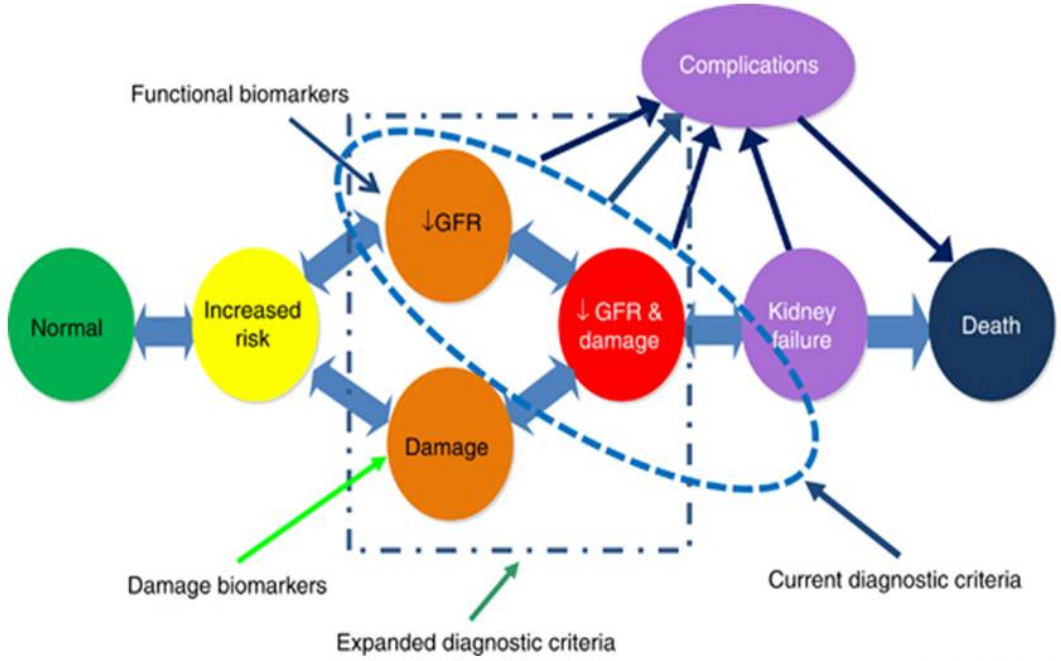
AKI Guidelines: Current Status of Criteria for Diagnosis & Staging

- *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: Kidney Int 2014;85:513-521

The New Spectrum of AKI Diagnostics

	NO STRUCTURAL DAMAGE	STRUCTURAL DAMAGE NGAL, KIM-1, IL18, Others
NO FUNCTIONAL CHANGE	No functional or structural changes	Structural changes without loss of function
FUNCTIONAL CHANGE SCr, CysC, BUN, UO	Loss of function without structural damage	Structural changes with loss of function

www.ADQI.org

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

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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

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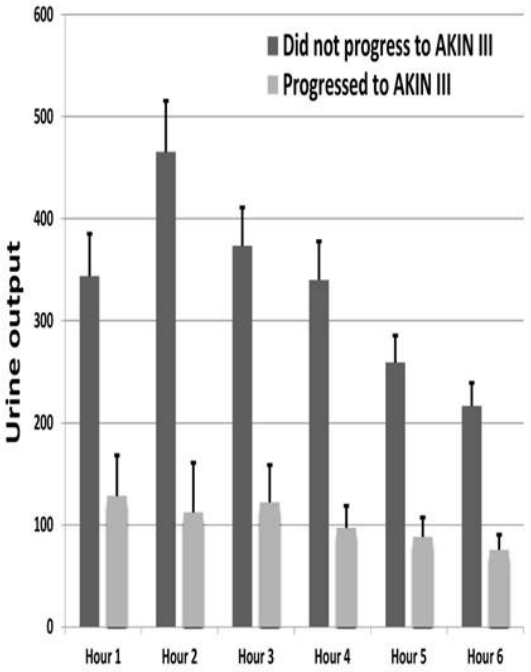
Multicentre FST Trial

- 5-centre study of 92 ICU patients with AKI I/II
- 23 patients progressed to stage III AKI and had significantly lower UOP (p<0.0001)
- UOP during the first 2 h most predictive of progression to stage III AKI (AUC=0.87)
- Ideal cut-off <200ml; sensitivity of 74%, specificity of 90%
- Conclusion: In ICU patients without severe CKD with mild AKI, a UOP of less than 200ml in the first 2 h after an FST is predictive of progression to stage III AKI



Rewa OG, et al: Journal of Critical Care 52 (2019) 109–114

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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

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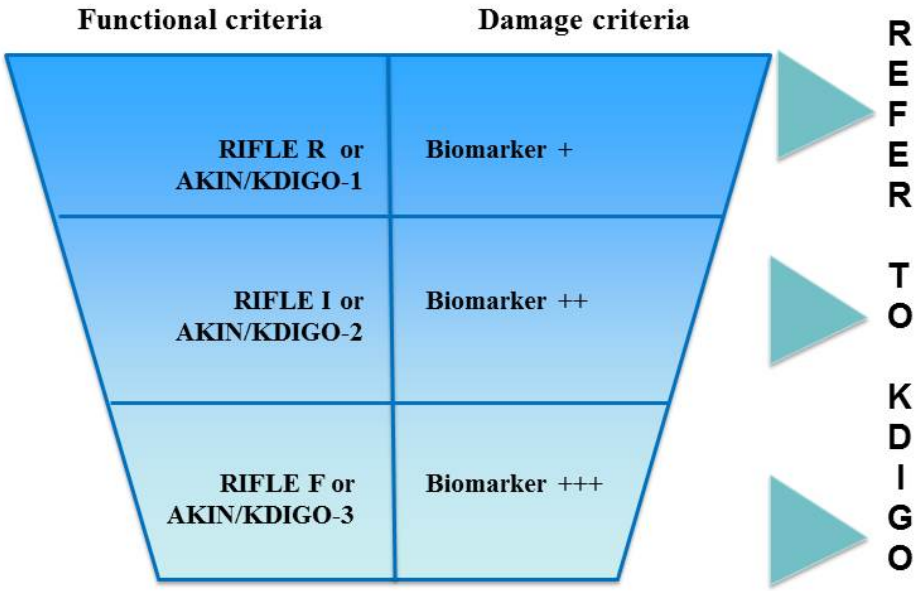
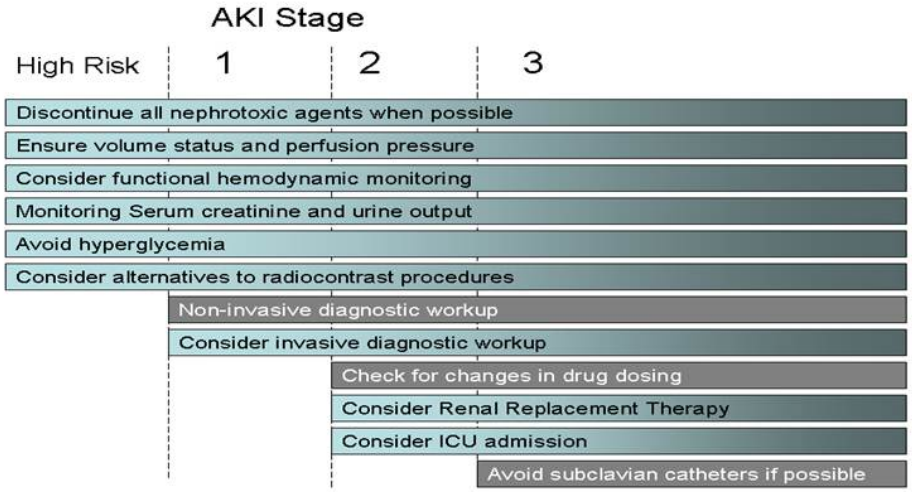
The New Spectrum of AKI Diagnostics



www.ADQI.org

Nephro Update Europe 2019 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

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Take-Home Messages

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 and management of AKI
- Combination of functional and damage biomarkers, implementation research required

