Roma, 26-4-2019

AKI
Past, Present and Future

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University of Padova – Chair of Nephrology
Department of Nephrology Dialysis and Transplantation
International Renal Research Institute
St. Bortolo Hospital, Vicenza - Italy

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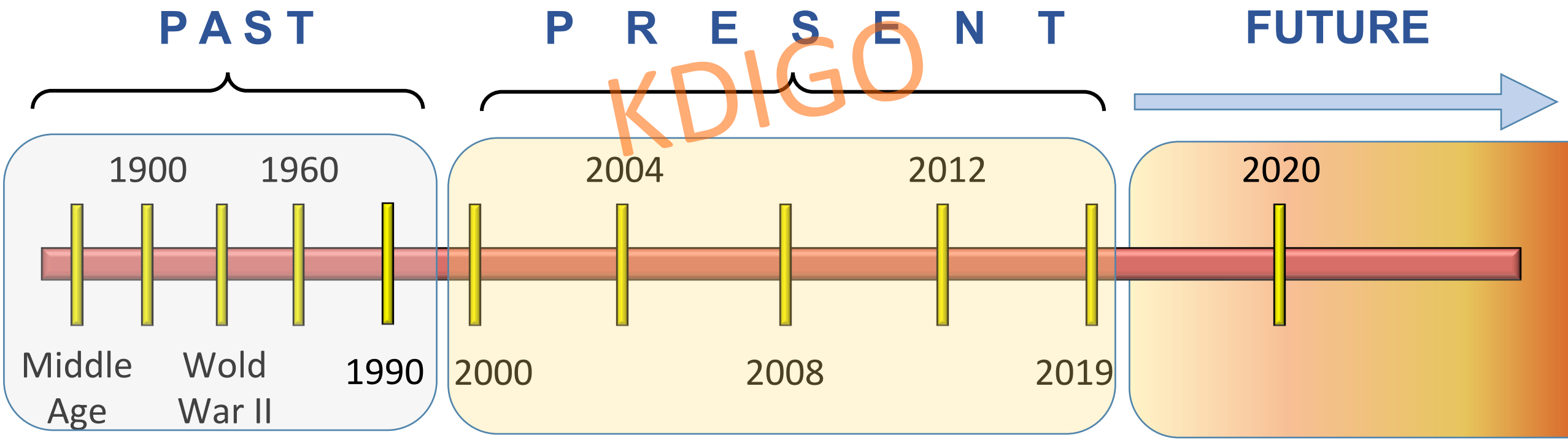
DISCLOSURES

Consultant: Astute, Baxter, OCD, Medtronic, Asahi Medical, Jaffron, Biomerieux

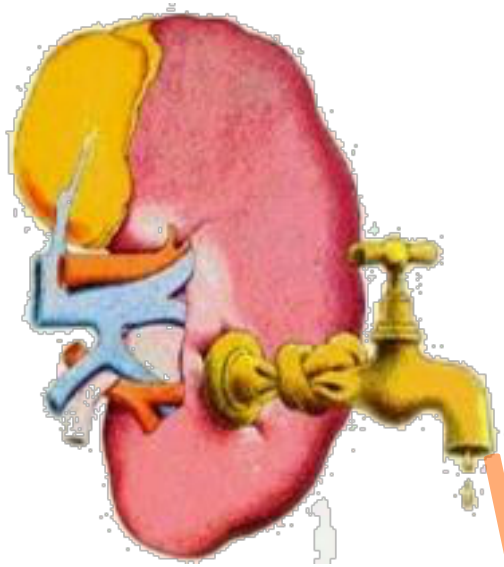
Advisory Board: GE, Kaneka, Cytosorbents,

Speaker Bureau: Toray, Estor, FMC, B.Braun

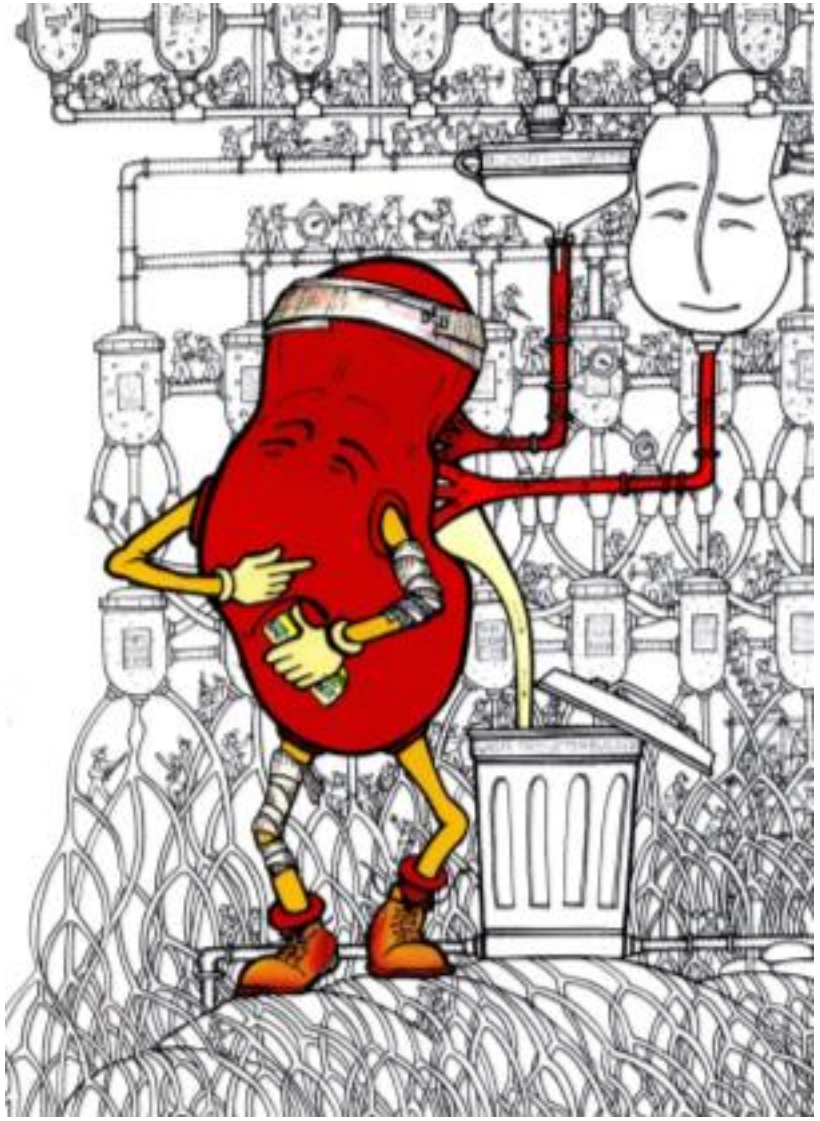
AKI
Past, Present and Future



AKI in 1900: the clinical diagnosis



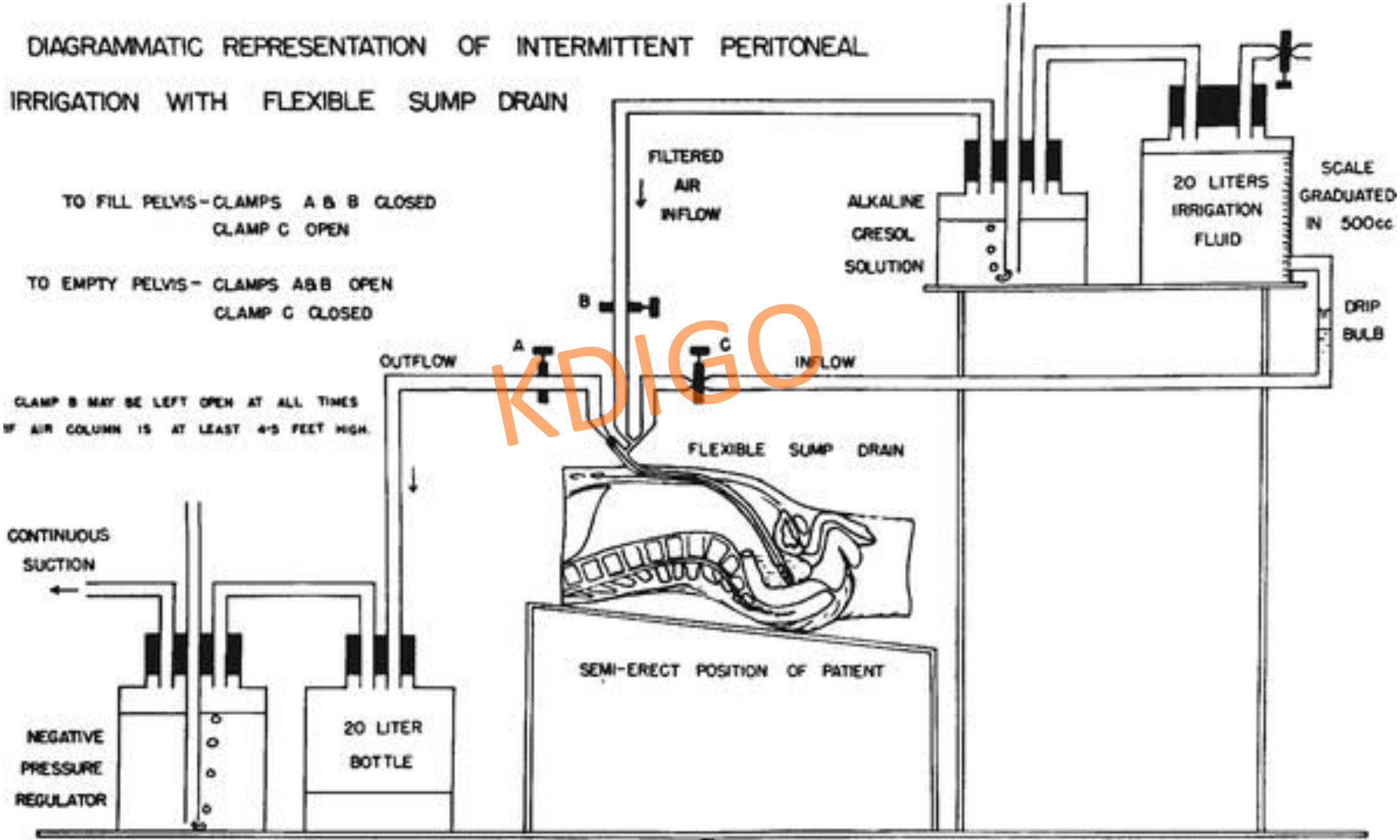
KDIGO



ARF was diagnosed from signs and symptoms such as oliguria, fatigue, vomiting, GI bleeding.

