REDISCOVERING URINE ELECTROLYTES FOR DIFFERENTIAL DIAGNOSIS AND PROGNOSIS OF AKI

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UNIVERSITY OF SÃO PAULO

CRRT Conference – February 2012
Friday, February 17, 7:30-7:45

Outline

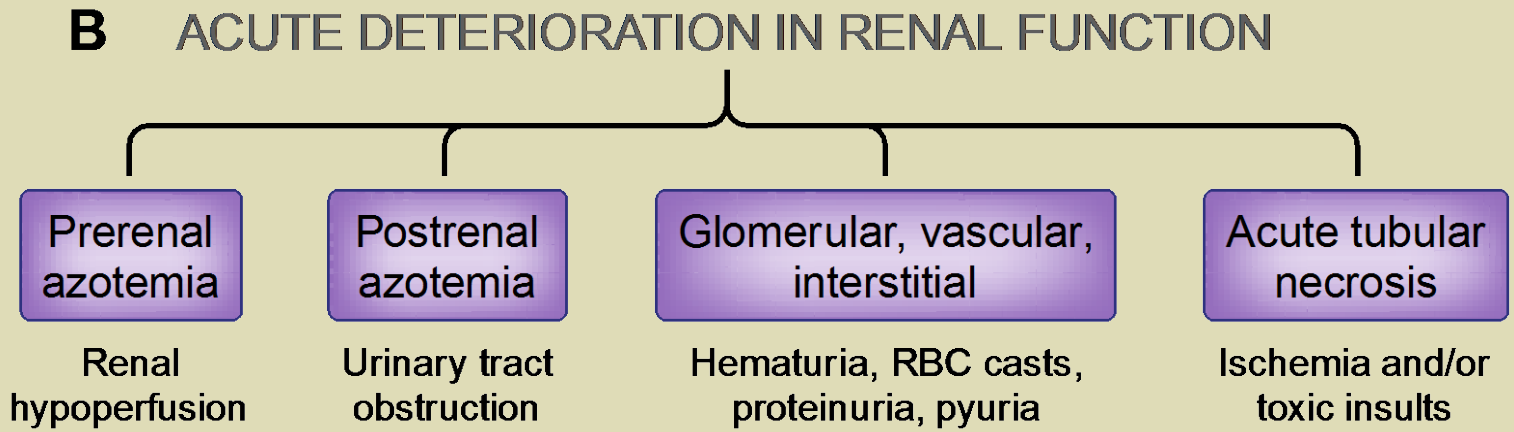
- Factors affecting the sensitivity and specificity of urine electrolytes to determine
  - reversibility of acute kidney injury
  - severity
- Discuss the interpretation of urine electrolytes in acid-base imbalances.
- Propose the use of SIDu to monitor tubular acidifying capacity in AKI.

Urine electrolytes

- Differential diagnosis of natremia disorders
- Correct interpretation of urinary electrolytes
- Pre-renal versus acute tubular necrosis

Diagnostic Value of Urinary Sodium, Chloride, Urea, and Flow

Robert W. Schrier



Urinary sodium reflects ECFV

- modest changes in ECFV (extra-cellular fluid volume) or total body sodium
  - stimulation of renin-angiotensin-aldosterone system - . sympathetic nervous system
    - Decreases urinary excretion of Na
      - Urine Na concentration
      - FE Na

When Urinary Sodium does not Reflect ECFV (or Total Body Sodium)

- Diuretics
- Bicarbonaturia – in metabolic alkalosis or proximal tubular acidosis
- Increase in solute excretion may also increase urinary sodium losses by the normal kidney
  - Glucosuria
  - Mannitol

Chronic Kidney Disease

- GFR < 60 ml/min)
  - the renal response not maximal
  - Can take days
  - can still decrease in patients with CKD who are not at end-stage

Established Acute Tubular Necrosis

- Urinary sodium concentration will not be minimal, even with substantial ECFV depletion

Causes of falsely low Urine Na in patients with an intrinsic cause of AKI

- Selected causes of acute tubular necrosis
  - Early in contrast-mediated acute renal dysfunction
  - Rhabdomyolysis
  - Myoglobinuria, hemoglobinuria
  - Nonoliguric acute tubular necrosis
- Acute glomerulonephritis
- Acute interstitial nephritis
- Early in sepsis – functional AKI?

Low Urine Na with high ECFV Underfilling

- Stimulus of the normal kidney to retain sodium is not ECFV depletion or even decreased total plasma volume
  - Arterial baroreceptors in the carotid sinus, aortic arch, and juxtaglomerular apparatus are unloaded with reversal of tonic inhibition to central nervous system
  - Can be associated with ECFV expansion
    - Decrease in stroke volume
    - Primary systemic arterial vasodilation
- Differentiate a reversible renal dysfunction ("pre-renal") with acute tubular necrosis (ATN)
  - Cannot by a parameter to guide fluid resuscitation

Diagnostic Value of Urinary Sodium, Chloride, Urea, and Flow

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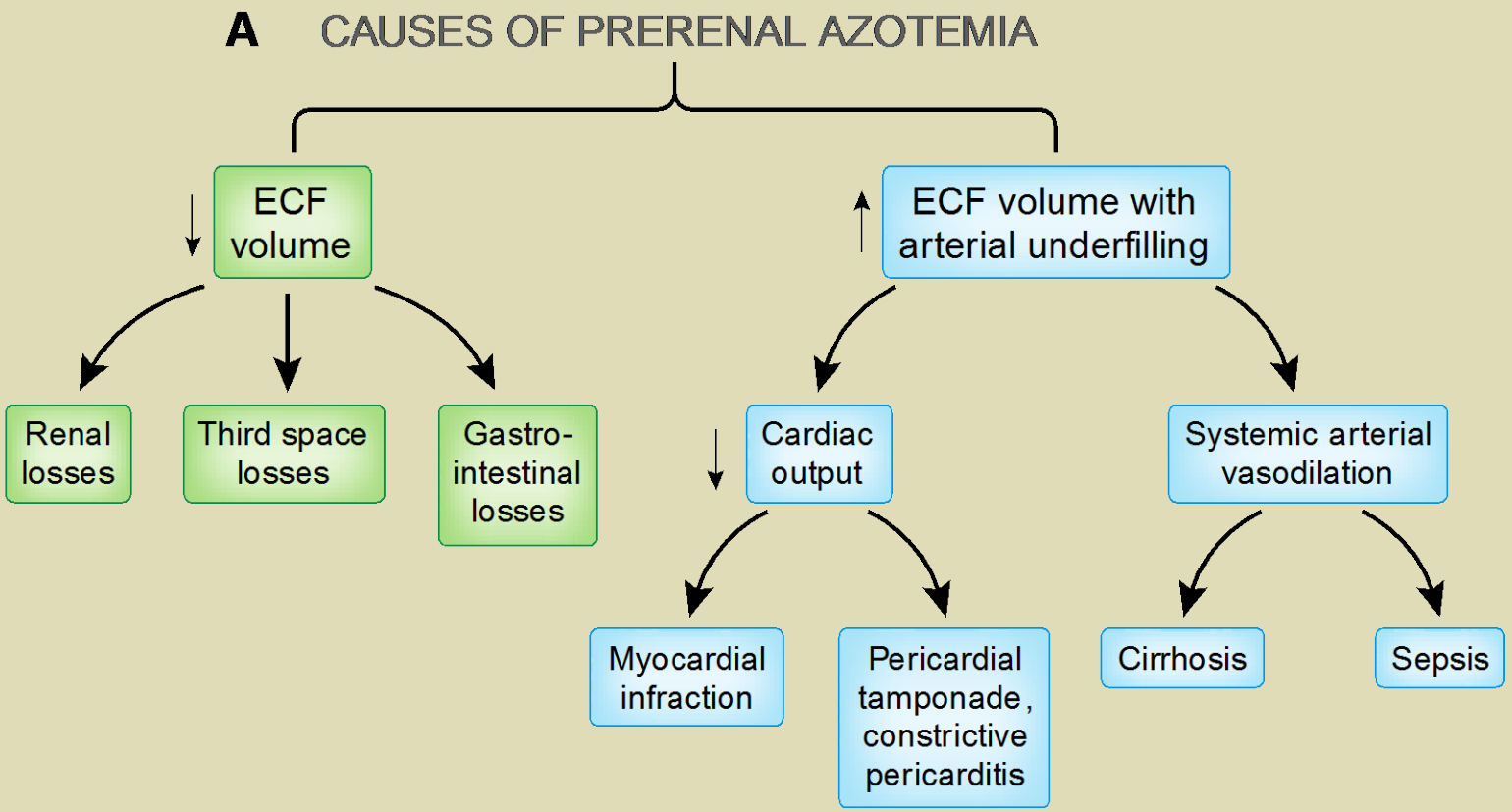


Urinary diagnostic indices in AKI

FE_{Na} vs FE_{UREA}

- The FENa <1.0 in 85 to 94% of patients with prerenal azotemia
  - within 24 to 72 h
  - reversal of kidney function secondary to interventions:
    - such as fluid resuscitation or
    - improved cardiac output.

- Did not reverse their sCr and thus had oliguric ATN
  - FENa <1.0 in only 0 to 4%.

Miller TR and Schrier RW, *Ann Intern Med 89: 47–50*, 1978

What about the FE Urea?

Fractional Excretion of Urea

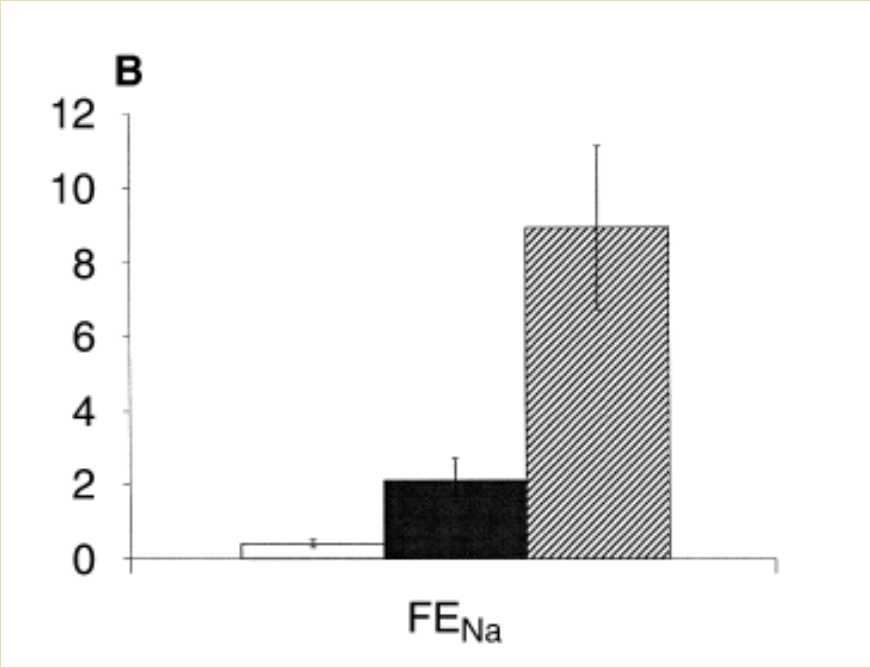
- More helpful than FENa in distinguishing prerenal azotemia from ATN in patients on diuretics
- Urea reabsorption in prerenal states
  - ECFV depletion
  - Heart failure
  - Cirrhosis
  - Is enhanced in the proximal tubule before the sites of diuretic action in the downstream tubule

Carvounis CP, Kidney International, Vol. 62 (2002), pp. 2223–2229

Significance of The Fractional Excretion of Urea in The Differential Diagnosis of Acute Renal Failure

CHRISTOS P. CARVOUNIS,SABEEHA NISAR, and SAMERAH GURO-RAZUMAN

- FEUN vs FENa in 102 episodes of ARF
- three groups:
  - Prerenal no diuretics n= 50
    - 92% FENa< 1%
  - Prerenal with diuretics n= 27
    - 48% FENa< 1%
  - ATN n = 25



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Significance of The Fractional Excretion of Urea in The Differential Diagnosis of Acute Renal Failure

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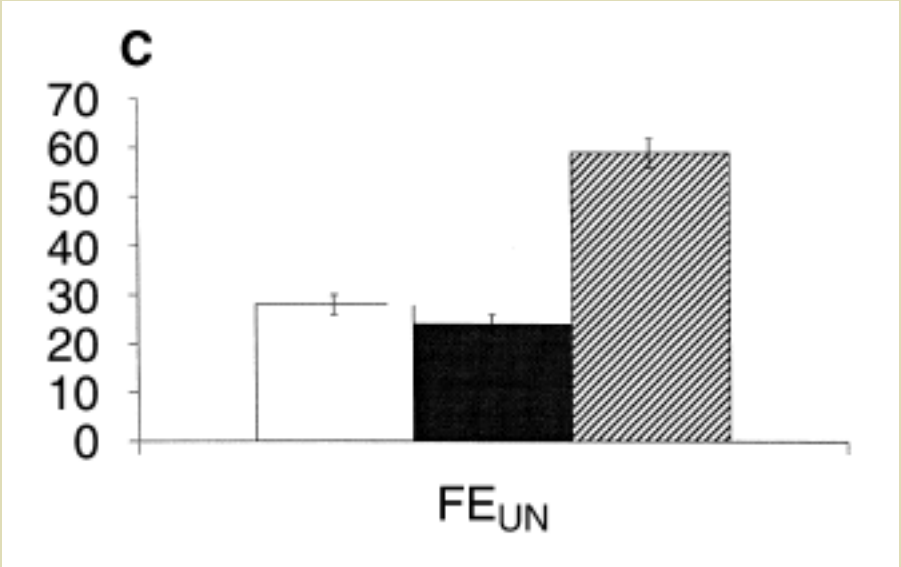
- Prerenal no diuretics n= 50
  - 92% FENa< 1%
- Prerenal with diuretics n= 27
  - 48% FENa< 1%
  - 89% Feurea < 85%
- ATN n = 25



- FE Urea identical in the two pre-renal groups
  - (27.9 2.4% vs. 24.5 2.3%)
  - ATN (58.6%)