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AKI Prevention & Therapy

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KDIGO Conceptual Framework for AKI Risk

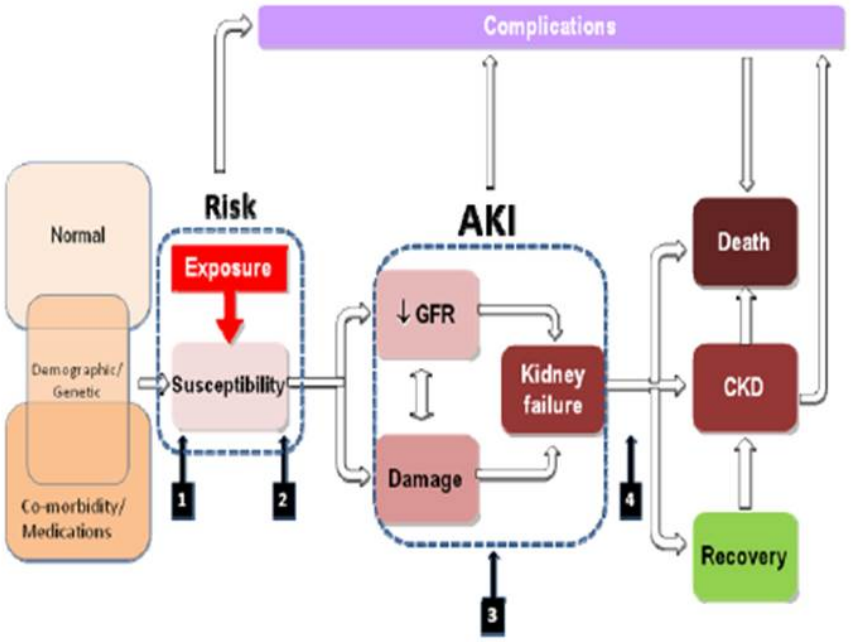

Figure 1: Suggested levels of risk assessment with relevance to AKI

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

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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) (hr)	57.8 (25.3-175) (hr)
		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

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Surviving Sepsis Campaign Guidelines

Initial Resuscitation Recommendations:

- IV antibiotics within 1hour of sepsis recognition
- IV crystalloid ≥ 30ml/kg within 1st three hours
  - Then fluids guided by dynamic re-assessment
- Initial MAP target of 65mmHg in patients with septic shock requiring vasopressors
  - Asfar P,et al; N Engl J Med 2014;370:1583-93

Rhodes A, et al: Intensive Care Med (2017) 43:304–377

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Perioperative Fluid Management: Liberal vs. Restrictive - Primary & Secondary Outcomes

Table 3. Primary and Secondary Outcomes.*

Outcome	Restrictive Fluid (N=1490)	Liberal Fluid (N=1493)	Hazard or Risk Ratio (95% CI)†	P Value
Primary outcome				
Disability-free survival at 1 yr — no. (%)‡	1223 (81.9)	1232 (82.3)	1.05 (0.88–1.24)	0.61
Death or persistent disability — no.	267	261		
Death	95	96		
Persistent disability	172	165		
Secondary outcomes§				
Composite septic outcome or death — no./total no. (%)¶	323/1481 (21.8)	295/1487 (19.8)	1.10 (0.96–1.27)	0.19
Surgical-site infection — no./total no. (%)	245/1481 (16.5)	202/1487 (13.6)	1.22 (1.03–1.45)	0.02‖
Sepsis — no./total no. (%)	157/1481 (10.6)	129/1487 (8.7)	1.22 (0.98–1.52)	0.08
Anastomotic leak — no./total no. (%)	49/1481 (3.3)	35/1487 (2.4)	1.41 (0.92–2.16)	0.12
Pneumonia — no./total no. (%)	54/1481 (3.6)	57/1487 (3.8)	0.95 (0.66–1.37)	0.79
Acute kidney injury — no./total no. (%)**	124/1443 (8.6)	72/1439 (5.0)	1.71 (1.29–2.27)	<0.001
Renal-replacement therapy — no./total no. (%)	13/1460 (0.9)	4/1462 (0.3)	3.27 (1.01–13.8)	0.048‖
Pulmonary edema — no./total no. (%)	20/1481 (1.4)	32/1487 (2.2)	0.63 (0.36–1.09)	0.10
Unplanned admission to ICU — no./total no. (%)	161/1487 (10.8)	145/1491 (9.7)	1.11 (0.90–1.38)	0.32
Median peak serum lactate level (IQR) — mmol per liter††	1.6 (1.1–2.5)	1.6 (1.1–2.4)	NA	NA
Median C-reactive protein level on day 3 (IQR) — mg per liter‡‡	136 (82–198)	133 (80–200)	NA	0.66
Median duration of mechanical ventilation (IQR) — hr§§	17 (5–65)	14 (3–31)	NA	0.07
Median score on quality-of-recovery scale (IQR)¶¶	106 (89–121)	107 (90–122)	NA	0.31
Median duration of stay in HDU or ICU (IQR) — days‖	1.8 (1.0–3.1)	1.4 (0.9–2.9)	NA	0.13
Median duration of hospital stay (IQR) — days	6.4 (3.6–10.6)	5.6 (3.6–10.5)	NA	0.26
Death — no. (%)‡				
At 90 days	31 (2.1)	18 (1.2)	1.73 (0.97–3.10)	0.06
At 12 mo	95 (6.5)	96 (6.6)	1.03 (0.78–1.36)	0.86

* NA denotes not applicable.
† The hazard ratio or risk ratio is for the restrictive fluid group as compared with the liberal fluid group.
‡ Percentages in this category were estimated with the use of the Kaplan–Meier method. Among the patients who died, 9 in the restrictive fluid group and 12 in the liberal fluid group had persistent disability before death at 12 months. The risks of death at 90 days and at 12 months are listed in the table as predefined secondary outcomes.
§ All the secondary outcomes were assessed up to 30 days after surgery, with the exception of renal-replacement therapy and the duration of mechanical ventilation, which were assessed at 90 days.
¶ The composite septic outcome includes surgical-site infection, anastomotic leak, pneumonia, and sepsis.
‖ The P value was not significant after adjustment for multiple comparisons, with a threshold level of P=0.004 for renal-replacement therapy and P=0.003 for surgical-site infection.
** Values for acute kidney injury are the average number of events across 10 imputations in which fluid balance was imputed after adjustment for serum creatinine values on day 1 and day 3. Details regarding these analyses and sensitivity analyses are provided in the Supplementary Appendix.
†† Data regarding the peak serum lactate level were missing for 1057 patients in the restrictive fluid group and in 1086 in the liberal fluid group; the P value was not calculated.
‡‡ Data regarding the C-reactive protein level were missing for 422 patients in the restrictive fluid group and 420 in the liberal fluid group.
§§ Data regarding mechanical ventilation are for 102 patients in the restrictive fluid group and 100 in the liberal fluid group.
¶¶ Data regarding the quality of recovery on day 3 were missing for 73 patients in the restrictive fluid group and 75 in the liberal fluid group. The scores on this scale range from 0 (extremely poor) to 150 (excellent).
‖ Data regarding the duration of stay in the HDU or ICU data are for 483 patients in the restrictive fluid group and 473 in the liberal fluid group who were admitted at any time postoperatively.