«Disorders of the Renal Glands»

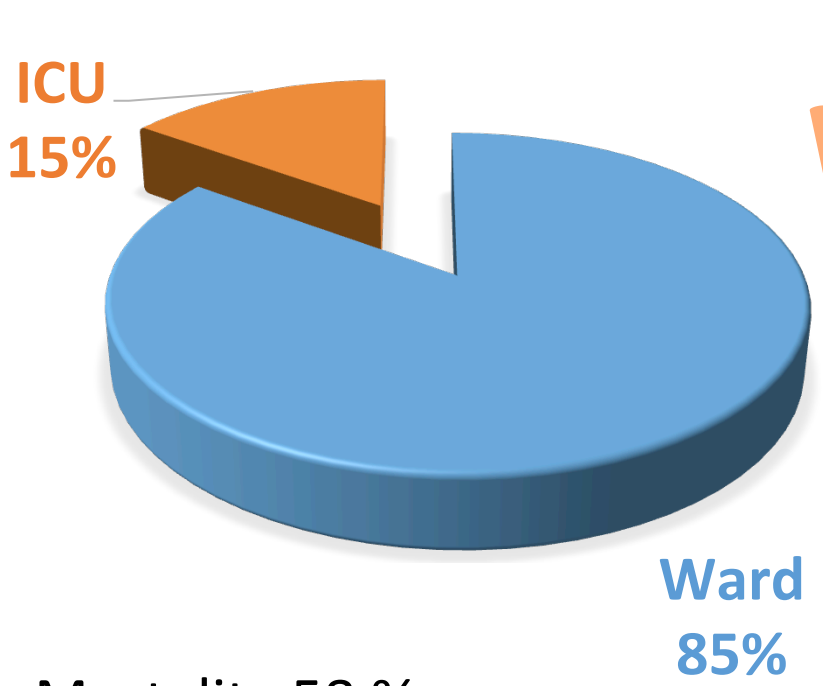
Acute Peritoneal Dialysis



AKI: Changing Pattern

1970-1980

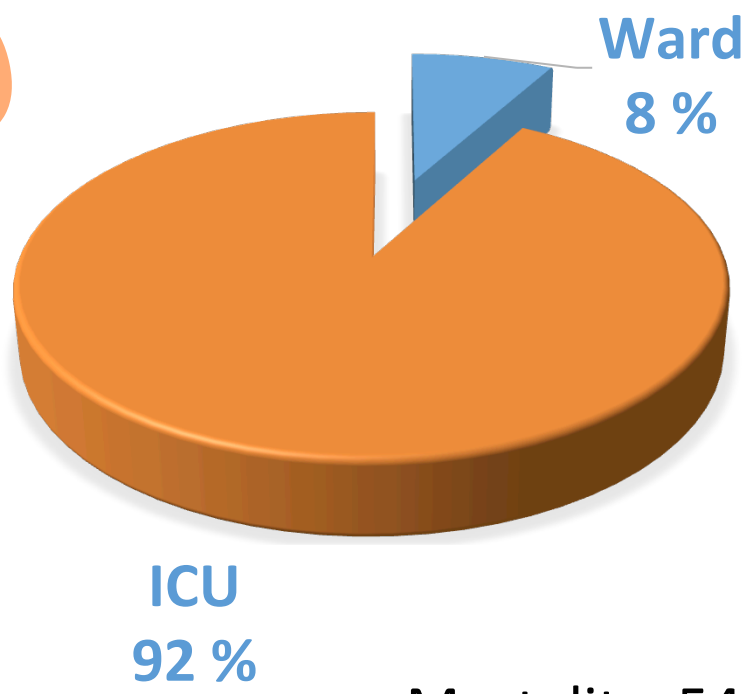
Total number of incident cases = 156



Mortality 58 %

1980-1990

Total number of incident cases = 925

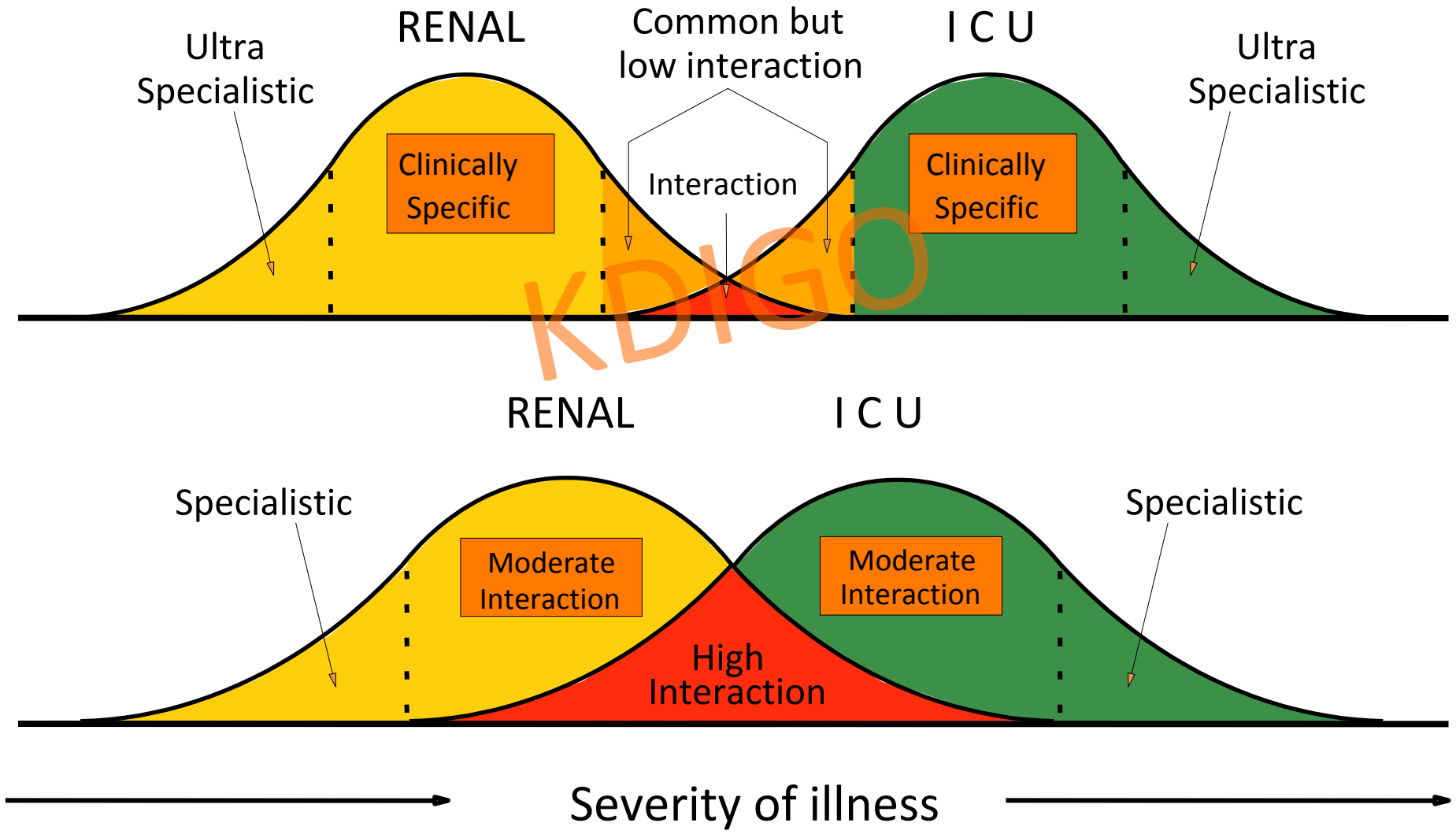


Mortality 54 %

KDIGO

Critical Care Nephrology

FROM SPECIALITY-ORIENTED TO PATIENT-ORIENTED



Nephrology
Dialysis
Transplantation

Claudio Ronco and Rinaldo Bellomo

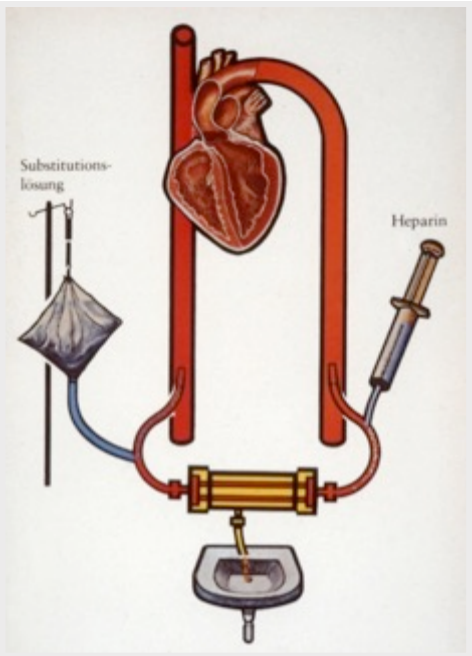
Critical Care Nephrology: The time has come

editorial entitled "Critical Care Nephrology: the time has come". *It was not so long ago that the term* "critical care nephrology" *was unknown or at least obscure to most physicians both in the nephrological and in the intensive care community; a push was definitely needed to move forward. Today, a few years later, a simple internet query on critical care nephrology leads to more than 157,000 references. For this reason I have decided to dedicate this*

acquired expertise and training in both areas.

In either case, by the late nineties, the formal development of a specialty field called Critical Care Nephrology was seen as something whose time had come.

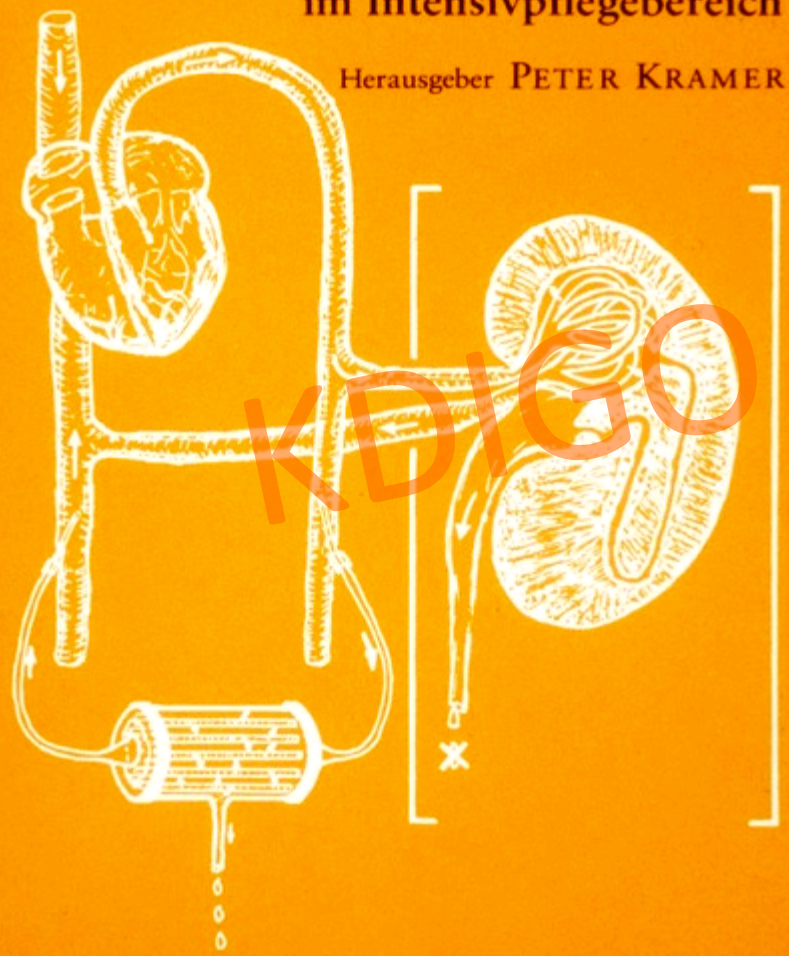
Why had this conceptually simple and effective approach not been developed before? Several issues were raised on the occasion of the First International Course on Critical Care Nephrology held in Vicenza in