Kidney International, Vol. 62 (2002), pp. 2223–2229

Diagnostic Performance of Fractional Excretion of Urea and Fractional Excretion of Sodium in the Evaluations of Patients With Acute Kidney Injury With or Without Diuretic Treatment

Marie-Noëlle Pépin, MD, Josée Bouchard, MD, Louis Legault, MD, and Jean Éthier, MD

- Prospective study
- Feur vs FENa - transient and persistent AKI
- 99 patients AKI
  - (>=30% sCr within 1 week)
  - returned to baseline within 7 days

American Journal of Kidney Diseases, Vol 50, No 4 (October), 2007: pp 566-573

Performance of FE <= 35% and FENA <= 1% for the Diagnosis of Transient Acute Kidney Injury

Irrespective of diuretic intake:

FENa was less in T-AKI than P-AKI (2±4% vs 5±6%; *P*=0.001)

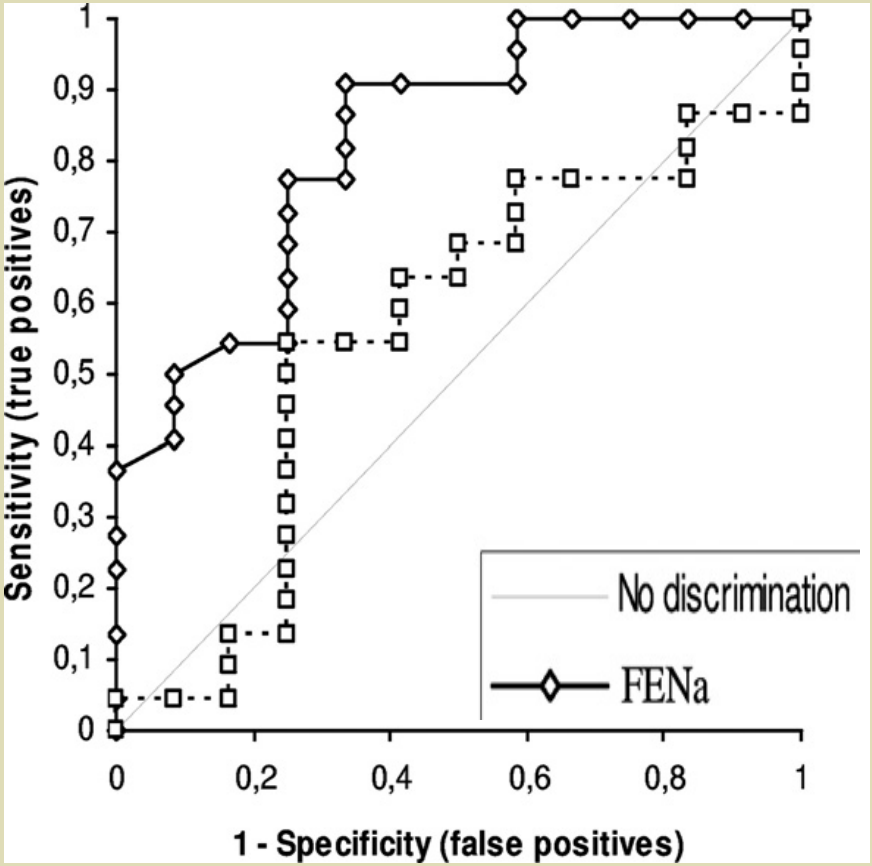
FEur was similar in T-AKI (29±19%) and P-AKI (32±19%; *P*=0.3).

	No Diuretics		Diuretics	
	FEur	FENa	FEur	FENa
Sensitivity (%)	48	78	79	58
Specificity (%)	75	75	33	81
Positive predictive value (%)	79	86	71	86
Negative predictive value (%)	43	64	44	49

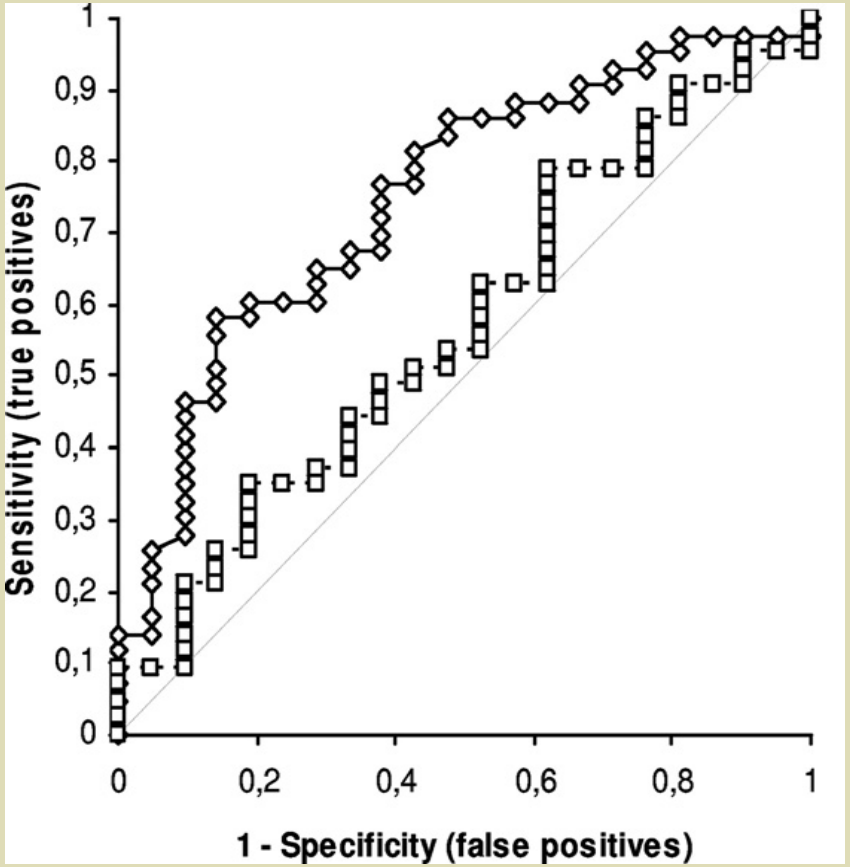
American Journal of Kidney Diseases, Vol 50, No 4 (October), 2007: pp 566-573

ROC Curves For FEur Fena for Diagnosis of Transient AKI Patients With and Without Diuretic Intake.

No diuretic – 0.56 vs 0.86



Diuretic – 0.57 vs 0.75



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Definition of Prerenal Azotemia

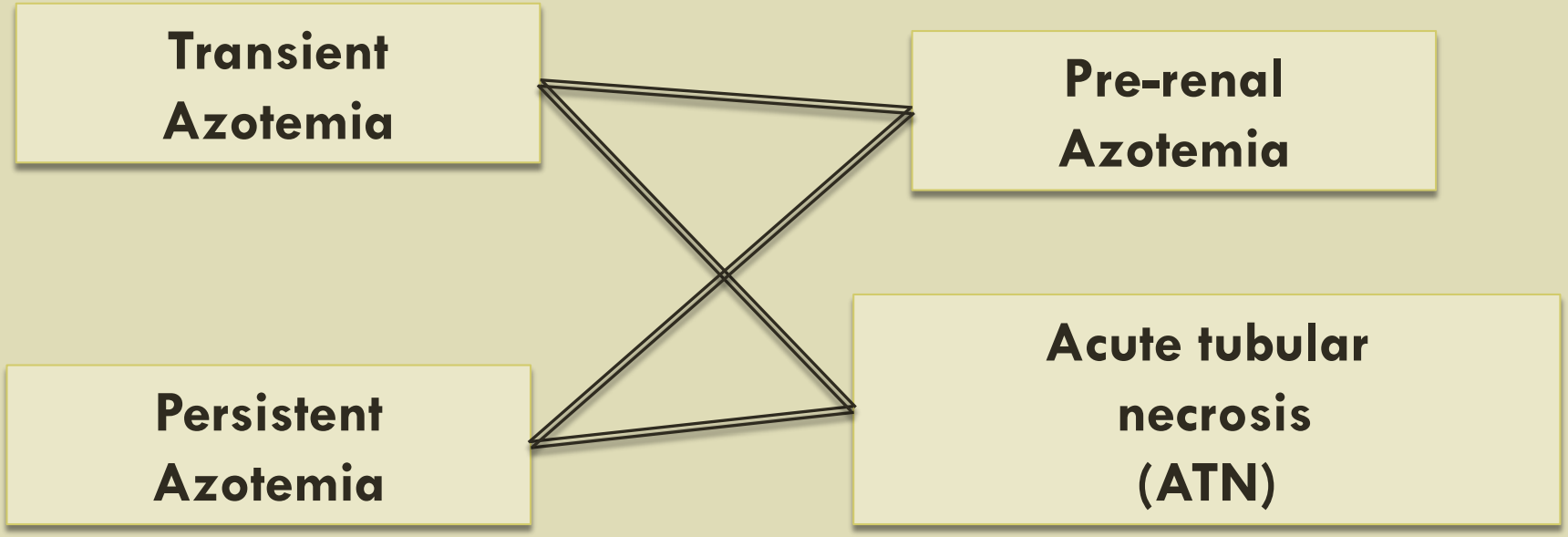
"Prerenal azotemia is classically defined as decreased GFR resulting from renal hypoperfusion in a structurally intact kidney, which is rapidly reversible when the underlying cause is corrected"

- ✓ No consensus definition for PRA
  - "reversible increase in serum creatinine and urea concentrations,
  - characterized by intact renal parenchymal function but renal hypoperfusion"

Functional vs Histopathological concepts

Reversible:
Functional

Intact Parenchyma
Histopathological



How Studies Classify Prerenal Patients

"Prerenal AKI was defined as an abrupt decline in baseline kidney function that improved to 10% of baseline after fluid resuscitation and/or hemodynamic manipulation within 48 h."

Definitions of PRA used in studies differentiating PRA and ATN

Author	Year	Test	Definitions of PRA
Perlmutter	1959	Urine-serum urea nitrogen ratio	Oliguria and azotemia lasting less than 48 hrs.
Espinel	1976	FE-Na	Prompt increase in urinary output and creatinine clearance effected by hemodynamic improvement.
Miller	1978	Urinary indices	Return of renal function to normal within 24 to 72 hrs after correction of hemodynamics.
Platt	1991	Doppler ultrasound	Clinical judgment (definitions not mentioned).
Chew	1993	Urinary enzymes	Rapid recovery of renal function after treatment of hypotension or dehydration.
Steinhauslin	1994	FE-lithium, FE-UA	Decrease in plasma creatinine toward normal values within 72 hrs of correction of hemodynamic abnormalities.
Izumi	2000	Doppler ultrasound	Not clearly mentioned, but FENa used.
Carvounis	2002	FE-urea	Prompt increase in urinary output and creatinine clearance after hemodynamic improvement.
Parikh	2004	Urinary IL-18	Multiple definitions but included improvement after treatment.
Pepin	2007	FE-Na, FE-urea	Two of 4 criteria (history, physical findings, urine analysis, rapid return to baseline renal function within 7 days).
Perazella	2008	Urine microscopy	Improvement to baseline after fluid resuscitation and/or hemodynamic manipulation within 48 hrs.
Nickolas	2008	Urinary NGAL	Resolved within 3 days or FENa <1%

Is it important to diagnose transient AKI?

Transient vs Prolonged AKI Difference in Outcomes

Rapid Reversal of AKI and Hospital Outcomes: A Retrospective Cohort Study

- Tian, J Am J Kidney Dis 53: 974-981; 2009

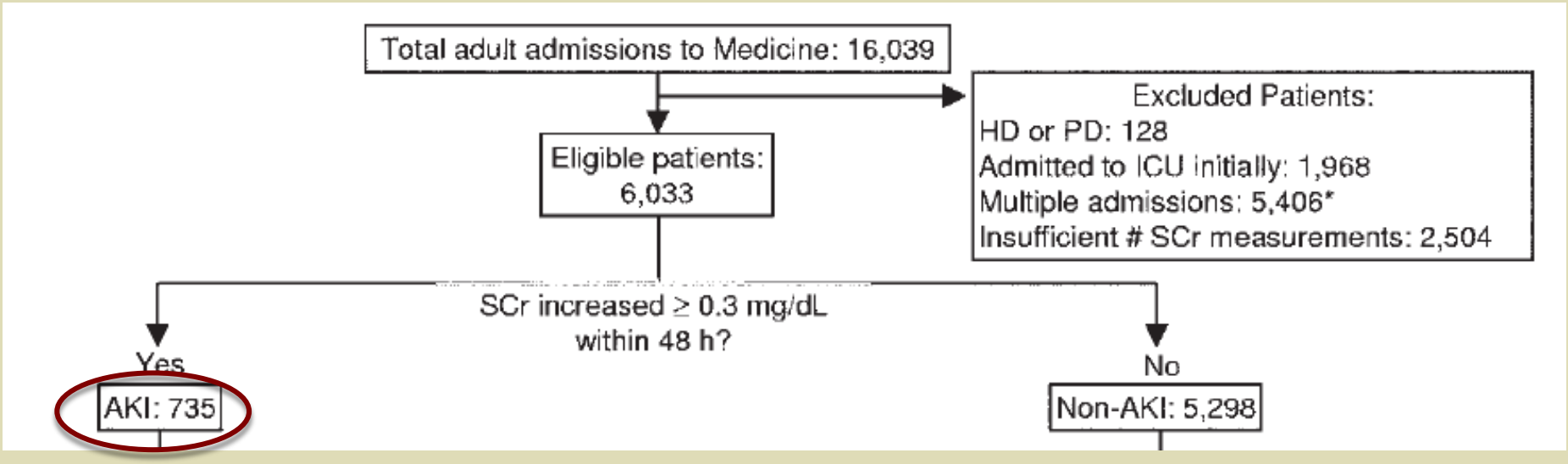
Transiente Azotemia is Associated with a high risk of death in hospitalized patients

- Uchino, Nephrol Dial Transplant; 2010

Rapid Reversal AKI

Rapid Reversal of Acute Kidney Injury and Hospital Outcomes: A Retrospective Cohort Study

Jianmin Tian, MD, MPH, Fidel Barrantes, MD, Yaw Amoateng-Adjepong, MD, PhD, and Constantine A. Manthous, MD