PS Myles et al. N Engl J Med 2018;378:2263-2274

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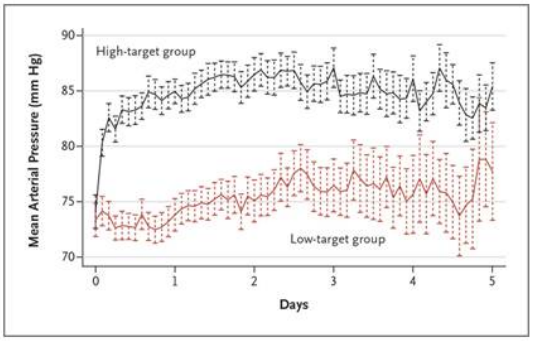
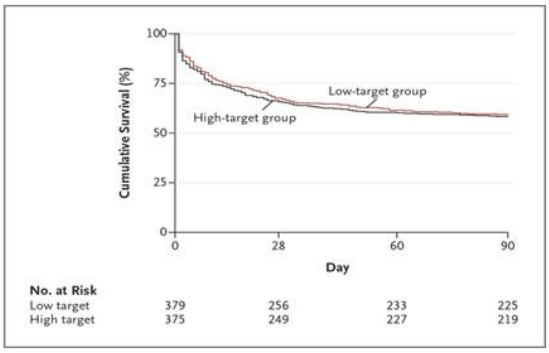
MAP Target in Septic Shock

Table 2. Clinical Results, Primary and Secondary Outcomes, and Serious Adverse Events.

Variable	Low-Target Group (N=388)	High-Target Group (N=388)	P Value
Cumulative fluid intake from day 1 to day 5 — liters	10.0 (5.8–14.0)	10.5 (5.5–14.0)	0.89
Cumulative urine output from day 1 to day 5 — liters	6.7 (2.9–10.7)	6.9 (2.4–10.7)	0.87
Cumulative fluid balance from day 1 to day 5 — liters	2.8 (0.0–6.2)	2.4 (0.0–6.0)	0.74
Median dose of norepinephrine (IQR) — μg/kg/min			
Day 1	0.45 (0.17–1.21)	0.58 (0.26–1.80)	<0.001
Day 2	0.16 (0.03–0.48)	0.38 (0.14–0.90)	<0.001
Day 3	0.02 (0.00–0.16)	0.14 (0.01–0.50)	<0.001
Day 4	0.00 (0.00–0.05)	0.03 (0.00–0.22)	<0.001
Day 5	0.00 (0.00–0.03)	0.01 (0.00–0.15)	<0.001
Duration of catecholamine infusion — days	3.7±3.2	4.7±3.7	<0.001
Primary outcome: death at day 28 — no. (%)*	132 (34.0)	142 (36.6)	0.57
Secondary outcomes — no./total no. (%)			
Death at day 90†	164 (42.3)	170 (43.8)	0.74
Survival at day 28 without organ support‡	241 (62.1)	235 (60.6)	0.66
Doubling of plasma creatinine	161 (41.5)	150 (38.7)	0.42
No chronic hypertension	71/215 (33.0)	85/221 (38.5)	0.32
Chronic hypertension	90/173 (52.0)	65/167 (38.9)	0.02
Renal-replacement therapy from day 1 to day 7	139 (35.8)	130 (33.5)	0.50
No chronic hypertension	66/215 (30.7)	77/221 (34.8)	0.36
Chronic hypertension	73/173 (42.2)	53/167 (31.7)	0.046
Serious adverse events — no. (%)			
Any	69 (17.8)	74 (19.1)	0.64
Acute myocardial infarction§	2 (0.5)	7 (1.8)	0.18
Atrial fibrillation	11 (2.8)	26 (6.7)	0.02
Ventricular fibrillation or tachycardia	15 (3.9)	22 (5.7)	0.24
Digital ischemia	9 (2.3)	10 (2.6)	0.82
Mesenteric ischemia	9 (2.3)	9 (2.3)	1.00
Bleeding	42 (10.8)	31 (8.0)	0.22

* The hazard ratio for death at 28 days was 1.07 (95% confidence interval [CI], 0.84 to 1.38) in the high-target group, as compared with the low-target group.
† The hazard ratio for death at 90 days was 1.04 (95% CI, 0.83 to 1.30) in the high-target group, as compared with the low-target group.
‡ Organ support refers to the use of vasopressors, mechanical ventilation, or renal-replacement therapy.
§ Acute myocardial infarction was defined as typical electrocardiographic changes, with a concomitant increase in troponin, and segmental echocardiographic hypokinesia or akinesia, with the infarction confirmed, when possible, by means of coronary angiography.





Asfar P, et al: N Engl J Med 2014;370:1583-93

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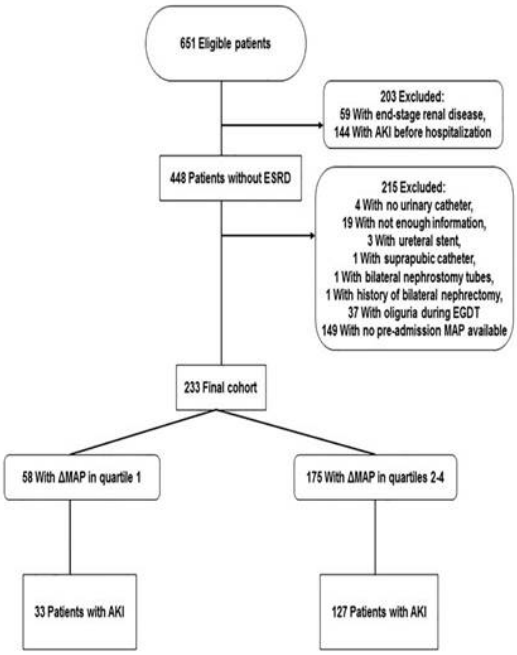
Individualised MAP Targets in Septic Shock?