Arterio-venöse Hämofiltration

Nieren-(Ersatz)-Therapie im Intensivpflegebereich

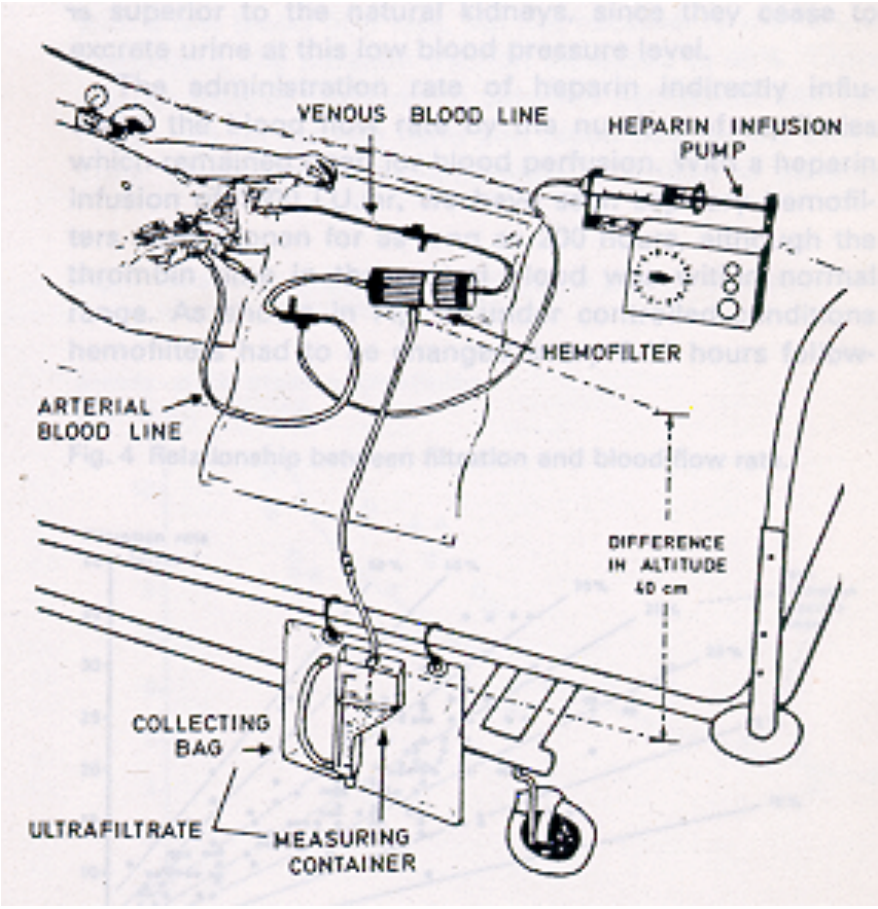
Herausgeber PETER KRAMER



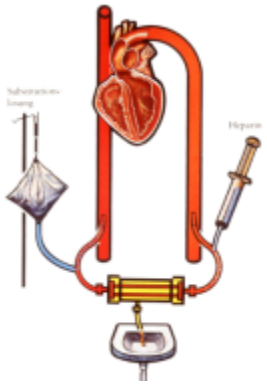
Vandenhoeck & Ruprecht Göttingen · Zürich

P. Kramer, G. Kaufhold, H.J. Gröne, W. Wigger, J. Rieger, D. Matthaei, T. Stokke, H. Burchardi and F. Scheler

University Hospital
Department of Internal Medicine
Division of Nephrology
Göttingen, Federal Republic of Germany



Beginning of CRRT

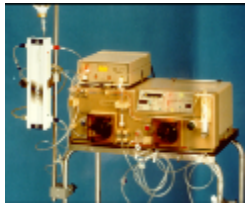


1977

First CAVH
In Gottingen
and
First CAVH
in Vicenza

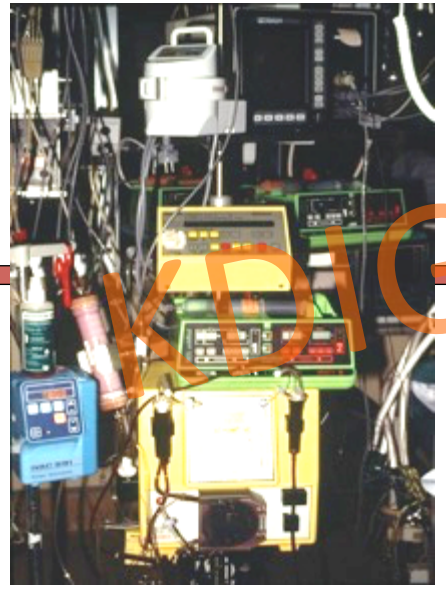
CAVHD
CAVHDF
Fluid
Balance
systems

1983



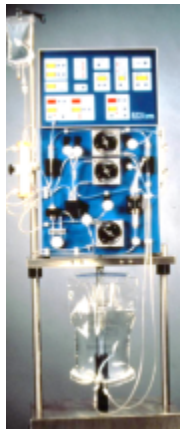
1986

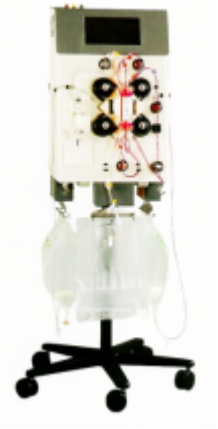
CVVH
CVVHD
and
Adoptive
Technology



First
generation
CRRT
machines
CVVH
CVVHD
CVVHDF

1990





1995

Second
generation
CRRT
machines
CVVH
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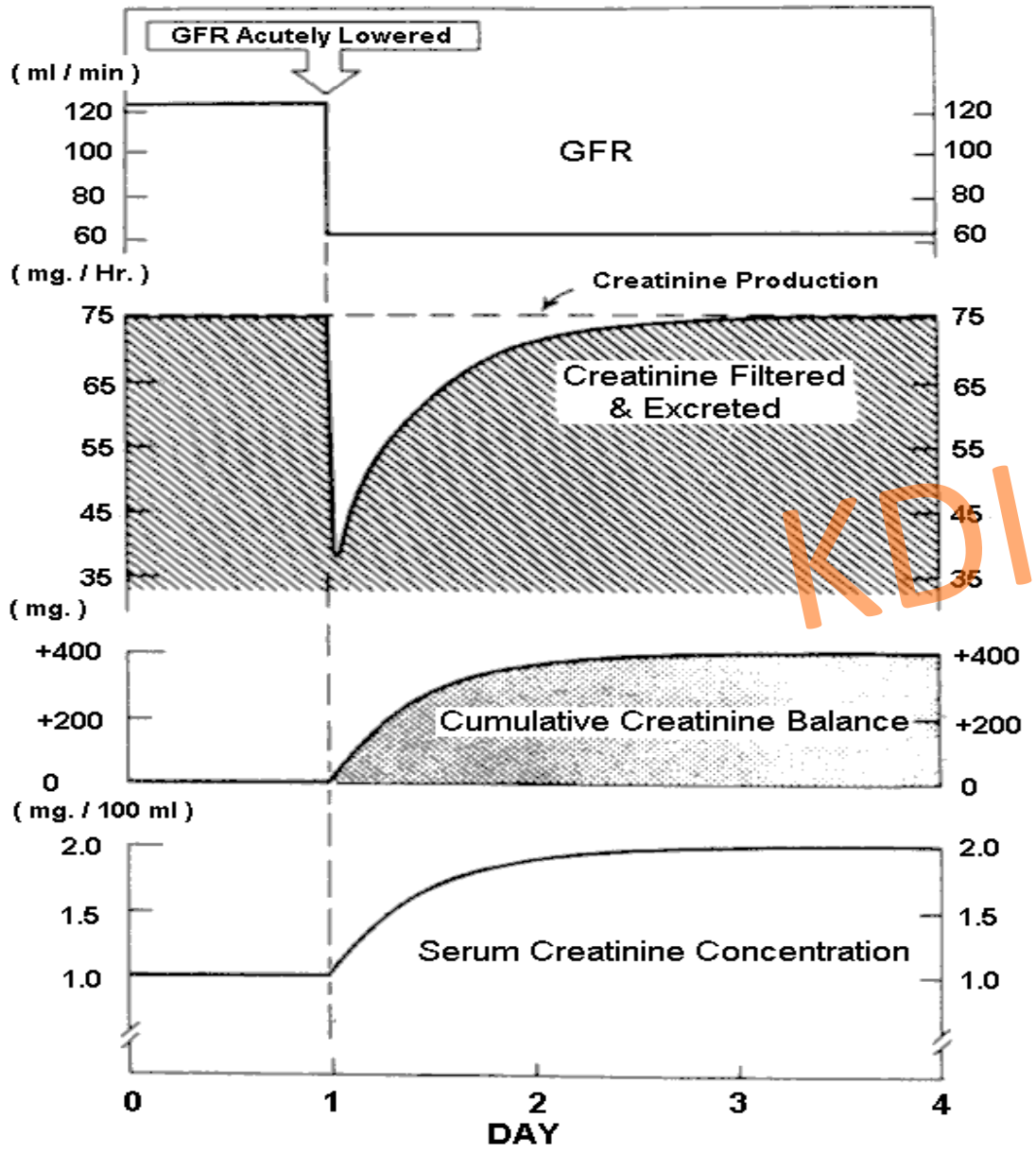
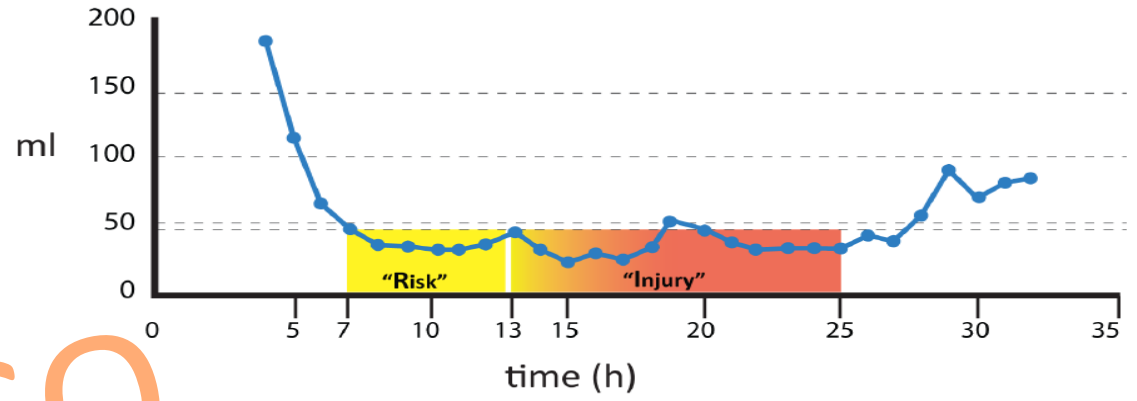
CVVHDF