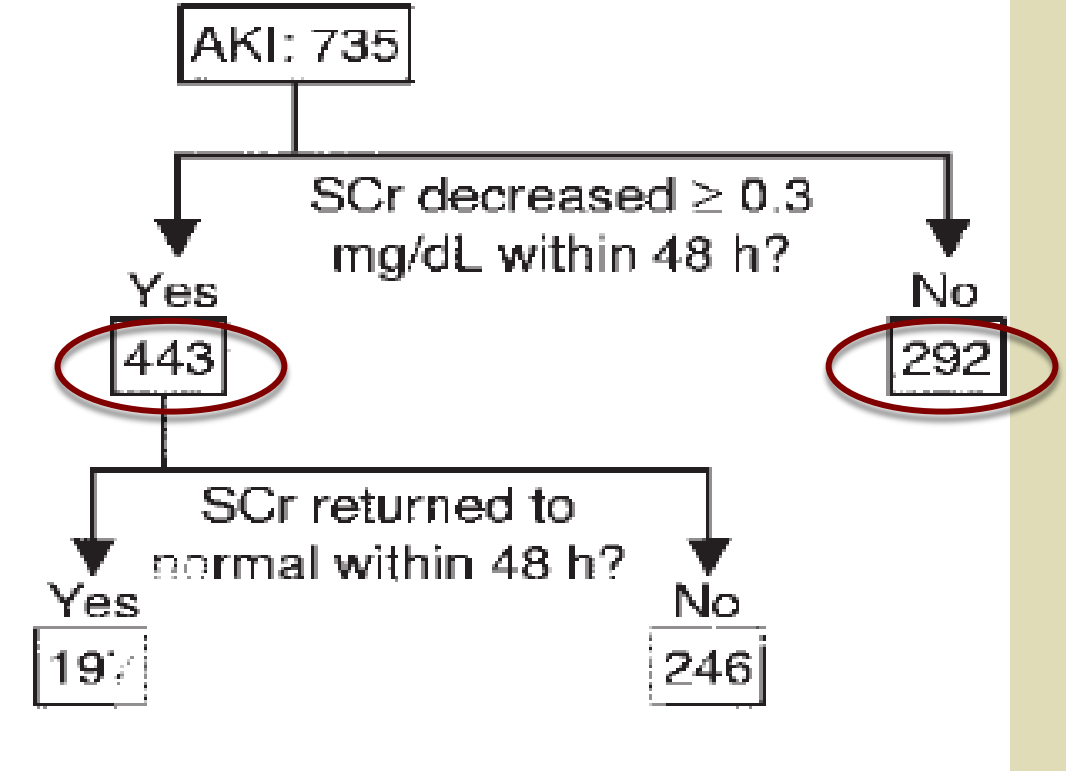


Tian, J Am J Kidney Dis 2009

Rapid Reversal AKI

443 rapid reversal AKI – more than 0.3mg/dL decrease within 48 h

292 prolonged AKI – no improvement after 48 h of the diagnosis

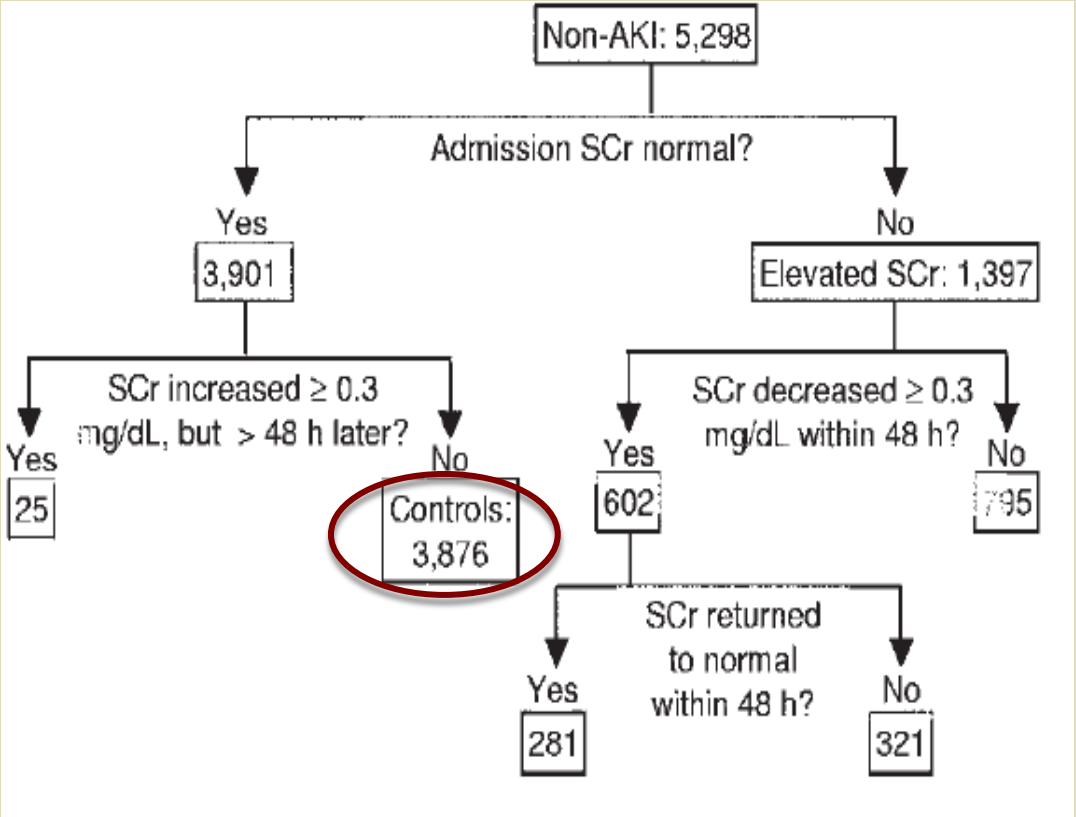


Tian, J Am J Kidney Dis 2009

Rapid Reversal AKI

Controls:

No AKI no AKI ate ICU admission or during ICU stay



Tian, J Am J Kidney Dis 2009

Rapid Reversal AKI

- Older
- More comorbidity
- Worse outcomes
- Than controls

	Control	Patients With AKI With SCr That Decreased ≥ 0.3 mg/dL Within 48 h	
	No. of Patients (%)	No. of Patients (%)	*P**
No. of patients	3,876	443	
Age (y)			<0.001
≥65	1,842 (47.5)	304 (68.6)	
<65	2,034 (52.5)	139 (31.4)	
Mean ± SE	62 ± 0.3	71 ± 0.7	
Sex			0.005
Men	1,662 (42.9)	221 (49.9)	
Women	2,214 (57.1)	222 (50.1)	
Race			<0.001
White	2,575 (66.4)	302 (68.2)	
African American	621 (16.0)	95 (21.4)	
Other	680 (17.6)	46 (10.4)	
Deyo-Charlson comorbidity index score‡			<0.001
0	2,134 (55.1)	100 (22.6)	<0.001
1-2	1,437 (37.1)	222 (50.1)	<0.001
3-4	197 (5.1)	81 (18.3)	<0.001
≥5	105 (2.7)	40 (9.0)	<0.001
Transfer to intensive care unit	184 (4.7)	160 (36.1)	<0.001
Mean length of stay (d)	5 ± 0.1	14 ± 0.6	<0.001
Hospital mortality	49 (1.3)	59 (13.3)	<0.001
Discharge§			<0.001
Home	3,049 (78.7)	202 (45.6)	
Extended-care facility	655 (16.9)	170 (38.4)	
Hospice care	16 (0.4)	0 (0)	

Tian, J Am J Kidney Dis 2009

Rapid Reversal AKI Associated mortality

	Unadjusted Odds Ratio (95% confidence interval)	Adjusted Odds Ratio (95% confidence interval)
AKI fully reversed*†	12.9 (7.9-21.1)	4.4 (2.6-7.3)
AKI with SCr that did not return to normal*	11.3 (7.0-18.0)	4.4 (2.7-7.1)
AKI with SCr that did not decrease ≥ 0.3 mg/dL within 48 h*	16.1 (10.7-24.4)	8.0 (5.4-11.8)
Age (≥65 y)	4.3 (2.9-6.4)	3.2 (2.1-4.8)
Intensive care unit transfer	7.5 (5.5-10.3)	4.0 (2.8-5.8)
Deyo-Charlson comorbidity index score‡	2.5 (1.8-3.5)	1.4 (1.1-1.6)

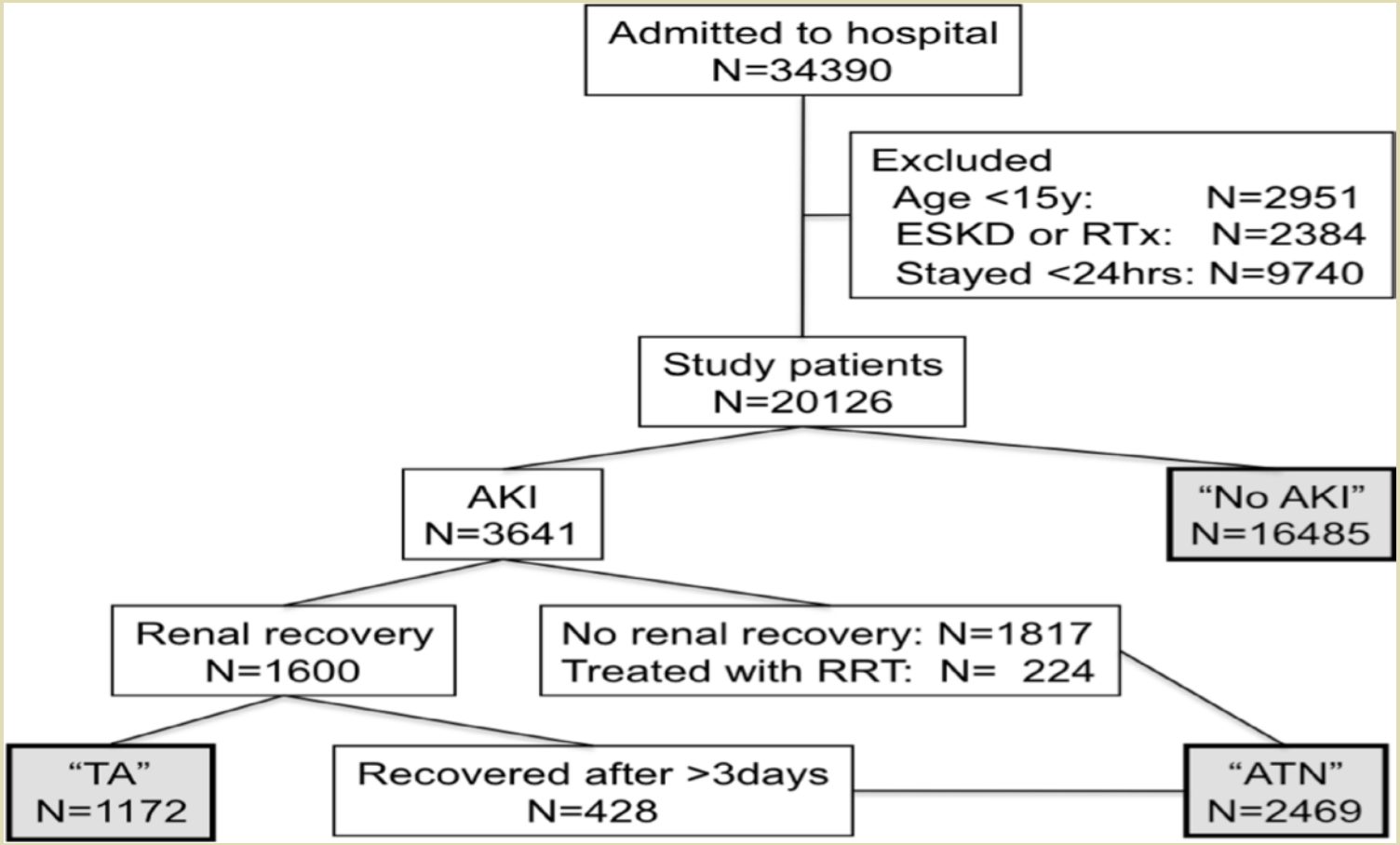
Transient AKI

Prolonged AKI

Tian, J Am J Kidney Dis 2009

Transient azotaemia is associated with a high risk of death in hospitalized patients

Shigehiko Uchino[1], Rinaldo Bellomo[2], Sean M. Bagshaw[3] and Donna Goldsmith[2]



Uchino, Nephrol Dial Transplant (2010)