- Single-centre, retrospective septic shock cohort (n=233)
- Lowest ΔMAP quartile (−24.5 to 3.9 mmHg):
  - No demographic differences compared with the rest of the cohort
  - Odds ratio for AKI was 0.26 (95% CI 0.11–0.57) after adjustment for other known AKI risk factors
- In subset with history of hypertension, the lowest quartile had adjusted OR 0.12 (95% CI 0.04–0.37) for AKI
- Conclusion: incidence of AKI was lowest among those whose post-resuscitation MAP was closest to or higher than their pre-admission MAP



Moman RN, et al: Ann. Intensive Care (2018) 8:124

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SMART Trial: Balanced Crystalloids vs. Saline in ICU

Table 2. Clinical Outcomes.*

Outcome	Balanced Crystalloids (N = 7942)	Saline (N = 7860)	Adjusted Odds Ratio (95% CI)†	P Value†
Primary outcome				
Major adverse kidney event within 30 days — no. (%)‡	1139 (14.3)	1211 (15.4)	0.90 (0.82 to 0.99)	0.04
Components of primary outcome				
In-hospital death before 30 days — no. (%)	818 (10.3)	875 (11.1)	0.90 (0.80 to 1.01)	0.06
Receipt of new renal-replacement therapy — no./total no. (%)§	189/7558 (2.5)	220/7458 (2.9)	0.84 (0.68 to 1.02)	0.08
Among survivors	106/6787 (1.6)	117/6657 (1.8)		
Final creatinine level ≥200% of baseline — no./total no. (%)§	487/7558 (6.4)	494/7458 (6.6)	0.96 (0.84 to 1.11)	0.60
Among survivors	259/6787 (3.8)	273/6657 (4.1)		
Among survivors without new renal-replacement therapy	215/6681 (3.2)	219/6540 (3.3)		
Secondary outcomes				
In-hospital death — no. (%)				
Before ICU discharge	528 (6.6)	572 (7.3)	0.89 (0.78 to 1.02)	0.08
Before 60 days	928 (11.7)	975 (12.4)	0.92 (0.83 to 1.02)	0.13
ICU-free days¶				0.94
Median	25.3	25.3	1.00 (0.89 to 1.13)	
Interquartile range	22.1 to 26.6	22.2 to 26.6		
Mean	21.8±8.3	21.7±8.6		
Ventilator-free days¶			1.06 (0.97 to 1.16)	0.22
Median	28.0	28.0		
Interquartile range	26.0 to 28.0	26.0 to 28.0		
Mean	24.2±8.6	23.9±8.9		
Vasopressor-free days¶			1.05 (0.97 to 1.14)	0.26
Median	28.0	28.0		
Interquartile range	27.0 to 28.0	27.0 to 28.0		
Mean	24.7±8.5	24.4±8.8		
Renal-replacement therapy–free days¶			1.11 (1.02 to 1.20)	0.01
Median	28.0	28.0		
Interquartile range	28.0 to 28.0	28.0 to 28.0		
Mean	25.0±8.6	24.8±8.9		
Secondary renal outcomes‖				
Stage 2 or higher AKI developing after enrollment — no./total no. (%)‖	807/7558 (10.7)	858/7458 (11.5)	0.91 (0.82 to 1.01)	0.09
Creatinine — mg/dl**				
Highest before discharge or day 30			1.01 (0.97 to 1.05)	0.58
Median	0.99	0.99		
Interquartile range	0.78 to 1.53	0.78 to 1.52		
Change from baseline to highest value			0.98 (0.94 to 1.02)	0.35
Median	0.04	0.04		
Interquartile range	−0.08 to 0.31	−0.08 to 0.32		
Final value before discharge or 30 days			1.02 (0.97 to 1.06)	0.51
Median	0.83	0.83		
Interquartile range	0.70 to 1.11	0.70 to 1.11		

* Plus–minus values are means ±SD. To convert the values for creatinine to micromoles per liter, multiply by 88.4. ICU denotes intensive care unit.

† Categorical outcomes were compared with a generalized, linear, mixed-effects model, with adjustment for the ICU to which the patient was admitted as a random effect and prespecified covariates as fixed effects.[11] Continuous outcomes were compared between groups with a proportional-odds model, with adjustment for the same variables.

‡ A major adverse kidney event within 30 days is the composite of death, receipt of new renal-replacement therapy, or final creatinine level that was at least 200% of the baseline level, with all events censored at hospital discharge or at 30 days after admission to the ICU, whichever occurred first. The effect of study group on major adverse kidney events within 30 days is the conditional effect. The marginal effect yielded an odds ratio of 0.91 and a 95% confidence interval of 0.84 to 0.99.

§ Data on receipt of new renal-replacement therapy, final creatinine level that was at least 200% of the baseline level, and secondary renal outcomes are provided for the 13,016 patients not known to have received renal-replacement therapy before ICU admission.

¶ ICU-free, ventilator-free, vasopressor-free, and renal-replacement-therapy–free days refer to the number of days on which a patient was alive and free from the specified therapy in the first 28 days after enrollment. Odds ratios of higher than 1.0 indicate a better outcome (i.e., more days alive and free from the specified therapy) with balanced crystalloids than with saline.

‖ The development of acute kidney injury (AKI) of stage 2 or higher after enrollment was defined in accordance with the Kidney Disease: Improving Global Outcomes plasma creatinine criteria[12] as any creatinine level between enrollment and discharge or 30 days that increased by at least 0.3 mg per deciliter (27 μmol per liter) from a preceding post-enrollment value and was at least 200% of the baseline value, at least 200% of a preceding post-enrollment value, or at least 4.0 mg per deciliter (350 μmol per liter) or as new receipt of renal-replacement therapy.

** Among patients who had not received previous renal-replacement therapy, the plasma creatinine level was measured a mean of 8.0 times between enrollment and the first of discharge or 30 days in each group; the plasma creatinine level was not measured between enrollment and the first of discharge or 30 days for 418 of 7558 patients (5.5%) in the balanced-crystalloids group and 443 of 7458 patients (5.9%) in the saline group.

MW Semler et al. N Engl J Med 2018;378:829-839

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SMART Trial: Balanced Crystalloids vs. Saline in Sepsis

- Secondary analysis of 1,641 patient subset with sepsis, from the SMART RCT
- Lower 30-day in-hospital mortality(26.3%) in balanced crystalloids group 26.3%, vs 31.2% in the saline group (adjOR, 0.74; 95% CI, 0.59 - 0.93; P = 0.01)
- Lower incidence of major adverse kidney events within 30 days (35.4% vs 40.1%; aOR 0.78; 95% CI 0.63 - 0.97) in balanced crystalloid group
- Greater number of renal replacement therapy-free days (20 ± 12 vs 19 ± 13; aOR 1.35 [1.08 - 1.69]), and vasopressor-free days (20 ± 12 vs 19 ± 13; aOR 1.25; 95% CI 1.02 - 1.54), in the balanced crystalloid group, compared to the saline group
- Conclusion: Among patients with sepsis in the SMART RCT, use of balanced crystalloids was associated with a lower 30-day in-hospital mortality and renal adverse events compared to use of saline

Brown RM, et al: Am J Respir Crit Care Med. 2019 Aug 27

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Types and Compositions of Resuscitation Fluids