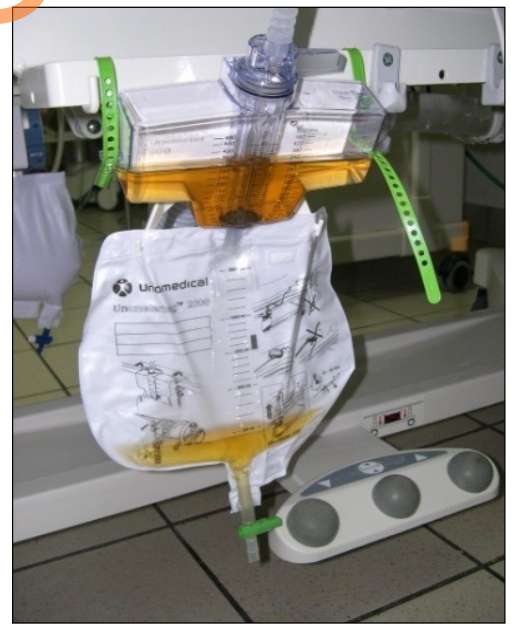
Creatinine Kinetics

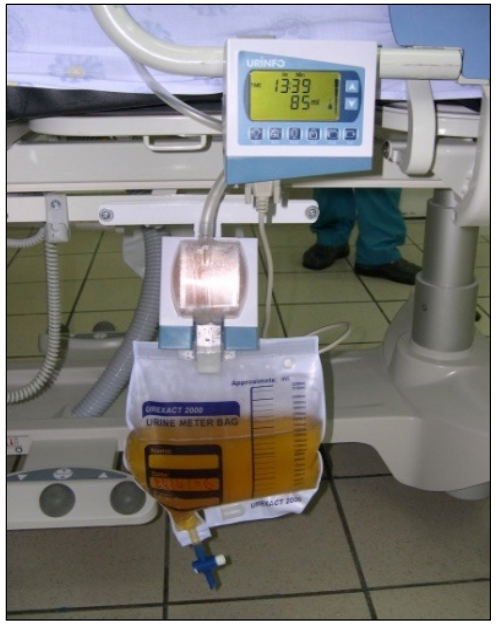


Urine Output

Accurate Real-Time Continous RIFLE Criteral Monitoring







Over 30 definitions of AKI/ ARF existed in the literature

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3. Creat>= 0.5 mg/dL
4. Creat >= 1.7 mg/dL
5. Creat >= 1.5 mg/dL
6. Creat >= 2 mg/dL
7. Creat>= 2.1 mg/dL and x 2
8. Creat >= 177μmol/L Δ>62μmol/L
9. Creat > 200μmol/L (2.36 mg/dL)
10. Creat> 3.2 mg/dL or x 2
11. Creat>5 mg/dL or K > 5.5
12. RIFLE
13. Creat increase >= 25%
14. Creat increase >= 50%
15. Creat increase >= 100%
16. ΔCr72h >0μmol/L
17. ΔCr72h >25μmol/L
18. ΔCr72h >44μmol/L
19. ΔCr72h >50μmol/L
20. ΔCr72h >100μmol/L
21. Cockcroft-Gault Cr Cl < 30 mL/min
22. Cockcroft-Gault Cr Cl 30–60 mL/min
23. ΔCockcroft-Gault72hr <0%
24. ΔCockcroft-Gault72hr <-15%
25. ΔCockcroft-Gault72hr <-25%
26. ΔCockcroft-Gault72hr <-50%
27. MDRD: 50% change in GFR
28. UO <100 q 8hr
29. U α1-microglob
30. U β2- microglobulin
31. U N-acetyl- β-D-glucosaminidase
32. U gluthation transferase-π
33. U gluthation transferase- α
34. NGAL
35. RRT

AKI situation in Y2K

Epidemiology: Uncertain or even unknown

Definition: Multiple discordant definitions

Diagnosis: Urine output and Serum Creatinine

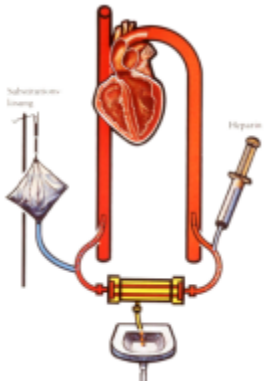
Case mix: Patients with multiple organ involvement

Mechanisms: Undefined for most clinical conditions

Therapy: CRRT/IRRT, Dose, Timing, Modality, undefined

Outcome: Basically uncanged compared to the past

Beginning of CRRT



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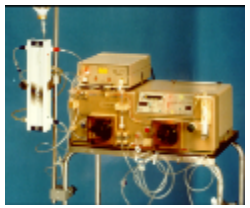

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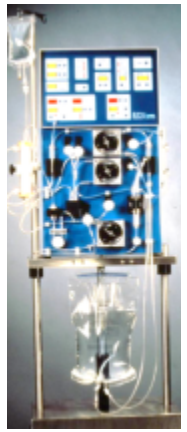
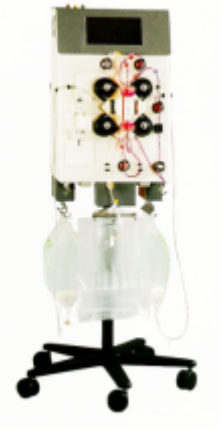




1995

Second
generation
CRRT
machines
CVVH
CVVHD
CVVHDF

KDIGO

Study on Dose & Adequacy 35 ml/Kg/ h.

2000


THE LANCET

Articles

Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial

The Birth of

ADQI

2000

Kidney International, Vol. 62 (2002), pp. 1855–1863

The first international consensus conference on continuous renal replacement therapy

JOHN A. KELLUM, RAVINDRA L. MEHTA, DEREK C. ANGUS, PAUL PALEVSKY, and CLAUDIO RONCO, for the ADQI WORKGROUP[1]

Departments of Critical Care Medicine and Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA; Department of Medicine, University of California, San Diego, CA; Veterans Administration Pittsburgh Healthcare System, Pittsburgh, PA; Department of Nephrology, St. Bortolo Hospital, Vicenza, Italy; and Renal Research Institute, New York, NY, USA

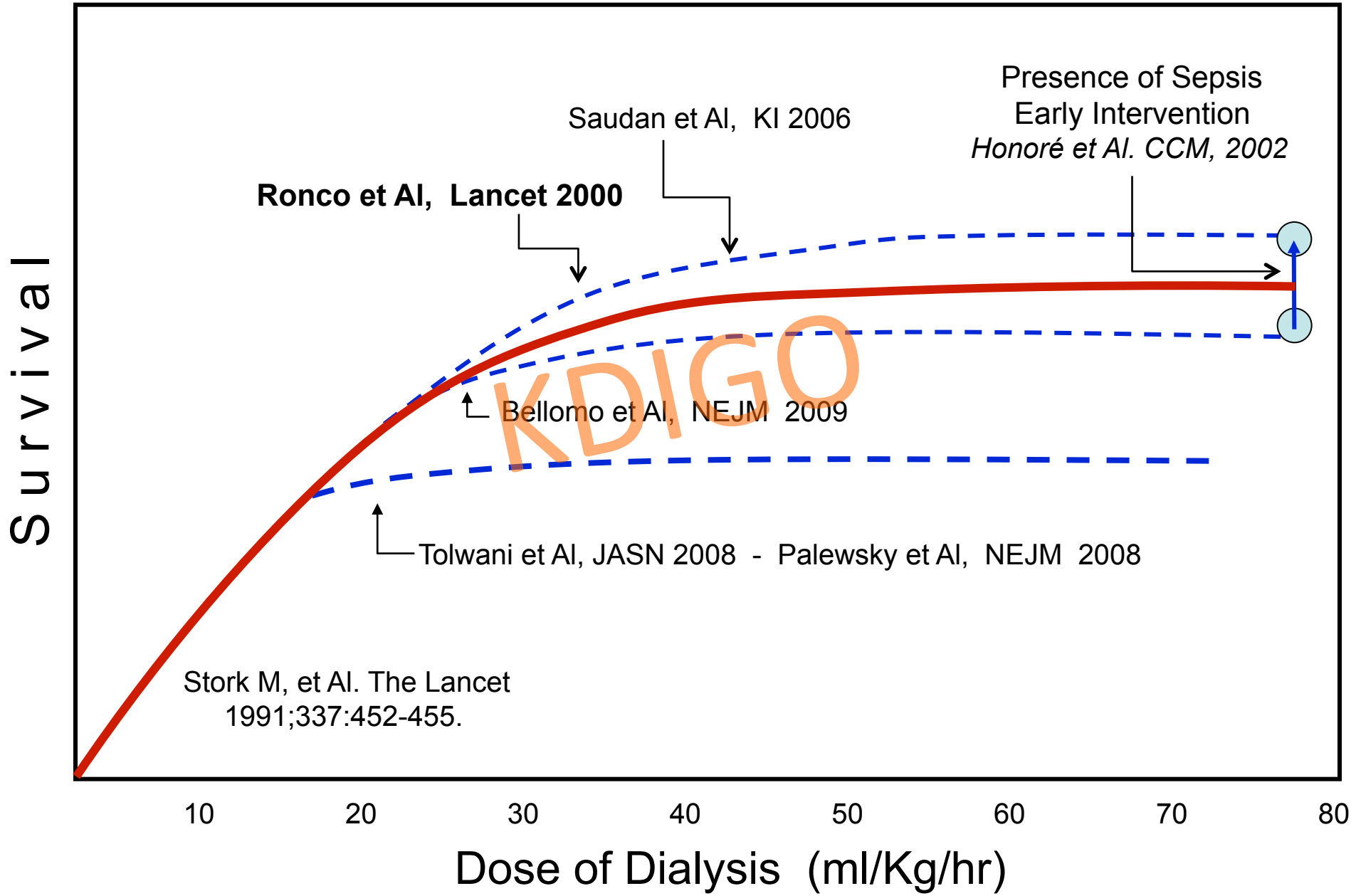
The first international consensus conference on continuous renal replacement therapy.

Background. Management of acute renal failure (ARF) in the critically ill is extremely variable and there are no published standards for the provision of renal replacement therapy in this population. We sought to review the available evidence, make evidence-based practice recommendations, and delineate key questions for future study.