Transient Azotemia

Risk for hospital mortality 3 times higher for patients with prolonged AKI

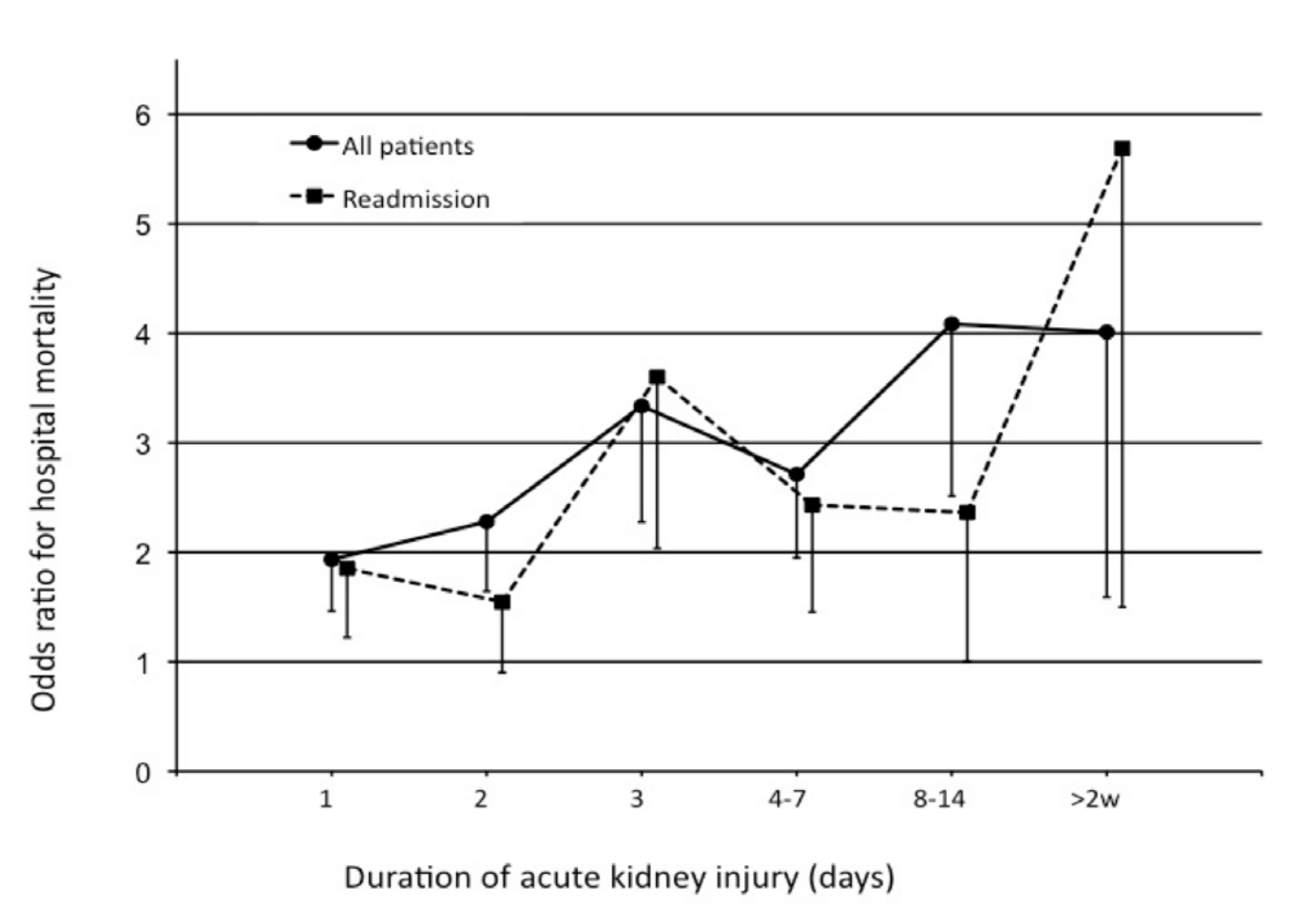
Table 4. Multivariate logistic regression analysis for hospital mortality

Variables	Odds ratios (95% CI)	
Age, years	1.036 (1.031–1.041)	$P < 0.0001$
Male gender	1.199 (1.060–1.356)	$P = 0.0038$
Readmission	1.860 (1.636–2.115)	$P < 0.0001$
Emergency admission	1.543 (1.327–1.795)	$P < 0.0001$
ICU admission	3.181 (2.500–4.048)	$P < 0.0001$
Mechanical ventilation	5.007 (3.826–6.552)	$P < 0.0001$
Baseline creatinine, mg/dL	1.514 (1.332–1.722)	$P < 0.0001$
Operation	0.809 (0.665–0.983)	$P = 0.033$
Renal condition		
No AKI	1.000 (Reference)	
ATN	6.070 (5.305–6.944)	$P < 0.0001$
TA	2.264 (1.856–2.762)	$P < 0.0001$

Uchino, Nephrol Dial Transplant (2010)

Transient Azotemia

Days with AKI and risk for mortality



Uchino, Nephrol Dial Transplant (2010)

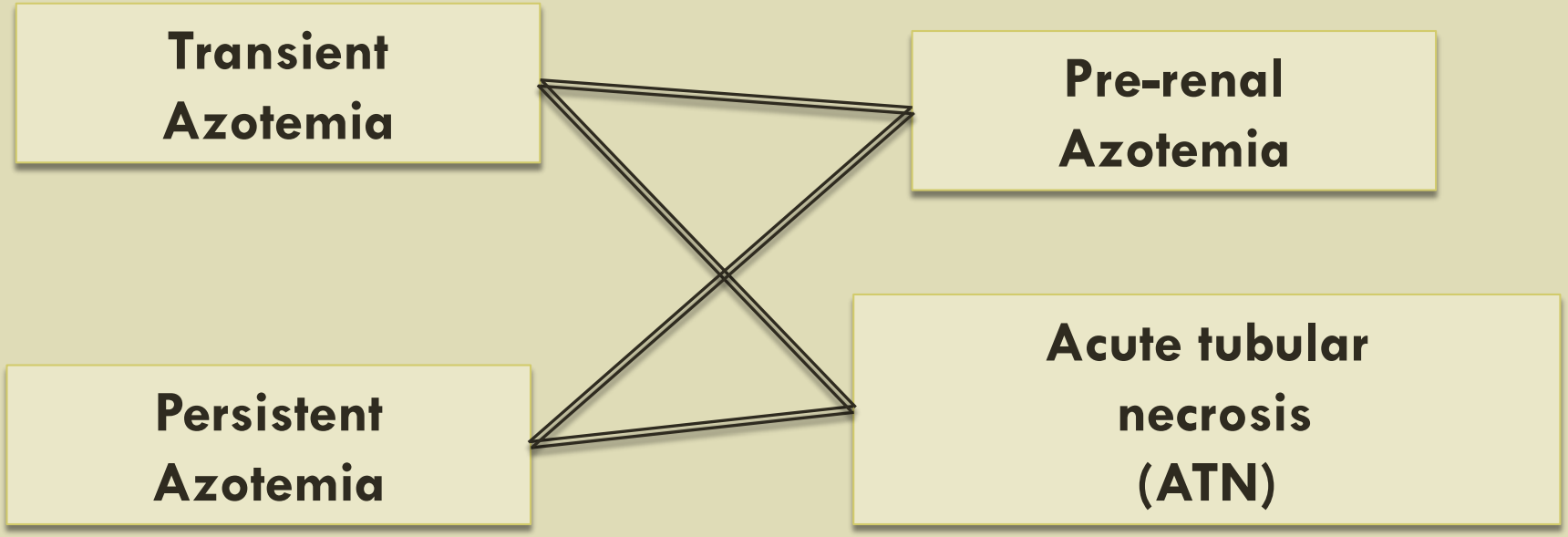
Transient AKI

- ✓ Is common (4-6% of hospitalized patients).
- ✓ Independent association with increased mortality.
- ✓ Associated with higher hospital mortality compared to patients with no AKI.
- ✓ Even one day of AKI had a significantly increased odds ratio for hospital mortality.

Functional vs Histopathological concepts

Reversible:
Functional

Intact Parenchyma
Histopathological



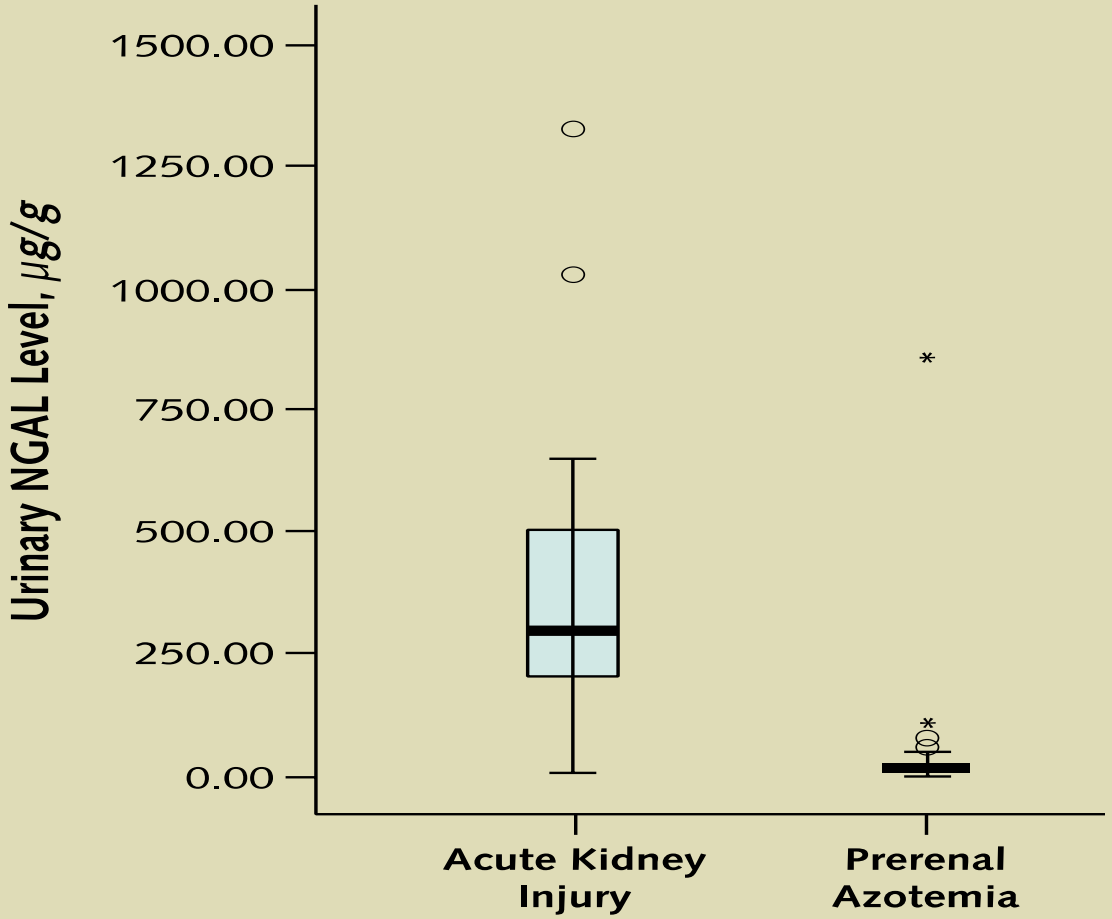
Sensitivity and Specificity of a Single ED Measurement of Urinary NGAL for Diagnosing AKI

Prerenal azotemia:

new-onset increase in sCr level (RIFLE)

And

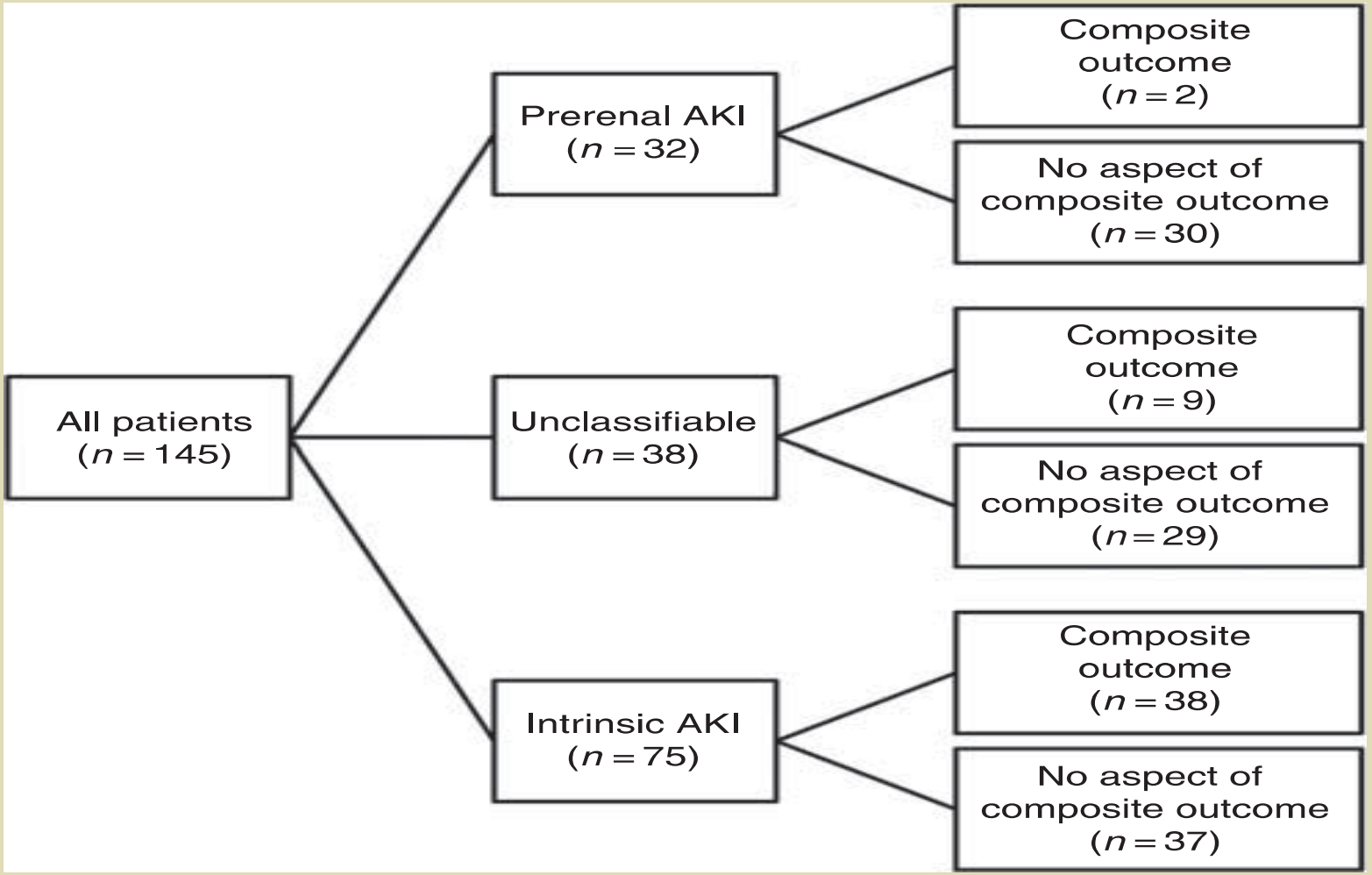
Resolved within 3 days with treatment aimed at restoring perfusion



Ann Intern Med. 2008;148:810-819.