Table 1. Types and Compositions of Resuscitation Fluids.*

Variable	Human Plasma	Colloids									Crystalloids		
		4% Albumin	Hydroxyethyl Starch						4% Succinylated Modified Fluid Gelatin	3.5% Urea-Linked Gelatin	0.9% Saline	Compounded Sodium Lactate	Balanced Salt Solution
			10% (200/0.5)	6% (450/0.7)	6% (130/0.4)		6% (130/0.42)						
Trade name		Albumex	Hemohes	Hextend	Voluven	Volulyte	Venofundin	Tetraspan	Gelofusine	Haemaccel	Normal saline	Hartmann's or Ringer's lactate	PlasmaLyte
Colloid source		Human donor	Potato starch	Maize starch	Maize starch	Maize starch	Potato starch	Potato starch	Bovine gelatin	Bovine gelatin			
Osmolarity (mOsm/liter)	291	250	308	304	308	286	308	296	274	301	308	280.6	294
Sodium (mmol/liter)	135–145	148	154	143	154	137	154	140	154	145	154	131	140
Potassium (mmol/liter)	4.5–5.0			3.0		4.0		4.0		5.1		5.4	5.0
Calcium (mmol/liter)	2.2–2.6			5.0				2.5		6.25		2.0	
Magnesium (mmol/liter)	0.8–1.0			0.9		1.5		1.0					3.0
Chloride (mmol/liter)	94–111	128	154	124	154	110	154	118	120	145	154	111	98
Acetate (mmol/liter)						34		24					27
Lactate (mmol/liter)	1–2			28								29	
Malate (mmol/liter)								5					
Gluconate (mmol/liter)													23
Bicarbonate (mmol/liter)	23–27												
Octanoate (mmol/liter)		6.4											

* To convert the values for potassium to milligrams per deciliter, divide by 0.2558. To convert the values for calcium to milligrams per deciliter, divide by 0.250. To convert the values for magnesium to milligrams per deciliter, divide by 0.4114.

Myburgh JA, Mythen MG. N Engl J Med 2013;369:1243-1251

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KDIGO Conceptual Framework for AKI Risk

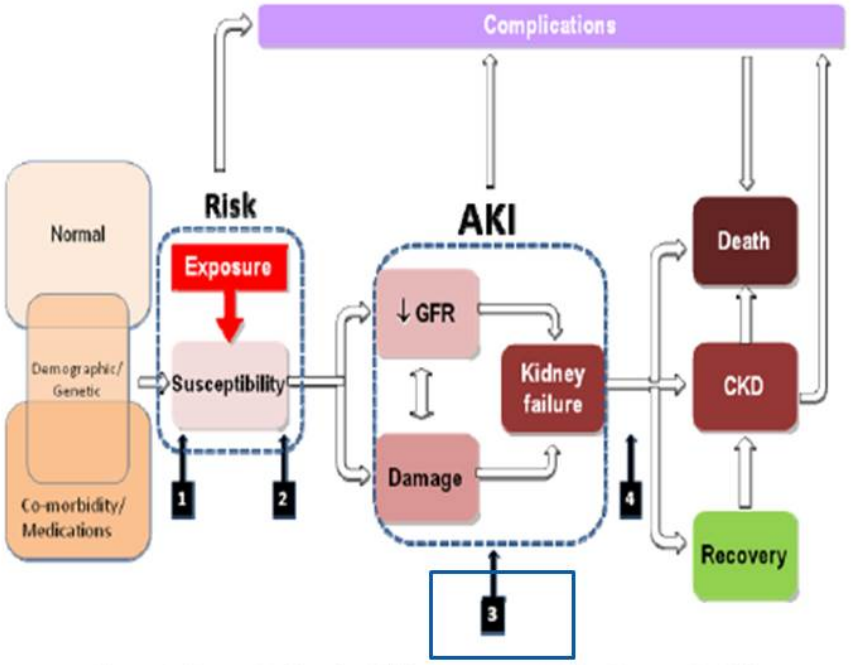

Figure 1: Suggested levels of risk assessment with relevance to AKI

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

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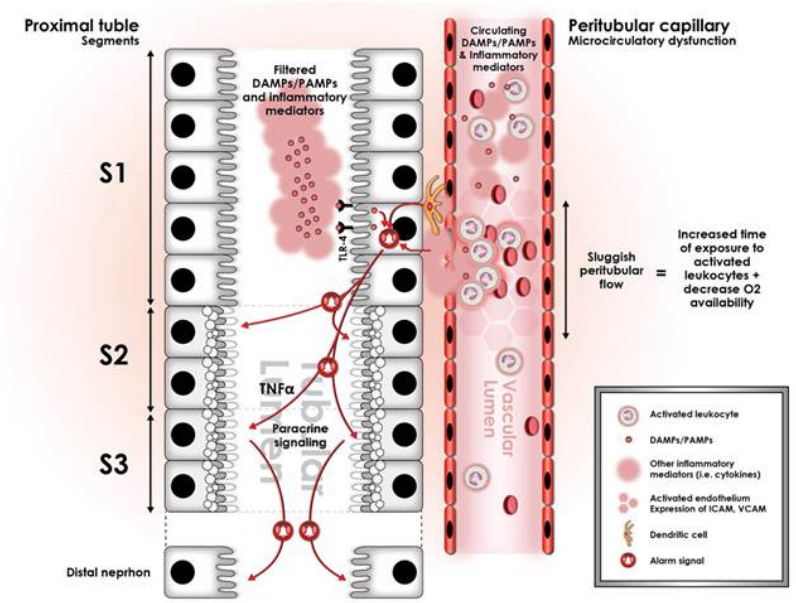
Pathogenesis of Septic AKI



Powell JT, et al: Clin Transplant 2013;27: 484–491

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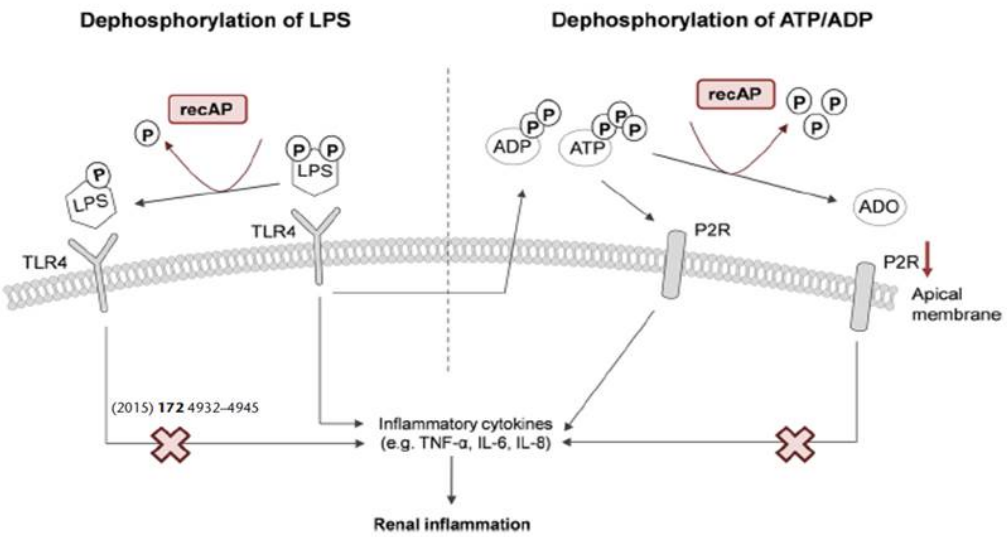
Protective Effects of Alkaline Phosphatase