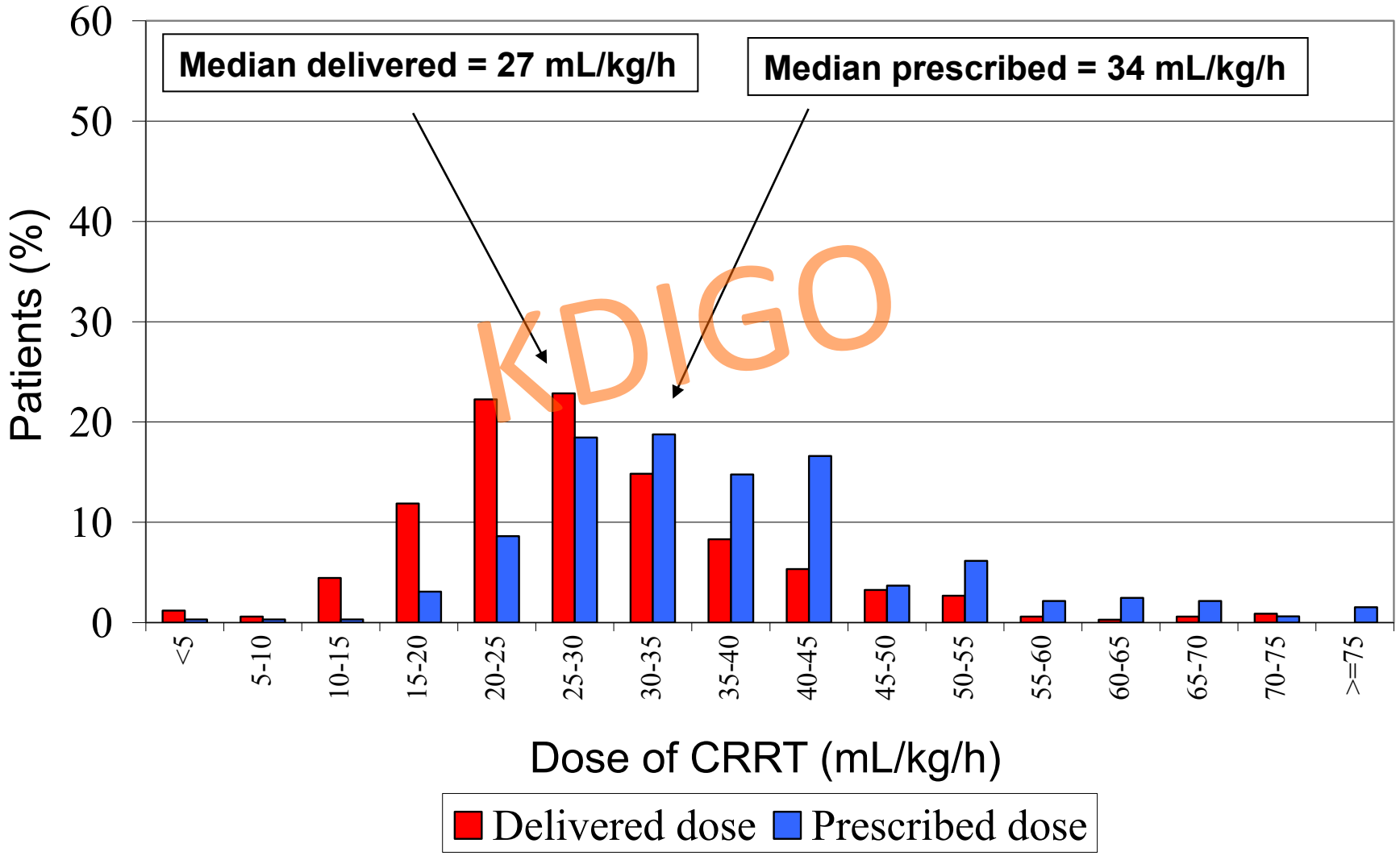
Methods. We undertook an evidence-based review of the

placement therapy (CRRT) [3] and use of this therapy is increasing worldwide. However, there are no standard guidelines for the application of CRRT and practice patterns vary widely between individual centers. Results from recent clinical trials on selection of dialysis membranes [4–7] and dialysis dose [8, 9] provide important evidence to guide therapy. Yet important questions re-

AKI and CRRT

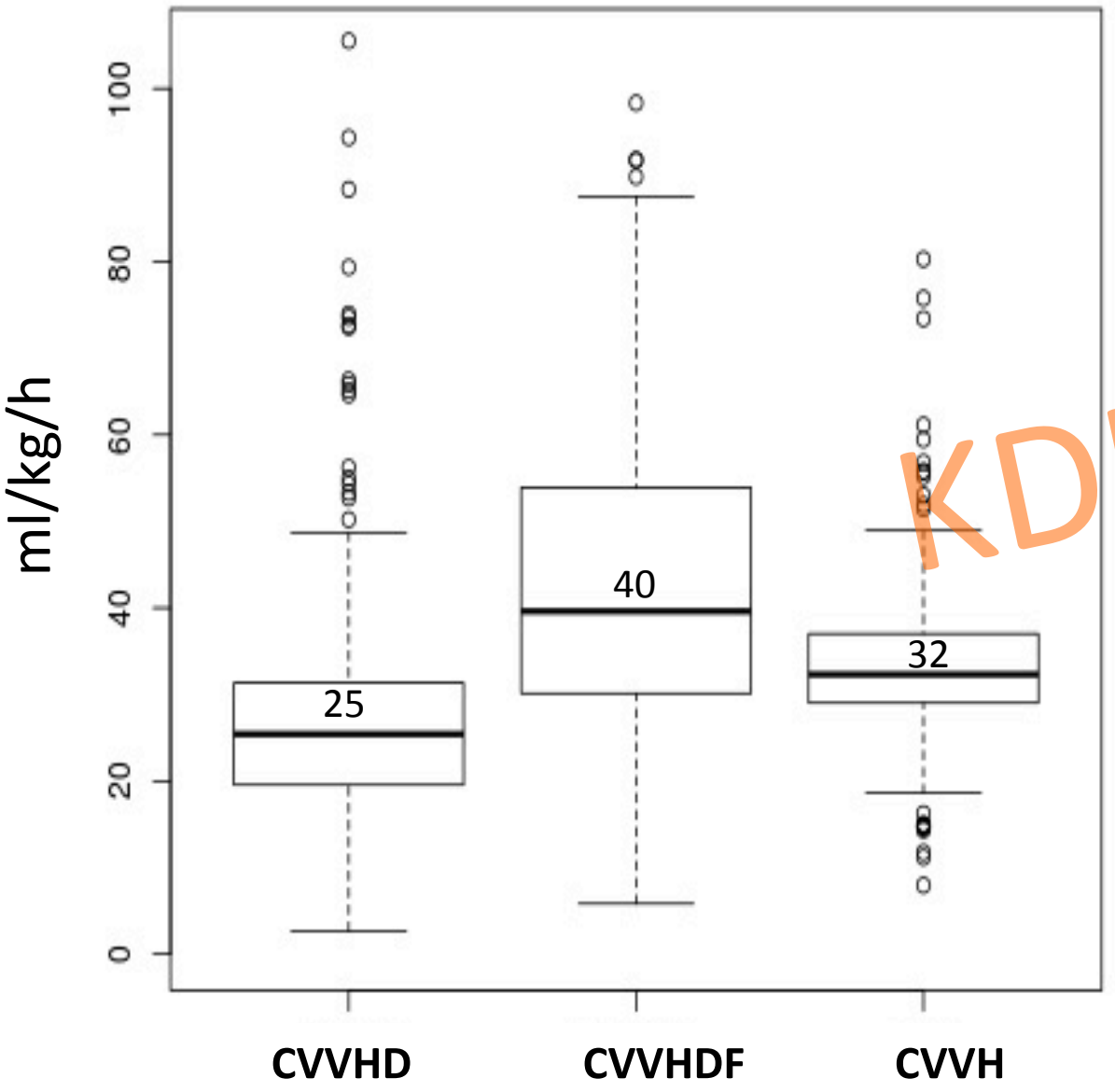

Survival
Presence of Sepsis
Early Intervention
Honoré et Al. CCM, 2002
Saudan et Al, KI 2006
Ronco et Al, Lancet 2000
KDIGO
Bellomo et Al, NEJM 2009
Tolwani et Al, JASN 2008 - Palewsky et Al, NEJM 2008
Stork M, et Al. The Lancet
1991;337:452-455.
10
20
30
40
50
60
70
80
Dose of Dialysis (ml/Kg/hr)

DoReMi Database (N=865)