Urinary NGAL distinguishes pre-renal from intrinsic renal failure and predicts outcomes

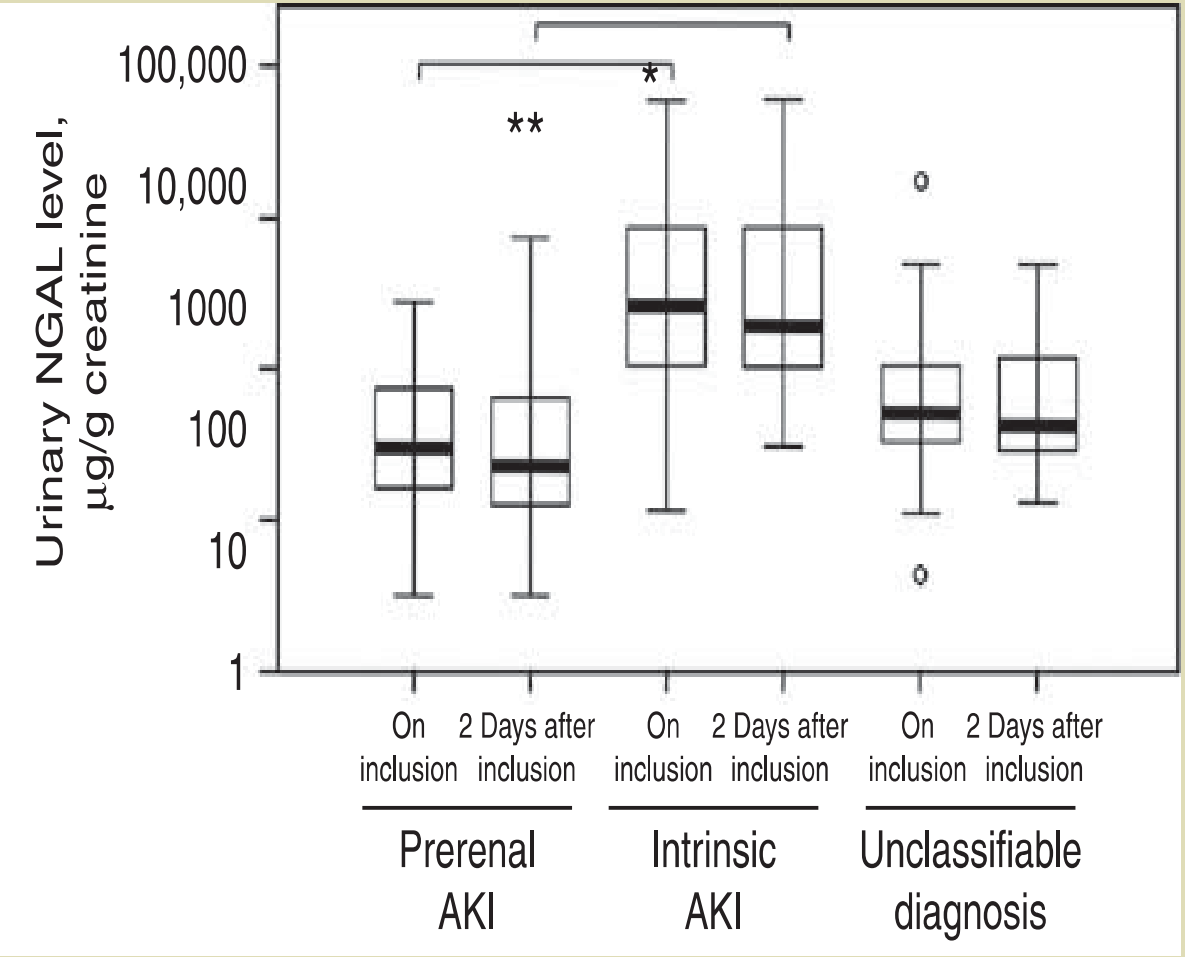
Eugenia Singer, Antje Elger, Saban Elitok2, Ralph Kettritz1, Thomas L. Nickolas, Jonathan Barasch3, Friedrich C. Luft1,2 and Kai M. Schmidt-Ott1,



Kidney International (2011) 80, 405–414

Biomarker levels in differential diagnosis of AKI and prediction of outcomes.

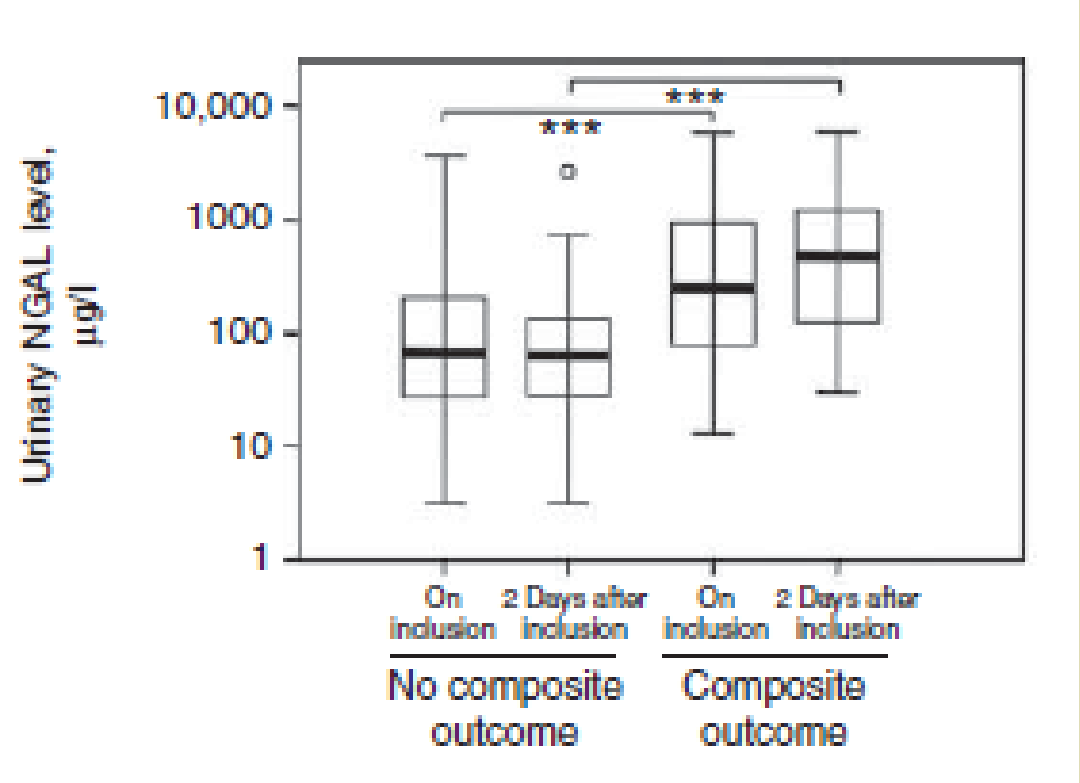
NGAL levels were significantly higher in patients with a clinical diagnosis of intrinsic AKI when compared with prerenal AKI



Kidney International (2011) 80, 405–414

Biomarker levels in differential diagnosis of AKI and prediction of outcomes.

Median NGAL levels on inclusion and 2 days after inclusion were significantly higher in patients, who later experienced the composite clinical outcome, when compared with all others



Kidney International (2011) 80, 405–414

Biomarkers in Predicting Intrinsic AKI vs Prerenal AKI

- NGAL levels effectively discriminated between intrinsic and prerenal AKI
  - area under the receiver-operating characteristic curve 0.87
- An NGAL level
  - over 104 lg/l indicated intrinsic
  - < 47 lg/l – unlikely intrinsic AKI

Kidney International (2011) 80, 405–414

Current Concepts of Reversibility

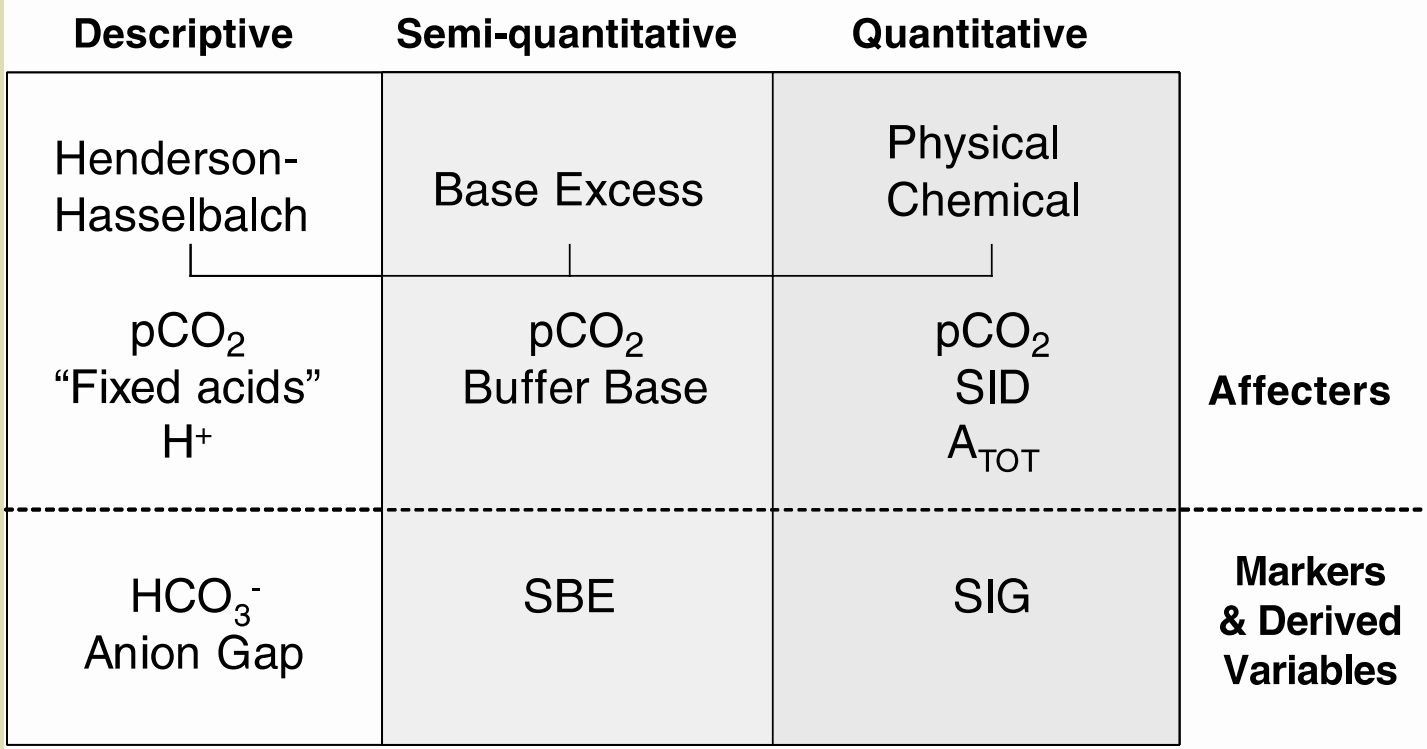
- Reversibility with manipulation
  - Fluid
  - Hemodynamics
- Common in certain settings
  - Dehydration
  - Hypotension
- Biomarkers
  - Urine output
  - Changes in BUN/Creatinine/Electrolytes in serum and urine

Review

Clinical review: Reunification of acid–base physiology

John A Kellum

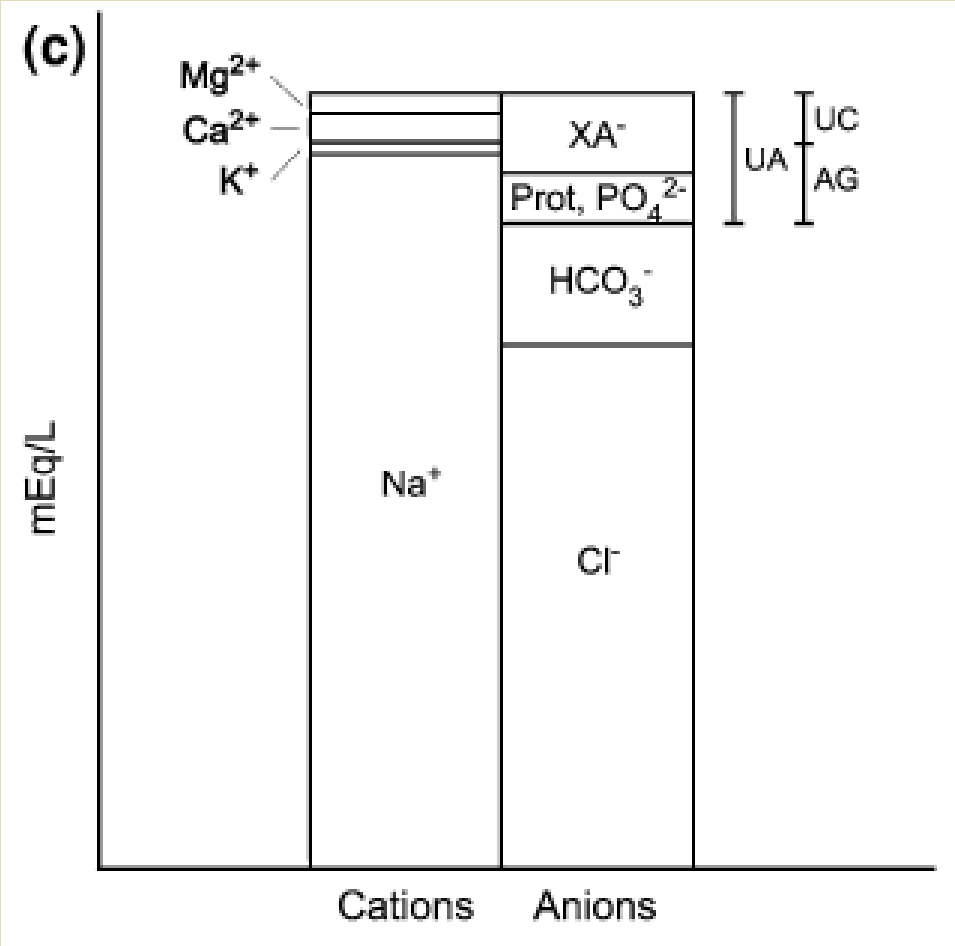
Figure 1



Critical Care 2005, 9:500-507 (DOI 10.1186/cc3789)

Diagnosing metabolic acidosis in the critically ill: bridging the anion gap, Stewart, and base excess