Peters E, et al: Br J Pharmacol 2015;172:4932-4945

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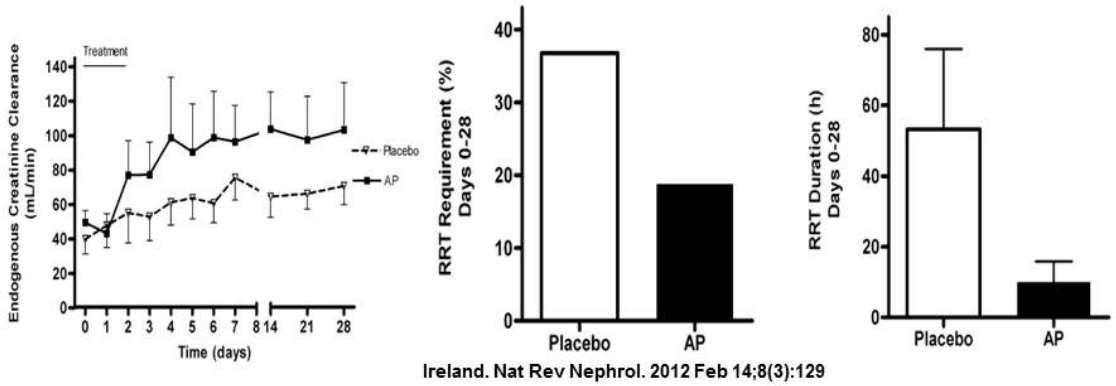
Stop-Aki

2 small Phase-II Studies – bovine AP

Alkaline phosphatase treatment improves renal function in severe sepsis or septic shock patients

Acute kidney injury: alkaline phosphatase in sepsis-induced AKI.

Alkaline phosphatase for treatment of sepsis-induced acute kidney injury: a prospective randomized double-blind placebo-controlled trial



Ireland. Nat Rev Nephrol. 2012 Feb 14;8(3):129

Heemskerk et al. Crit Care Med. 2009 Feb;37(2):417-23, e1

Pickkers et al. Crit Care. 2012 Jan 23;16(1):R14

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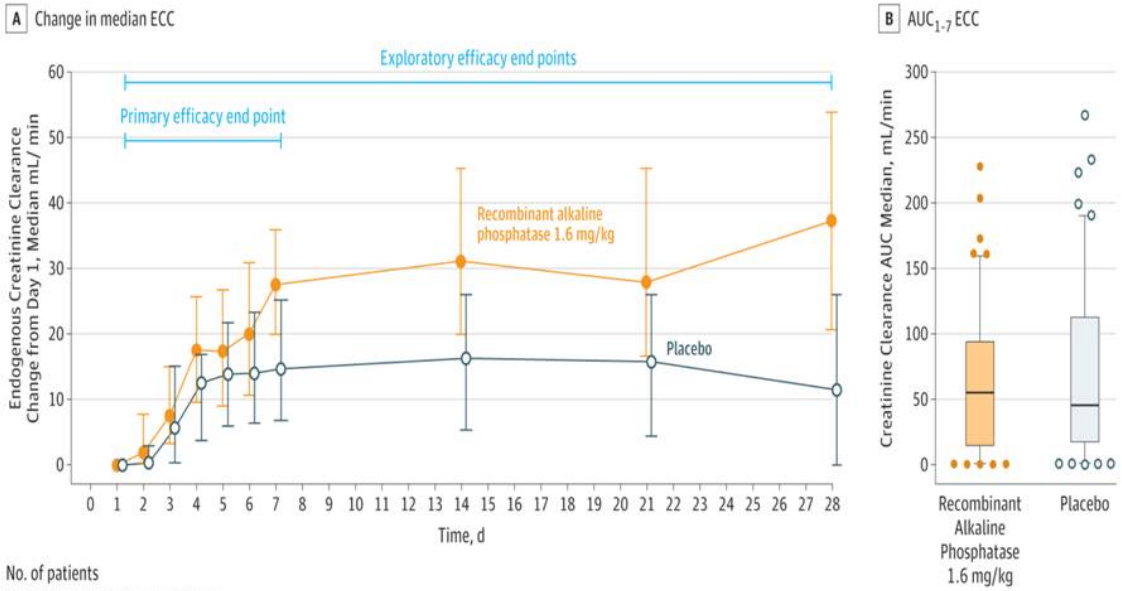
Renal Function: Primary & Secondary Endpoints



No. of patients

Recombinant alkaline phosphatase 1.6 mg/kg	111	102	95	92	92	86	82	82	64	47	38
Placebo	116	102	92	95	90	86	83	81	63	46	30

Pickkers P, et al: JAMA 2018; 320(19):1998-2009

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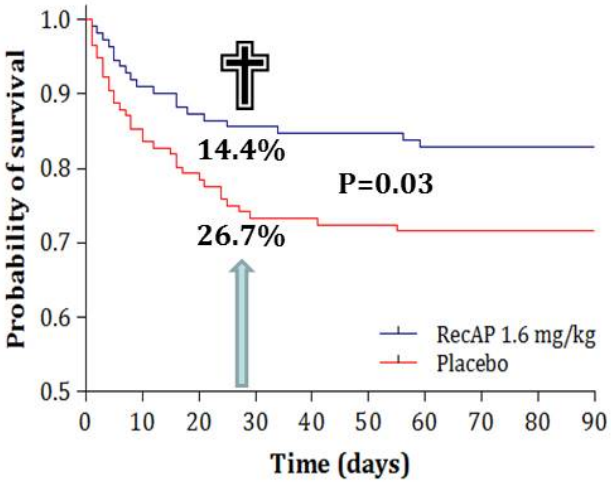
28-day Survival



No. at Risk					
RecAP 1.6 mg/kg	111	98	95	93	92
Placebo	116	92	86	84	83

Pickkers P, et al: JAMA 2018; 320(19):1998-2009

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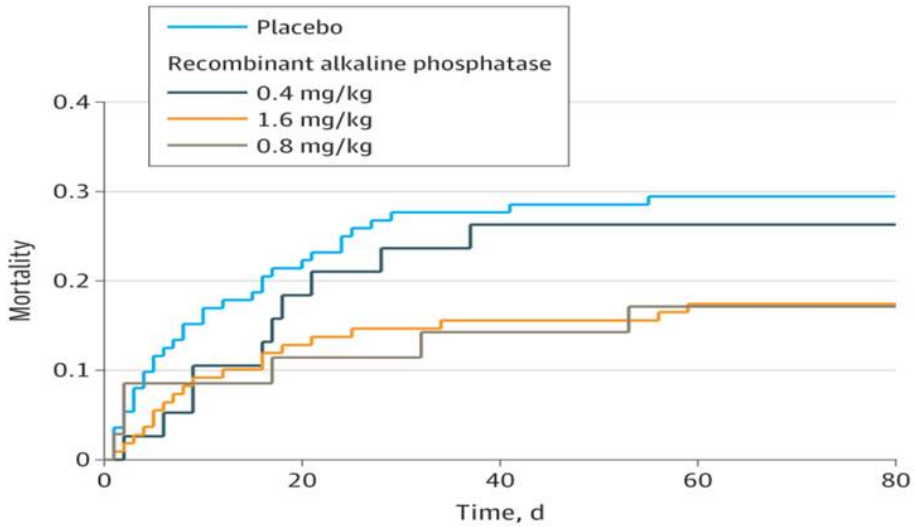
Dose-dependent Survival Effect?