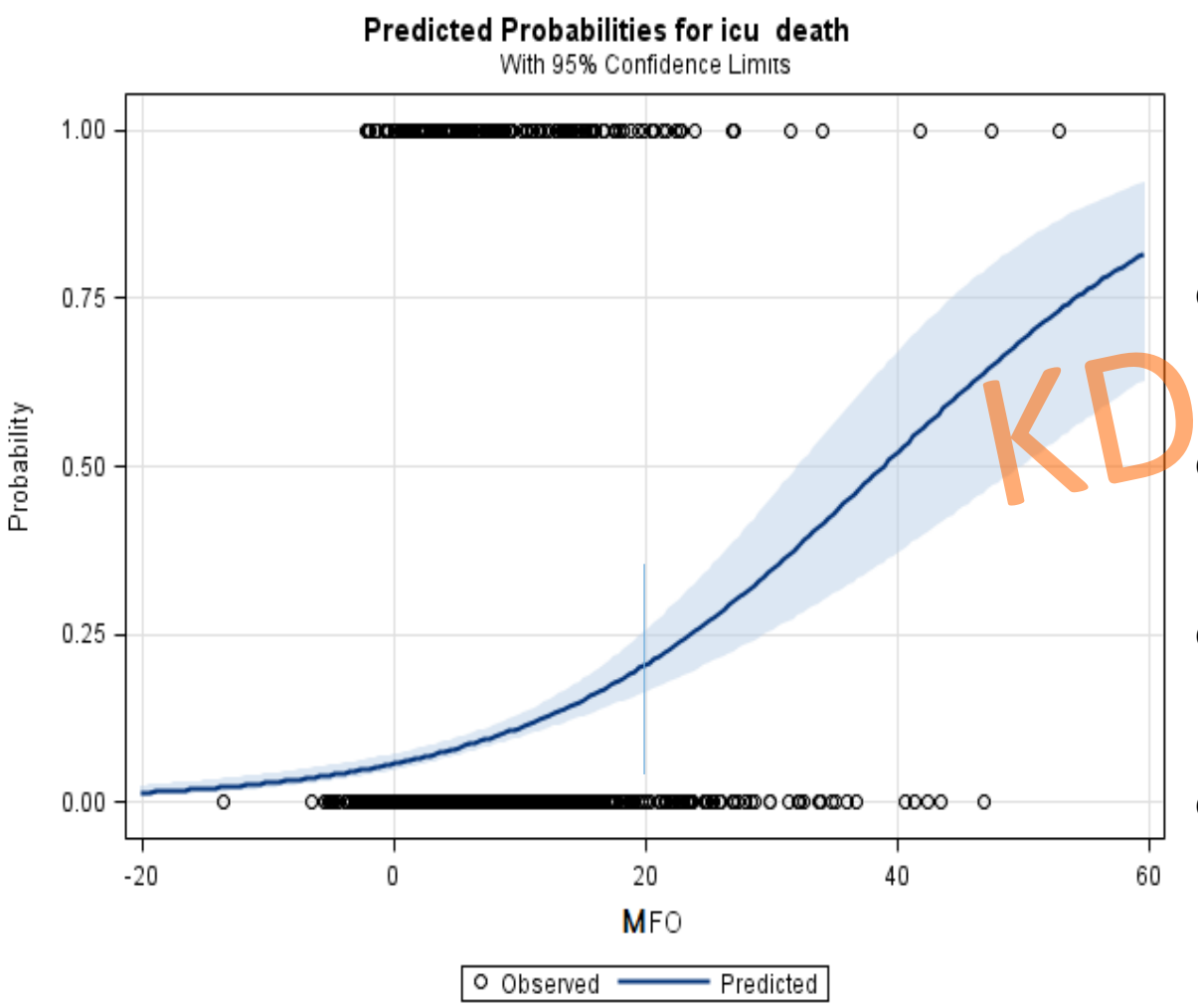


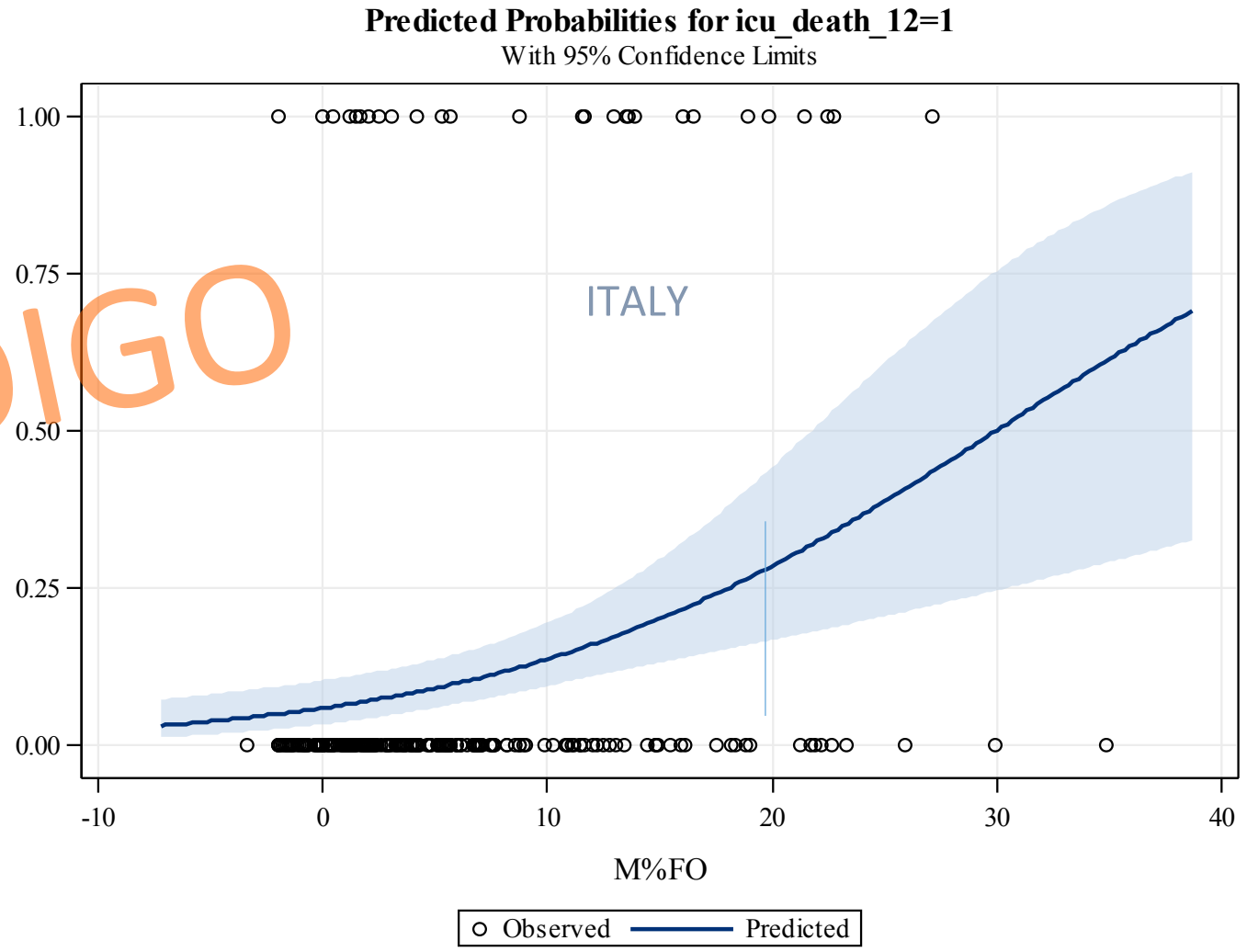
Delivered dose of CRRT

Delivery VS Prescription



Relationship between fluid accumulation and predicted probability of death



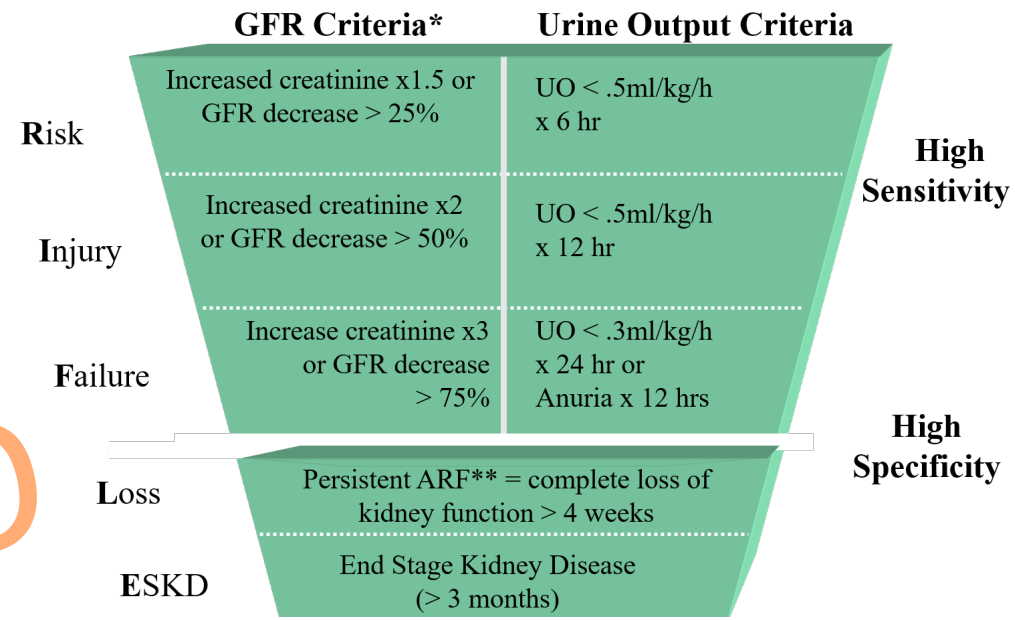


ITALY

ADQI 2

KDIGO

RIFLE



Research

Open Access

Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group

Rinaldo Bellomo[1], Claudio Ronco[2], John A Kellum[3], Ravindra L Mehta[4], Paul Palevsky[5] and and the ADQI workgroup[6]

[1]Department of Intensive Care and Medicine, Austin Health, Melbourne, Australia
[2]Department of Nephrology, San Bortolo Hospital, Vicenza, Italy
[3]Departments of Critical Care Medicine and Medicine, University of Pittsburgh Medical Center, and Renal Section, VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania, USA
[4]Department of Medicine, University of California, San Diego, California, USA
[5]Department of Medicine, University of Pittsburgh Medical Center, and Renal Section, VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania, USA
[6]For a complete list of authors, see Appendix 1

Corresponding author: Rinaldo Bellomo, rinaldo.bellomo@austin.org.au

From lab results to an organic classification

Over 30 definitions of AKI/ ARF in the literature

1. Creat Δ 0.1 mg/dL
2. Creat increase >0.5 mg/dL
3. Creat>= 0.5 mg/dL
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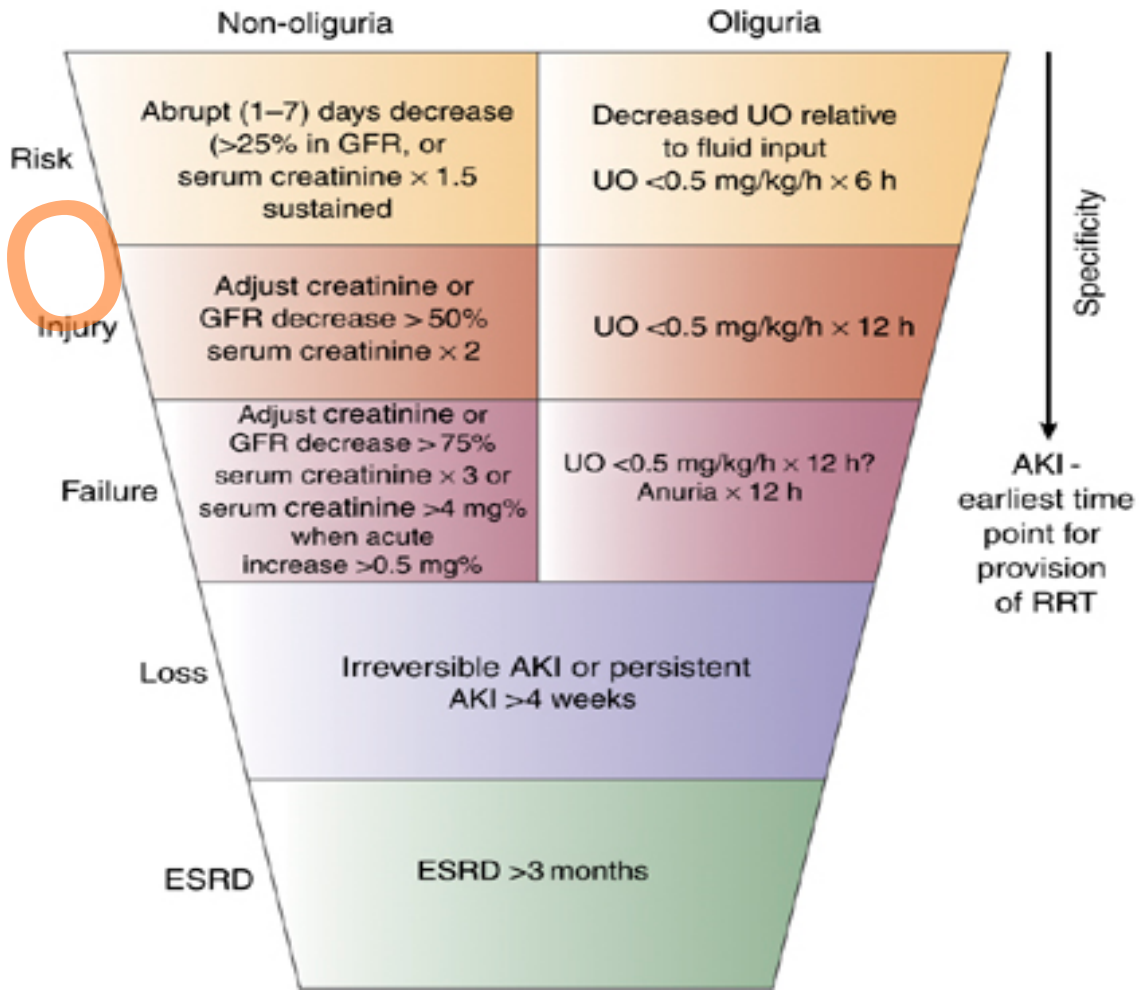
28. UO <100 q 8hr
29. U α1-microglob
30. U β2- microglobulin
31. U N-acetyl- β-D-glucosaminidase
32. U gluthation transferase-π
33. U gluthation transferase- α
34. NGAL
35. RRT
36. ….