Christina Fidkowski, MD Æ James Helstrom, MD



Can J Anesth/J Can Anesth (2009) 56:247–256

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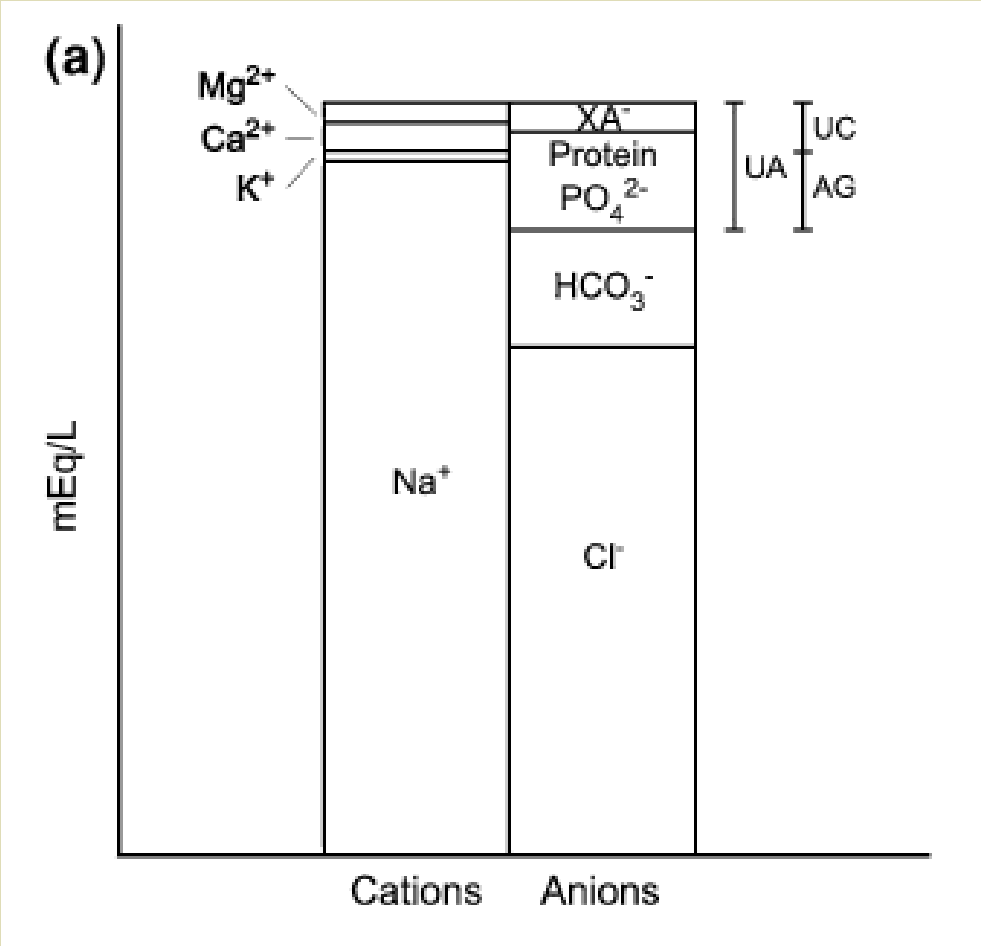

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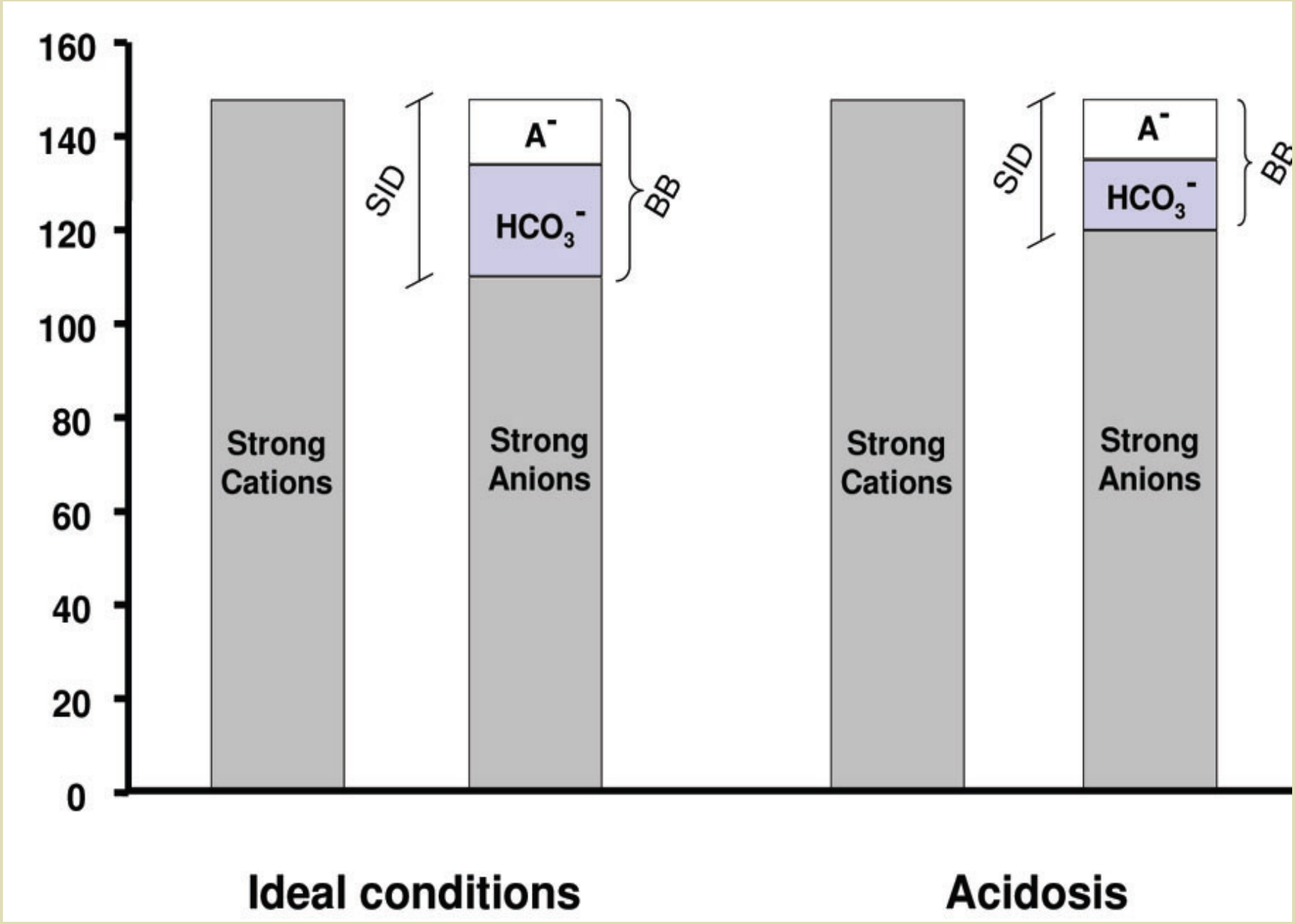
160
140
120
100
80
60
40
20
0
Strong Cations
SID
A-
HCO3-
BB
Strong Anions
Ideal conditions
Strong Cations
SID
A-
HCO3-
BR
Strong Anions
Acidosis

Kidney instant monitoring: a new analyzer to monitor kidney function

CAIRONI1, 2, T. LANGER1, P. TACCONE2, P. BRUZZONE2, S. DE CHIARA2, F. VAGGINELLI2, L. CASPANI2, C. MARENGHI2, L. GATTINONI

- As the kidney has been classically seen as a“slow” organ in the correction of acid-base disturbances, especially as compared to the “fast” lung

MINERVA ANESTESIOLOGICA 2010 – vol6:323

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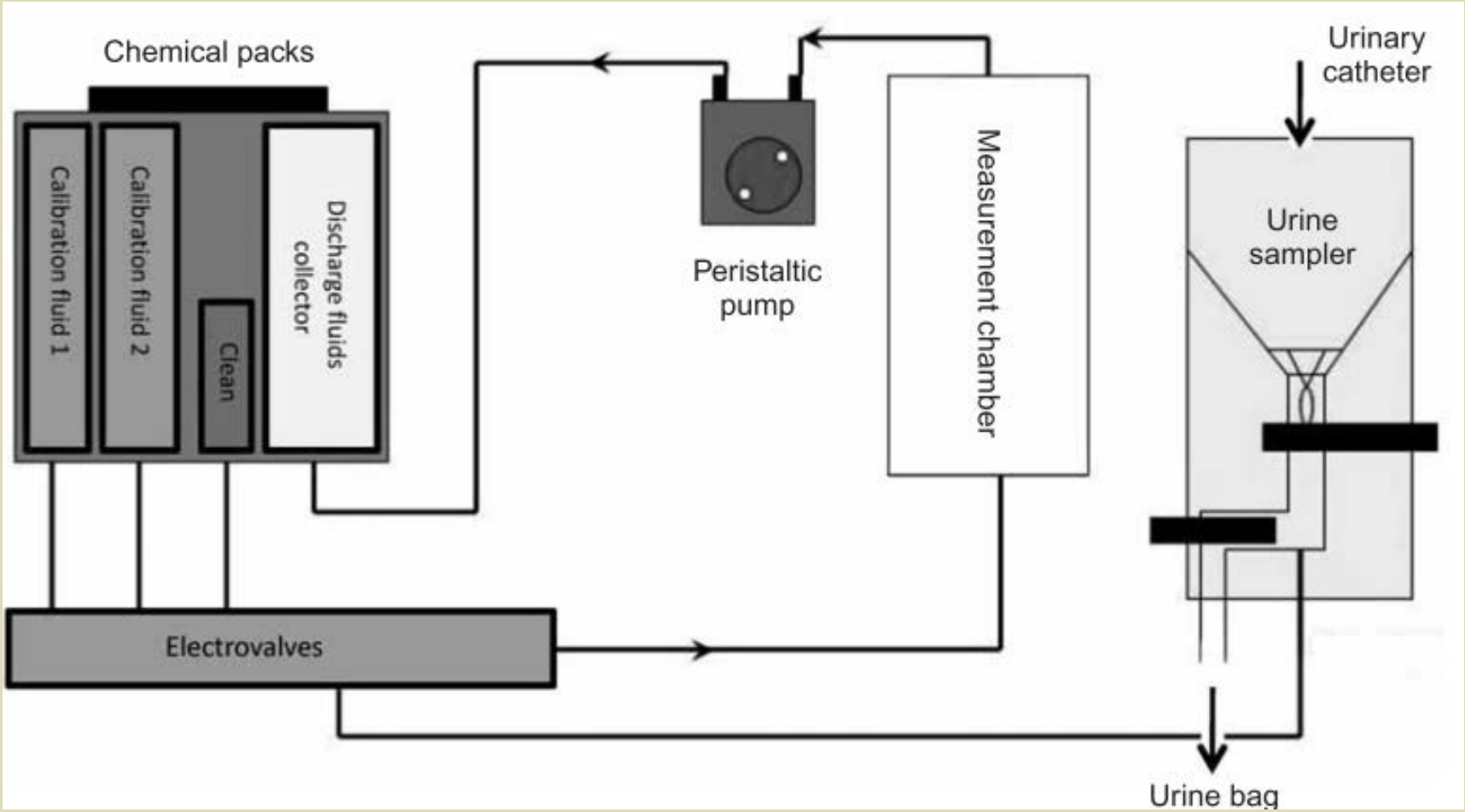

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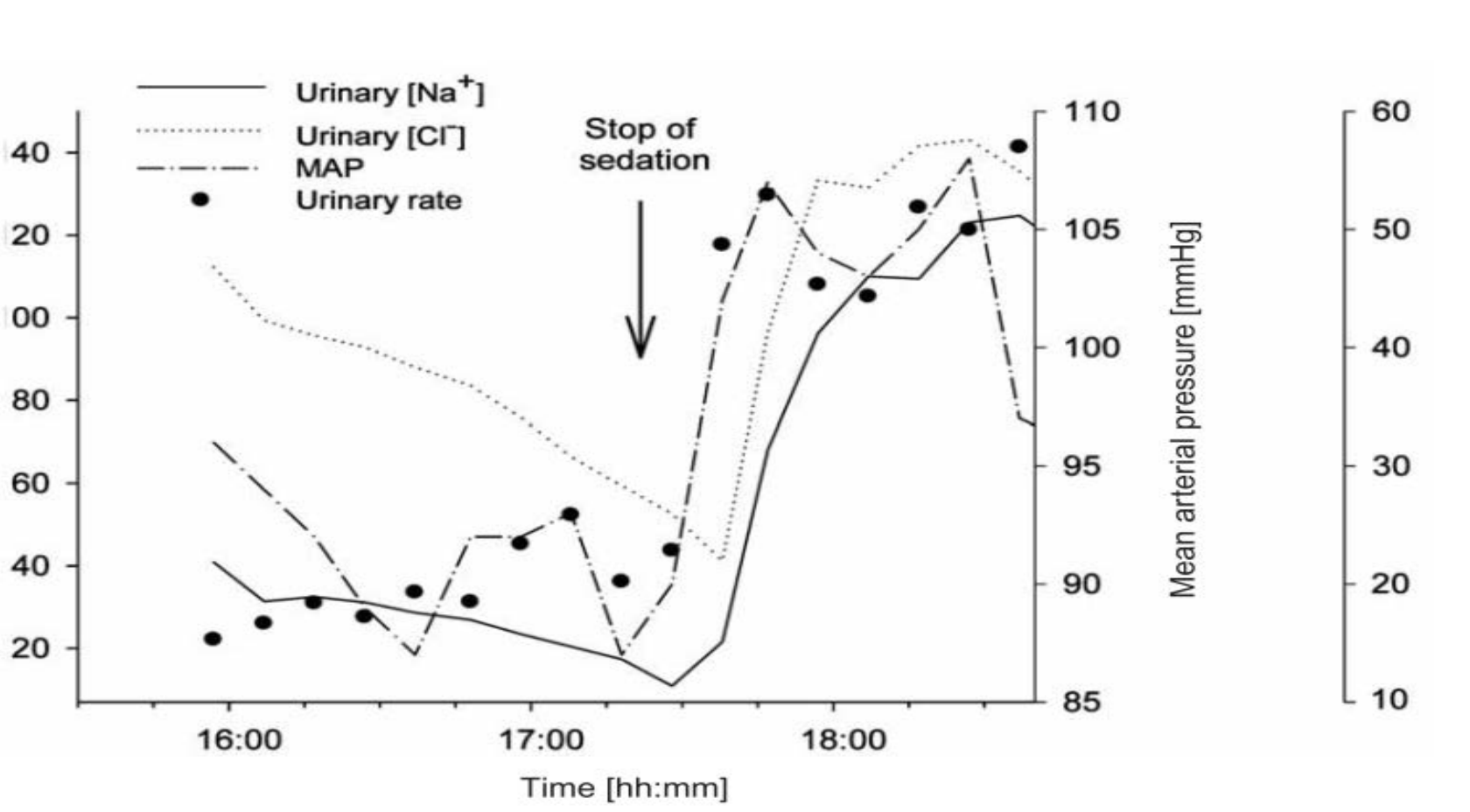