No. at risk					
Recombinant alkaline phosphatase					
Placebo	112	88	81	79	79
0.4 mg/kg	38	31	28	28	28
0.8 mg/kg	35	31	30	29	29
1.6 mg/kg	109	95	92	90	90

Pickkers P, et al: JAMA 2018; 320(19):1998-2009

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RBC Transfusion Threshold & AKI post-Cardiac Surgery

- Randomized Non-inferiority Trial: restrictive (Hb <7.5g/dl) vs.Liberal (Hb <8.5-9.5 g/dl)
- N= 4,531; Primary outcome: AKI (KDIGO)
- Restrictive-threshold group received 38% fewer transfusions than liberal-threshold group (avg.1.8 versus 2.9, p=0.001)
- AKI occurred in 27.7% restrictive vs 27.9% liberal (p=NS)
- Preoperative CKD: AKI in 33.6% restrictive-threshold group vs 32.5% liberal-threshold group (p=NS)
- Conclusions: Among patients undergoing cardiac surgery, a restrictive transfusion approach resulted in fewer red blood cell transfusions without increasing the risk of AKI

Garg AX, et al: JASN 2019;30: 1294–1304

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Take-Home Message

Recent Developments in AKI Prevention & Therapy Literature.....

- Sepsis:
  - Simple early resuscitation strategies decrease AKI incidence
  - Balanced crystalloids maybe preferred in sepsis and ICU
  - Newer therapies emerging
- Cardiac Surgery:
  - Conservative transfusion strategy preferred

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Acute Renal Replacement Therapy

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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

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The STandard vs Accelerated initiation of Renal Replacement Therapy in AKI Trial STARRT-AKI

- Randomized, open-label trial of accelerated vs standard initiation of RRT in critically ill patients with AKI
- 2,866 patients with KDIGO Stage 2-3
- 135 centres in Canada, USA, Australia, New Zealand, China, Brazil, UK, Ireland, Belgium, France, Germany, Italy, Austria, Switzerland and Finland
- ClinicalTrials.gov Identifier: NCT02568722

STARRT-AKI Investigators. Crit Care Resusc. 2019 Sep;21(3):162-170

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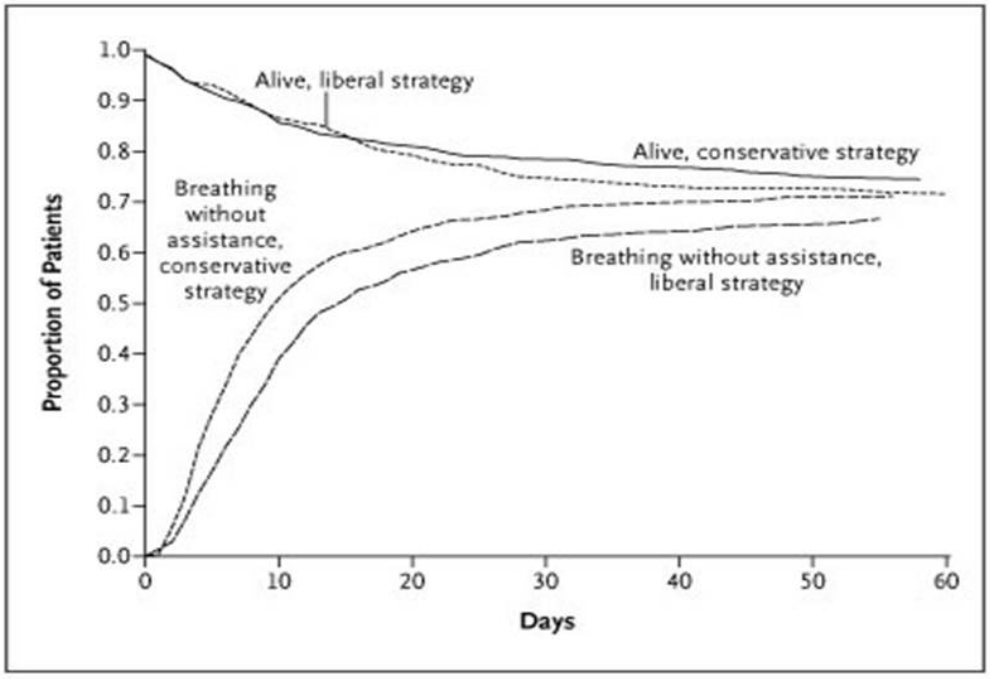
FACTT Trial: Fluid Management in ARDS- Outcomes



NHLBI ARDS Clinical Trials Network NEJM 2006;354:2564-2575

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Fluid Balance Control in AKI with AHRF

- **Diuretics (FACTT AKI Subset)**:
  - Grams ME, CJASN 2011;6:966-973
- 306/1,000 w AKI in 2 days
  - 137 in fluid liberal (+10.2L), 169 in fluid conservative (+3.7L)
    - Independently predictive of 60-d mortality: adjOR 1.61/L/d (1.29-2), p<0.001
    - Assoc. w cumulative 7-d furosemide doses 159mg vs. 562mg
    - OR 0.48/100mg/d (0.28-0.81), p=0.007; NS adjusted for fluid balance
- **RRT (AKIKI Trial- early vs late RRT in AKI)**:
  - Gaudry S, et al: NEJM 2016;375:122-133
  - No difference in ventilator-free days or survival (including ARDS subsets- 34% both arms); better UOP in late group

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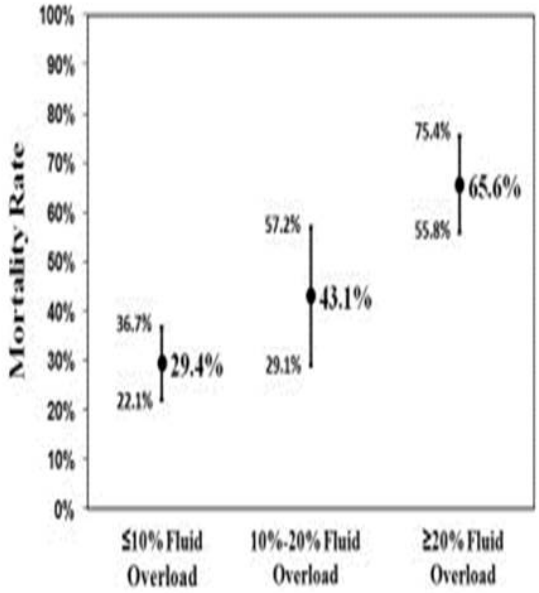
Fluid Overload & Outcome in Pediatric AKI