ADQI ISN KDIGO ASN NKF

The Vicenza Retreat

A cooperative, international, multidisciplinary, exploratory plan to develop consensus for the approach to development of recommendations and guidelines for Acute Renal Failure

The "Vicenza retreat" has been organized as an independent body, supported by the participating societies and completely free from industrial funding.

The absolute freedom from any external input represents a warranty for the quality and the meaning of the decisional process.

The "Vicenza Retreat"

An independent Group

Acute Kidney Injury Network

KDIGO

The Birth of AKIN

Vicenza - Italy

Hotel Michelangelo-Arcugnano

September 22-23, 2004

RIFLE

	Cr/ GFR Criteria	Urine Output (UO) Criteria
Risk	Increased Cr x1.5 or GFR decreases >25%	UO <0.5 ml/kg/hr x 6 hr
Injury	Increased Cr x 2 or GFR decreases >50%	UO <0.5 ml/kg/hr x 12 hr
Failure	Increased Cr x 3 or GFR decreases >75% or Cr ≥ 4 mg/dl (with acute rise of ≥ 0.5 mg/dl)	UO <0.3 ml/kg/hr x 24 hr or anuria x 12 hr
Loss	Persistent ARF = complete loss of renal function for > 4 weeks	
ESRD	End Stage Renal Disease	

AKIN

	Cr Criteria	Urine Output (UO) Criteria
Stage 1	Increased Cr x1.5 or ≥0.3 mg/dl	UO <0.5 ml/kg/hr x 6 hr
Stage 2	Increased Cr x 2	UO <0.5 ml/kg/hr x 12 hr
Stage 3	Increased Cr x 3 or Cr ≥ 4 mg/dl (with acute rise of ≥ 0.5 mg/dl)	UO <0.3 ml/kg/hr x 24 hr or anuria x 12 hr

Patients who receive renal replacement therapy (RRT) are considered to have met the criteria for stage 3 irrespective of the stage that they are in at the time of commencement of RRT.

From lab results to an organic classification

ADQI, AKIN & KDIGO definitions of AKI

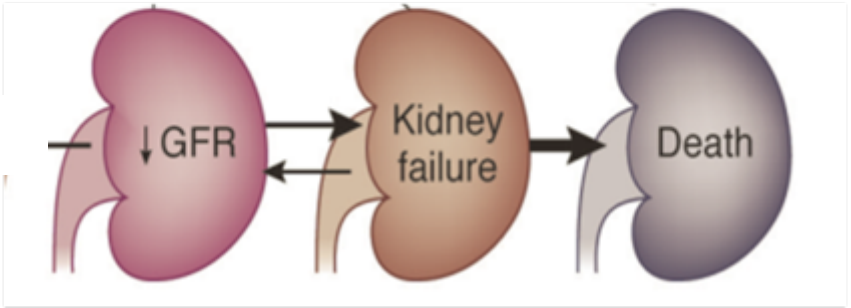
ADQI group (2004):	AKIN (2007):	KDIGO (2012):
Definition of AKI		
Abrupt (1-7 days) ↓ in renal function from base line	Abrupt (within 48 h) ↓ in renal function from base line	Abrupt (hours-days) ↓ in renal function from base line
Definition of decrease in renal function		
- ↑ in SCr of 0.5 mg/dL or more **or** - ↑ in SCr **1.5**-fold from baseline **or** - ↓ UO < 0.5 mL/kg/h for >6 h **or** - ↓ GFR > 25%	- ↑ in SCr of 0.3 mg/dL or more **or** - ↑ in SCr **1.5**-fold from baseline **or** - ↓ UO < 0.5 mL/kg/h for >6 h	- ↑ in SCr of 0.3 mg/dL or more within 48 h **or** - ↑ in SCr **1.5**-fold from baseline within the last 7 days **or** - ↓ UO < 0.5 mL/kg/h for >6 h

14

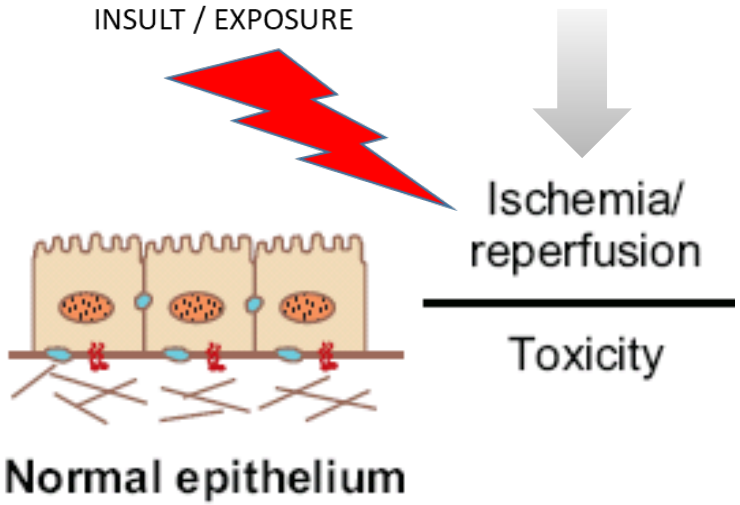
KDIGO

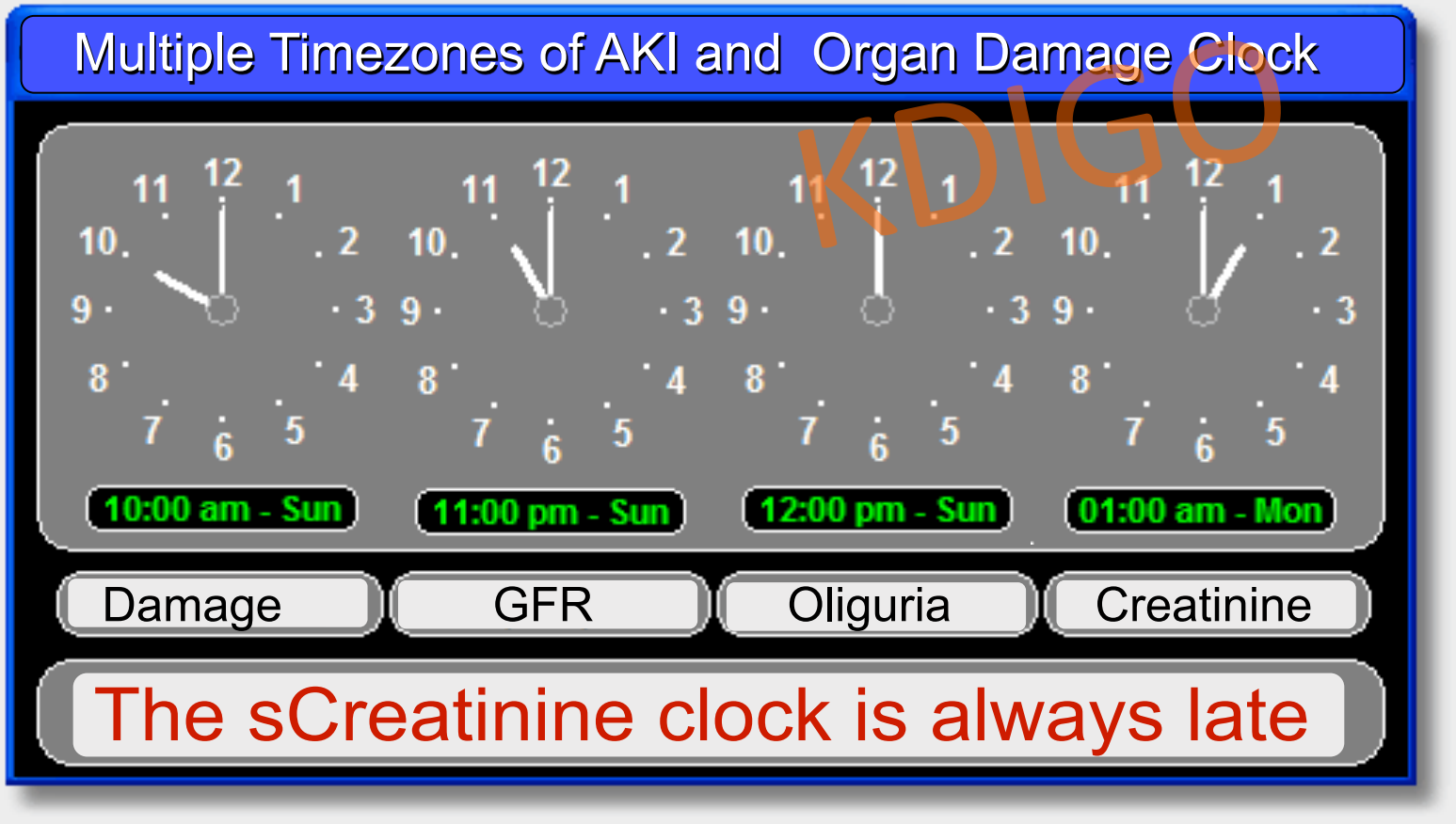
?

KDIGO Definition of AKI



Stage 1	Stage 2	Stage 3
Δ sCr > 0.3 mg/dL	sCr x 2	sCr x 3


INSULT / EXPOSURE
Ischemia/
reperfusion
Toxicity
Normal epithelium


Multiple Timezones of AKI and Organ Damage Clock
KDIGO
10:00 am - Sun
11:00 pm - Sun
12:00 pm - Sun
01:00 am - Mon
Damage
GFR
Oliguria
Creatinine
The sCreatinine clock is always late