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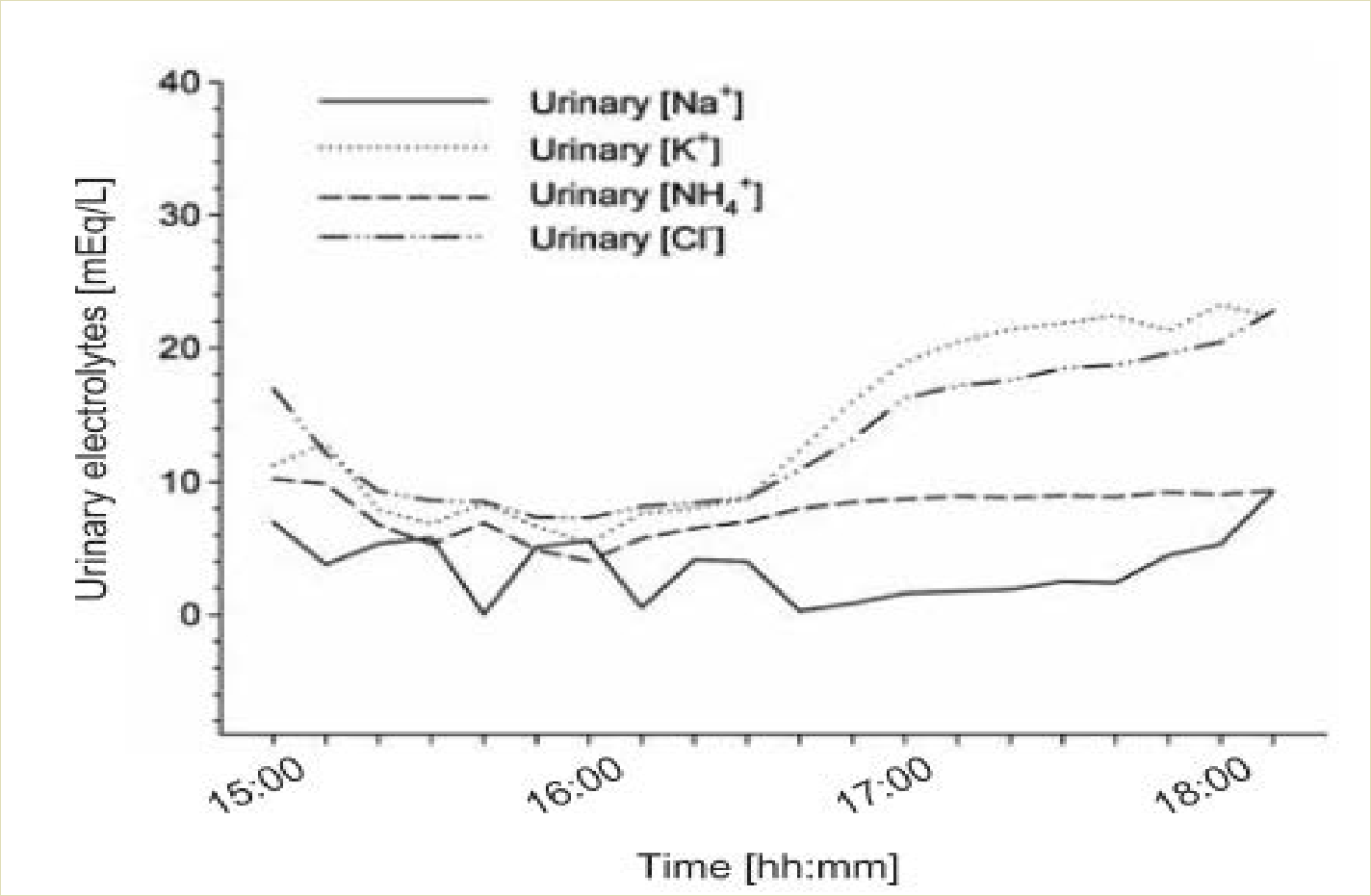
Kidney instant monitoring: a new analyzer to monitor kidney function

CAIRONI1, 2, T. LANGER1, P. TACCONE2, P. BRUZZONE2, S. DE CHIARA2, F. VAGGINELLI2, L. CASPANI2, C. MARENGHI2, L. GATTINONI



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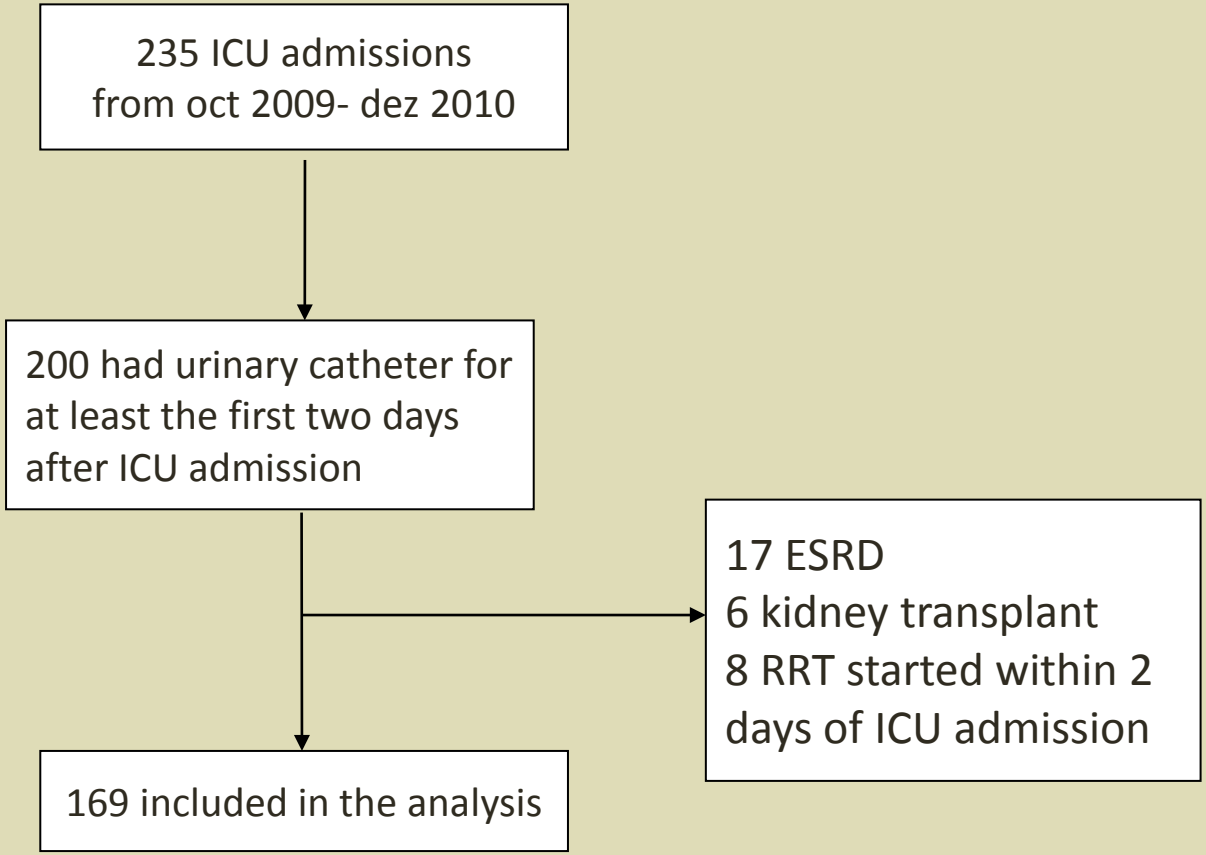
Monitoring of Urine Electrolytes in a Clinical ICU

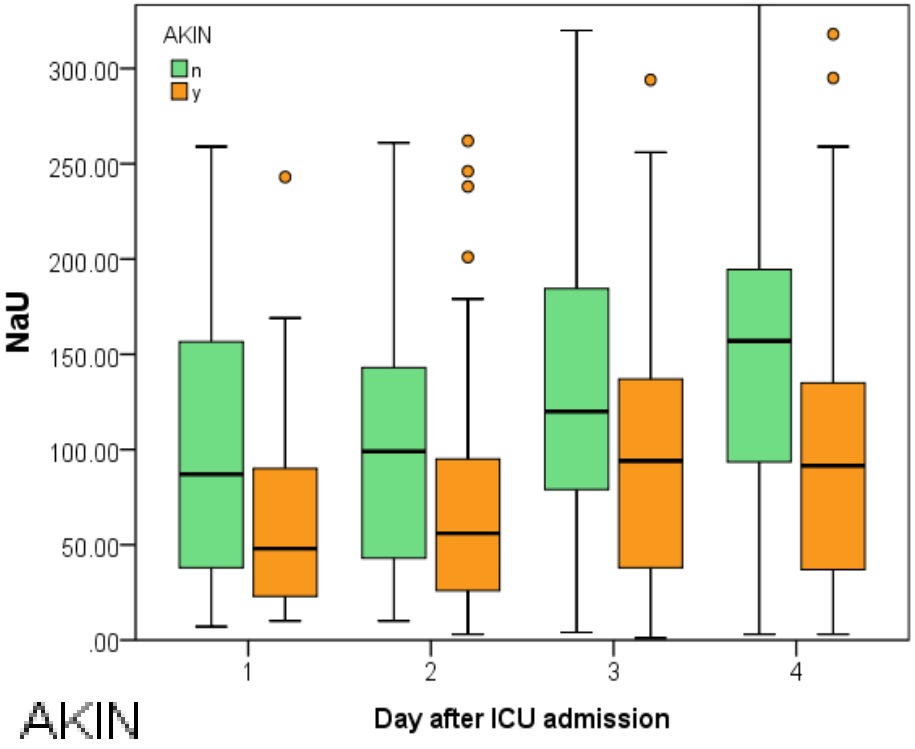
4 bedroom Clinical ICU

prospectively recorded daily blood and spot urinary electrolytes from patients with urinary catheters admitted to our ICU

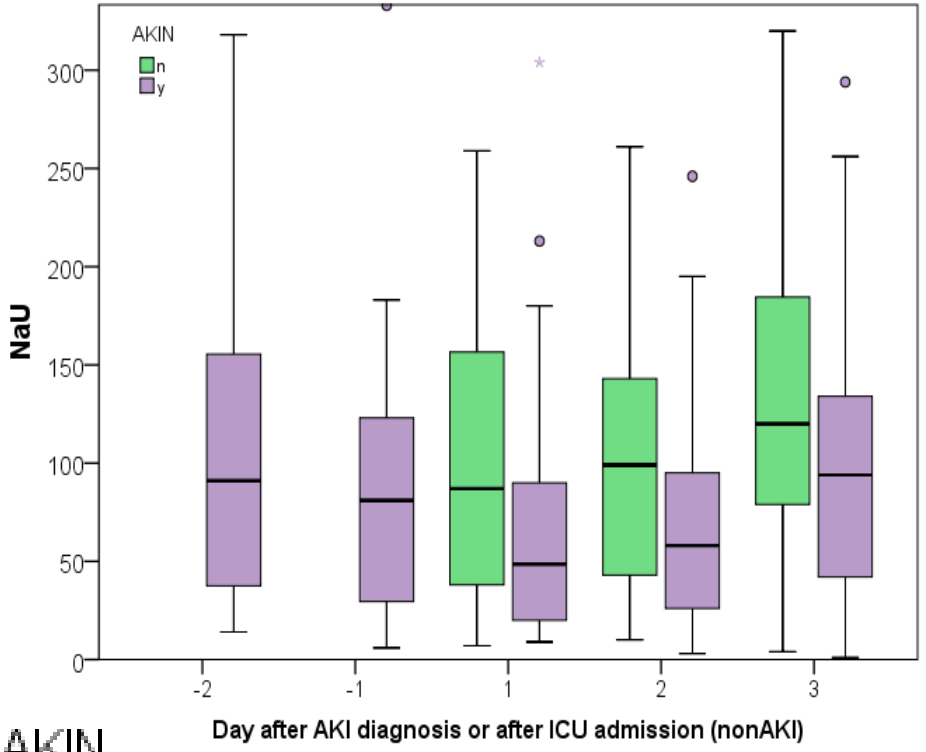


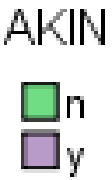
Urine Na

All patients after ICU admission



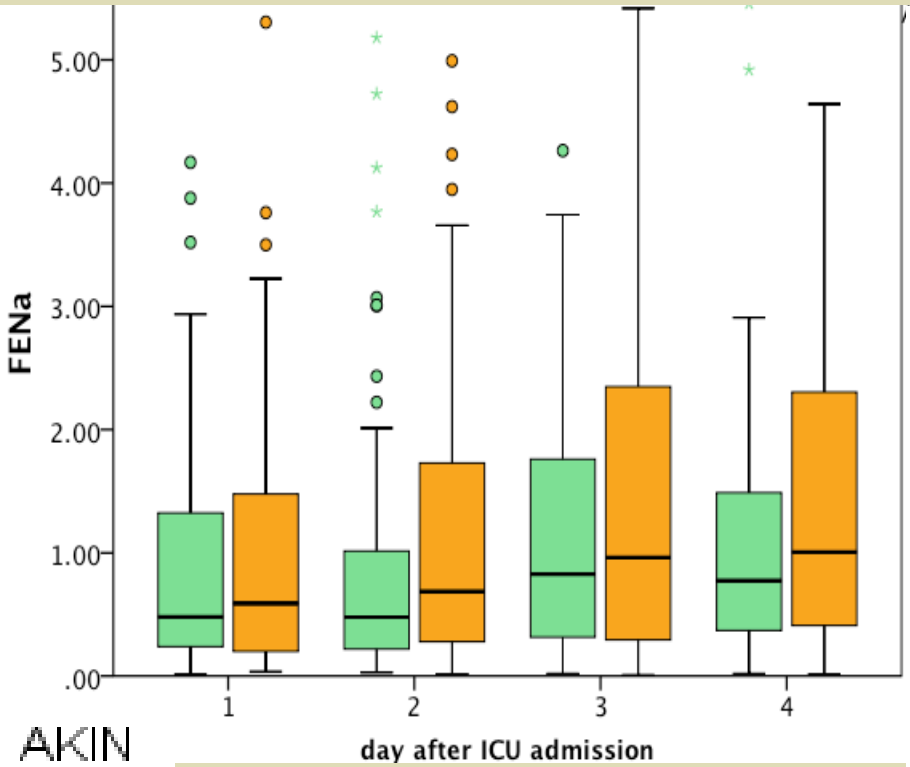
After AKI diagnosis or after ICU admission for non-AKI