% Fluid Overload =

(Fluid in – Fluid out) X 100
ICU Admission Weight

Sutherland SM, et al: Am J Kid Dis 2010;55:316-25

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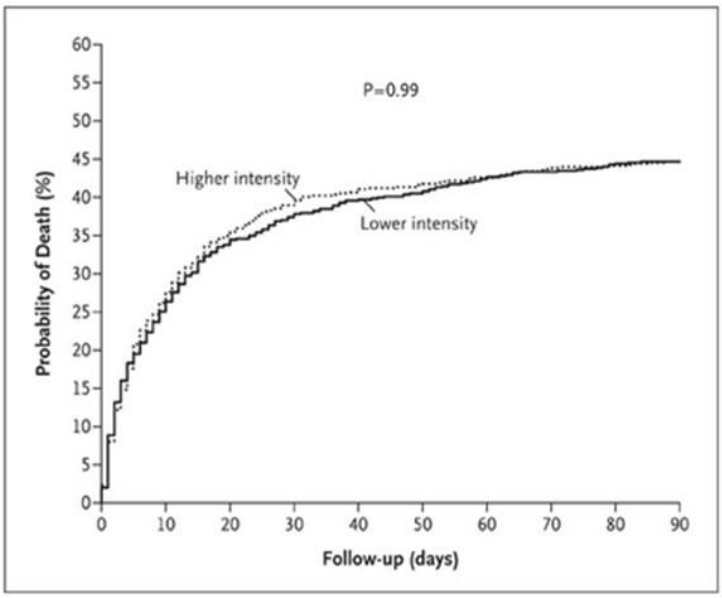
RENAL Trial Outcome (CRRT Dose)



RENAL Investigators; NEJM 2009 Oct 22;361(17):1627-38

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Fluid Balance & Outcomes in RENAL Trial

- Mean daily fluid balance among survivors was -234 mL/day, vs +560 mL/day among nonsurvivors ($p < .0001$)
- Mean cumulative fluid balance over the same period was -1941 vs. +1755 mL ($p = 0.0003$)
- A negative mean daily fluid balance during study treatment was independently associated with a decreased risk of death at 90 days (OR 0.318; 95% CI 0.24-0.43; $p < 0.0001$) and with increased survival time ($p < .0001$)
- Negative mean daily fluid balance was associated with significantly increased renal replacement-free days ($p = 0.0017$), ICU-free days ($p < 0.0001$), and hospital-free days ($p = 0.01$)
- Conclusions: in the RENAL study, a negative mean daily fluid balance was consistently associated with improved clinical outcomes

RENAL Investigators: Crit Care Med 2012;40(6):1753-60.

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CRRT Therapy Options

CVVH

Continuous

Veno-Venous

Hemofiltration

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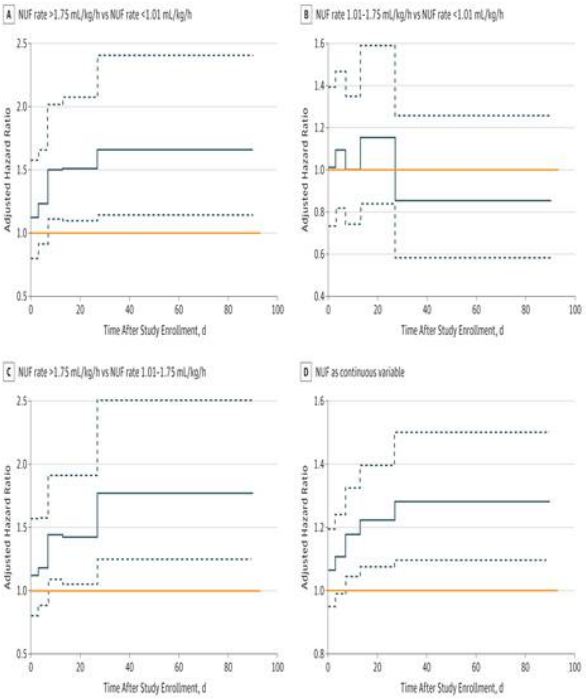
CRRT Ultrafiltration Rate & AKI Mortality

- Secondary analysis of 1,434 Renal trial pts: 44.2% mortality
- Tertiles of Net UFR:
  - High, NUFR >1.75 mL/kg/h
  - Middle, NUFR 1.01-1.75 mL/kg/h
  - Low, NUFR <1.01 mL/kg/h
- Time- and Dose- dependent increase in adjusted hazard ratio for death with highest vs lowest NUFR
  - Dose-dependently (aHR significantly increased per 0.5ml/kg/h NUFR increase)
  - Longditudinal analysis: increasing NUFR assoc. with lower survival (p<0.001)
- Conclusion: NUFR >1.75 mL/kg/h associated with lower survival than NUFR <1.01 mL/kg/h on CRRT



Murugan R,et al: JAMA Network Open. 2019;2(6):e195418

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Fluid Balance Details

Fluid balance	(median)	NUFR <1.01	NUFR 1.01-1.75ml/kg/h	NUFR >1.75	P value
Daily (ml/d)		641	-55.5	-658	<0.001
Cumulative (L)		2.3	-0.4	-3.6	<0.001
Net UFR	**(median)**				
Hourly (ml/hr)		32	106	167	<0.001
Cumulative (L)		1.7	8.5	16.5	<0.001
Fluid balance……	**excluding NUF (median)**				
Daily (ml/d)		1370	1683	2058	<0.001
Cumulative (L)		4.6	8.5	11.1	<0.001

Murugan R,et al: JAMA Network Open. 2019;2(6):e195418

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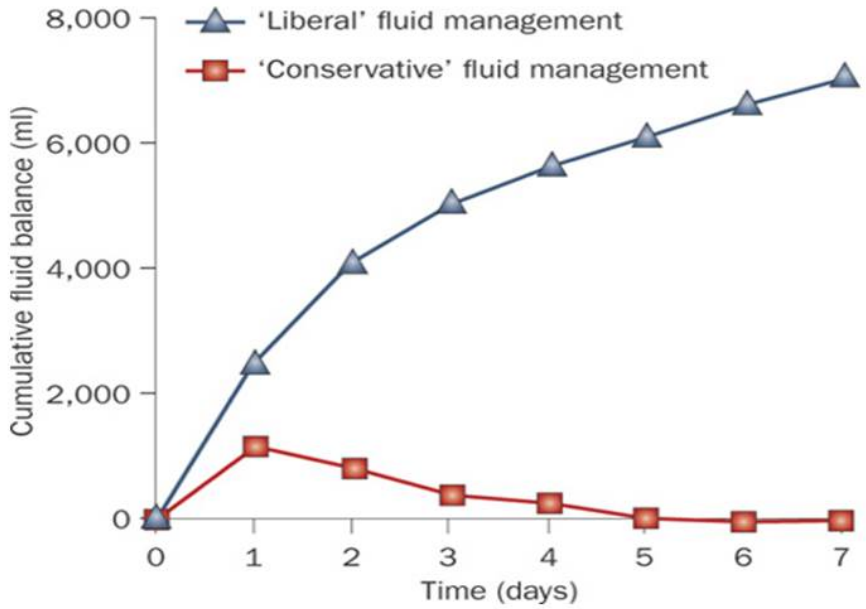
Achieved Cumulative Fluid Balance in FACTT trial



Prowle JR, et al: Nat. Rev. Nephrol. 2010;6(2):107-15

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Take-Home Messages

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

- Results of early vs. late initiation RCTs are conflicting; pivotal trial (STARRT) completing
- Fluid overload in AKI is associated with adverse outcomes
- Retrospective analysis raises concerns about use of aggressive ultrafiltration on CRRT
  - Clinical caution & prospective trials required

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List of Abbreviations

- AKI: acute kidney injury
- RRT: renal replacement therapy
- KDIGO: Kidney Disease Improving Globsal Outcomes
- ADQI:Acute Disease Quality Initiative
- UOP: urine output
- (N-)UFR: (Net) ultrafiltration rate

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