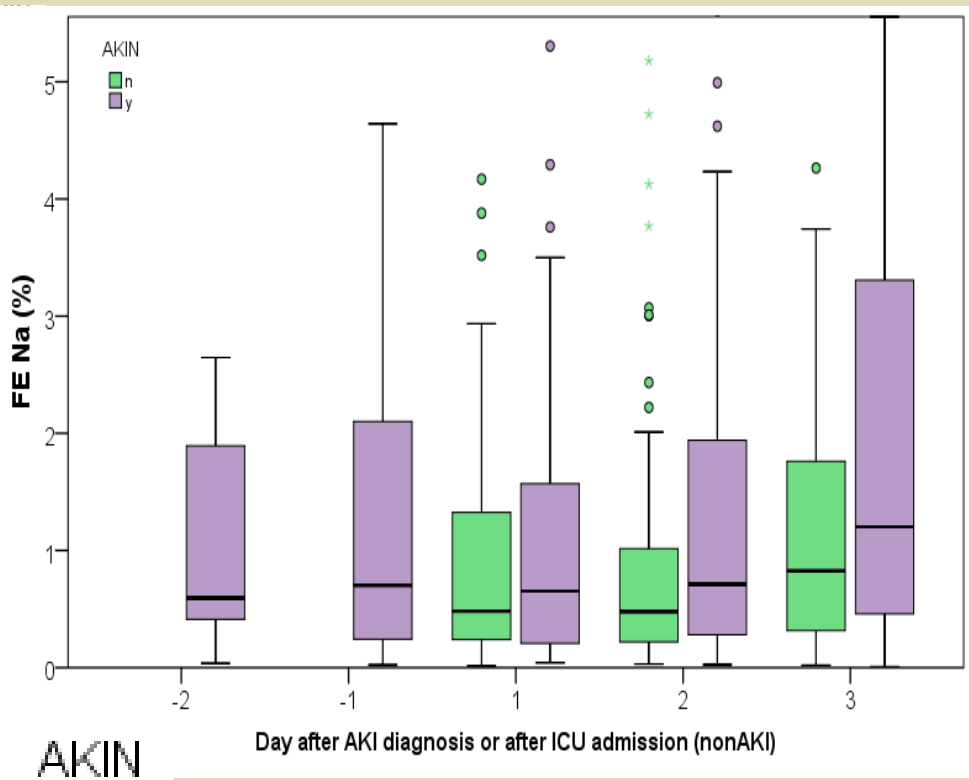


FE Na

All patients after ICU admission

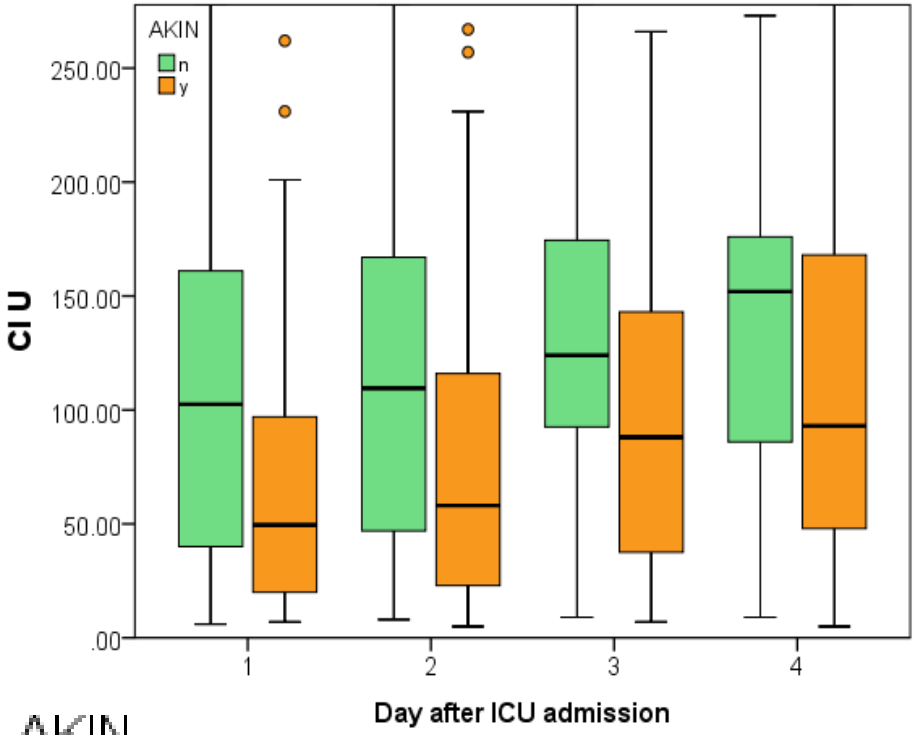


After AKI diagnosis or after ICU admission for non-AKI



Urine Cl

All patients after ICU admission



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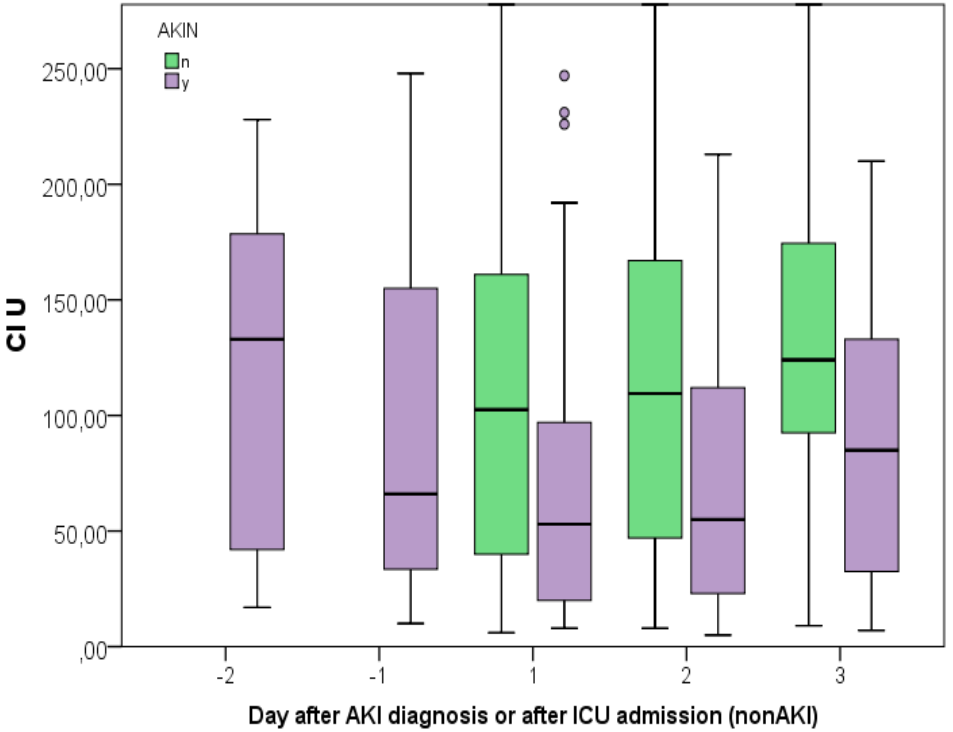
After AKI diagnosis or after ICU admission for non-AKI



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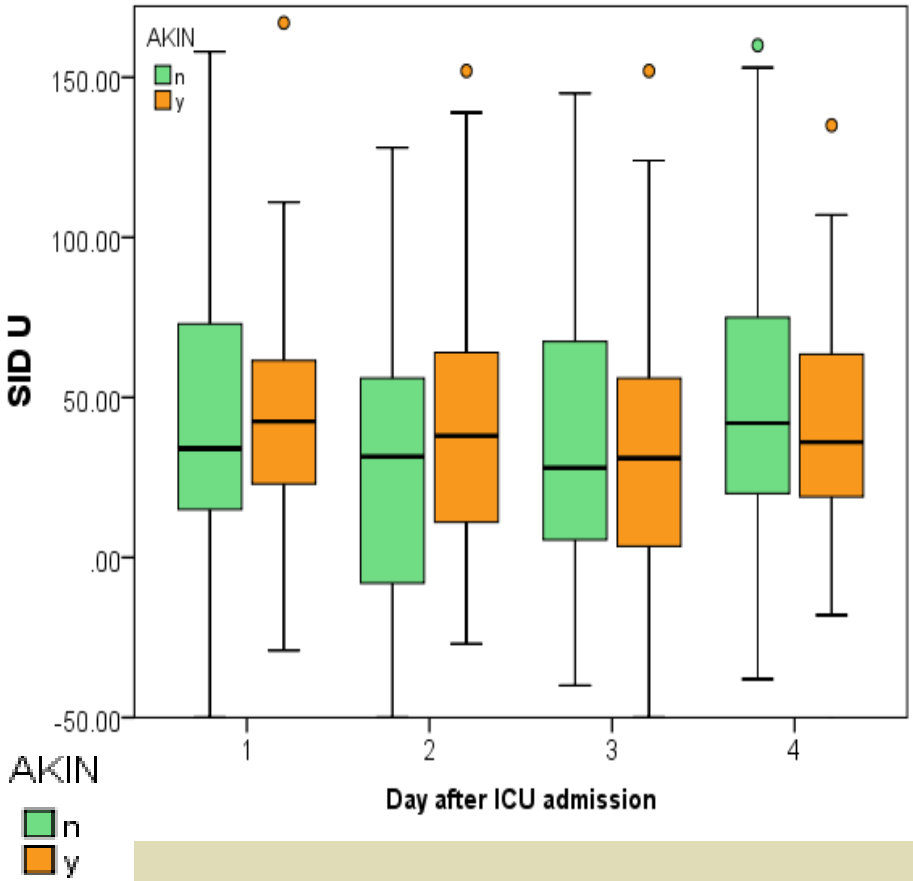
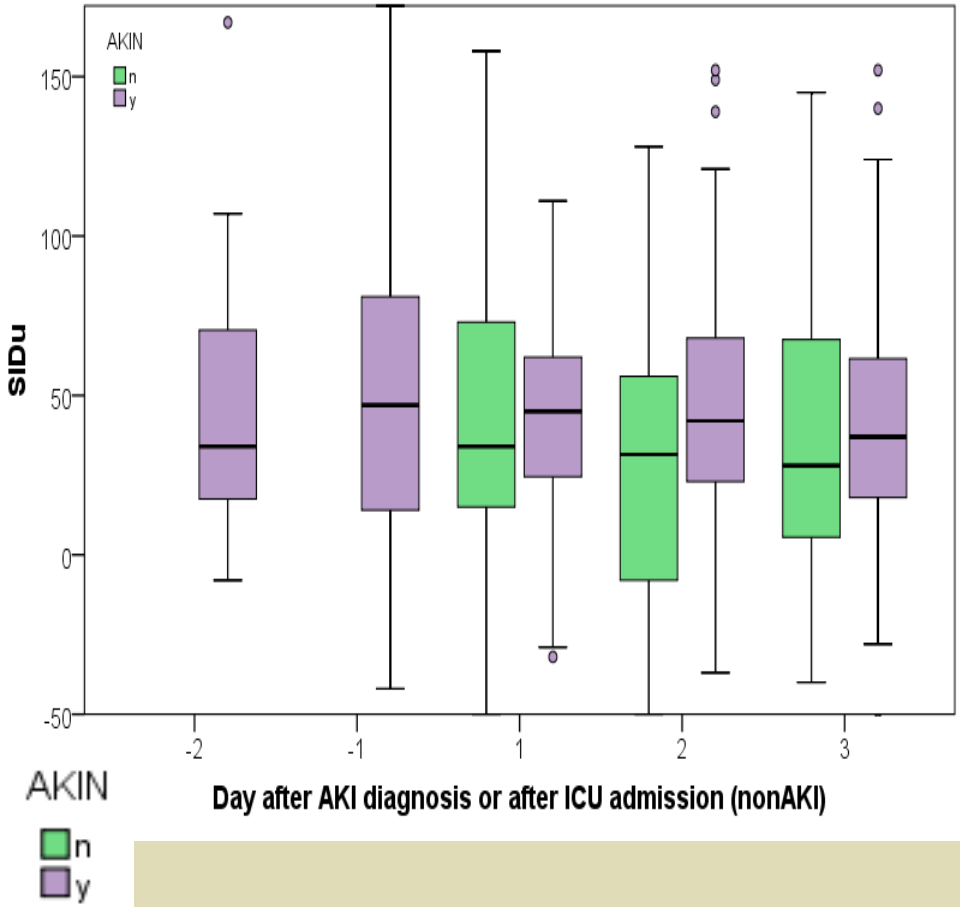
All patients after ICU admission



After AKI diagnosis



Summary

- Potential benefits of assessing urinary electrolytes
- Concept of functional and histopathological to distinguish between transient AKI
- Fluid administration: patient vs renal responsiveness
- Role of urine electrolytes as a useful tool in the interpretation of acid-base imbalances
- SIDu as a monitor of tubular acidifying capacity and early inability of urinary acidification in AKI

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