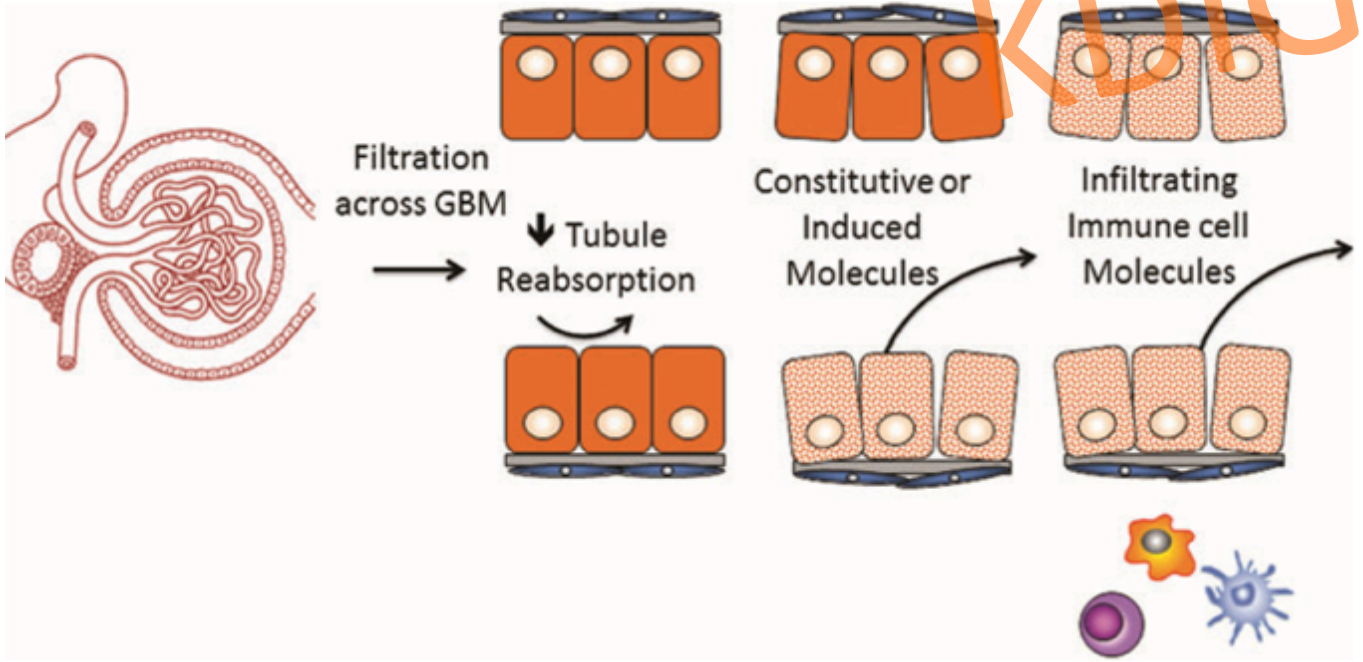
Nephrol Dial Transplant (2014) 0: 1–11
doi: 10.1093/ndt/gft510

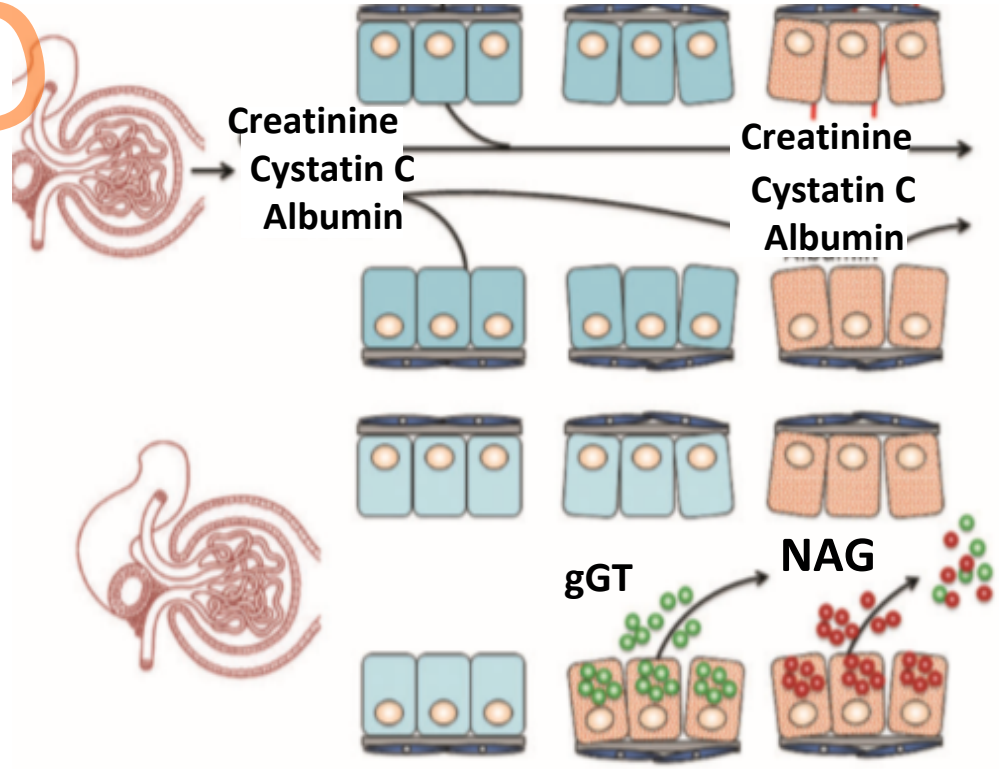
ndt
Nephrology Dialysis Transplantation

Editorial Review

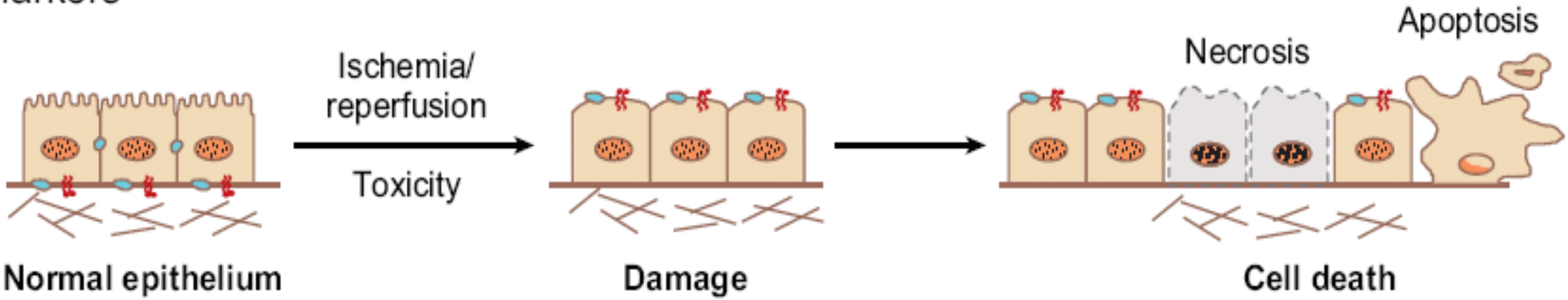
A basic science view of acute kidney injury biomarkers

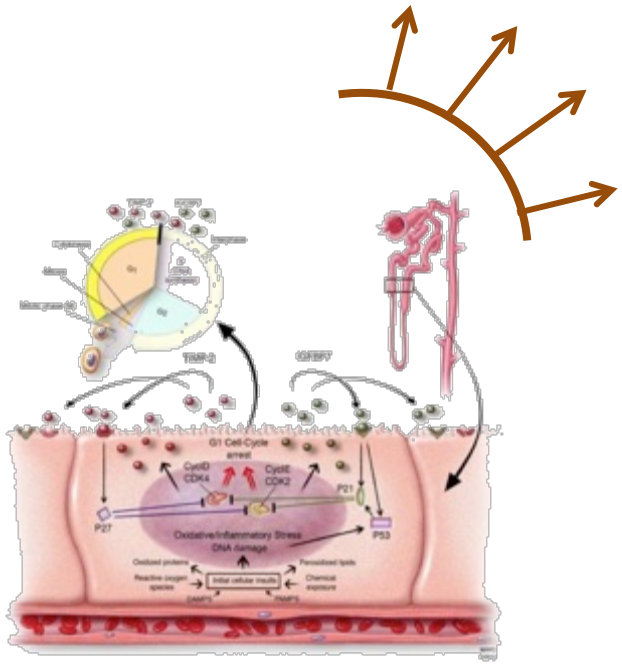
Jennifer R. Charlton[1,2], Didier Portilla[3] and Mark D. Okusa[2,4]





Biomarkers





TIMP-2 - IGFBP7

Potential urinary biomarkers for early diagnosis of AKI

NAG	NGAL
β_2M	CYR-61
α_1M	IL-18
RBP	OPN
Cystatin C	FABP
KIM-1	NHE3
Clusterin	Fetuin A
Microalbumin	

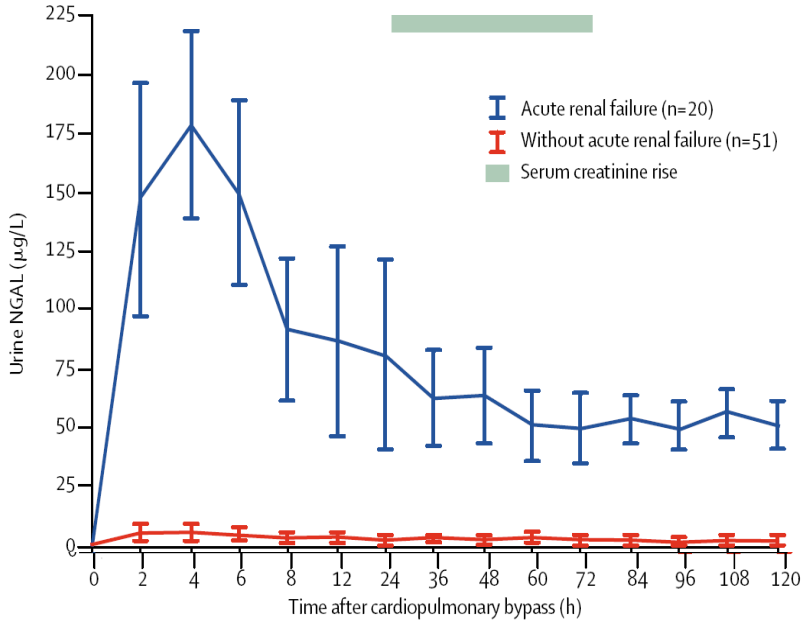
↓ GFR

Delayed biomarkers for kidney injury

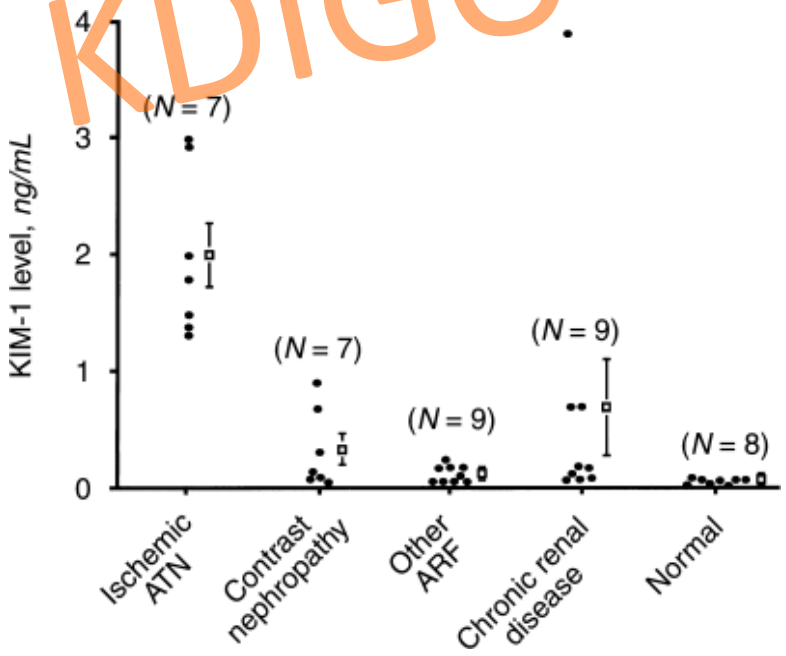
- ↑ Serum creatinine
- ↑ Blood urea nitrogen

AKI Biomarkers

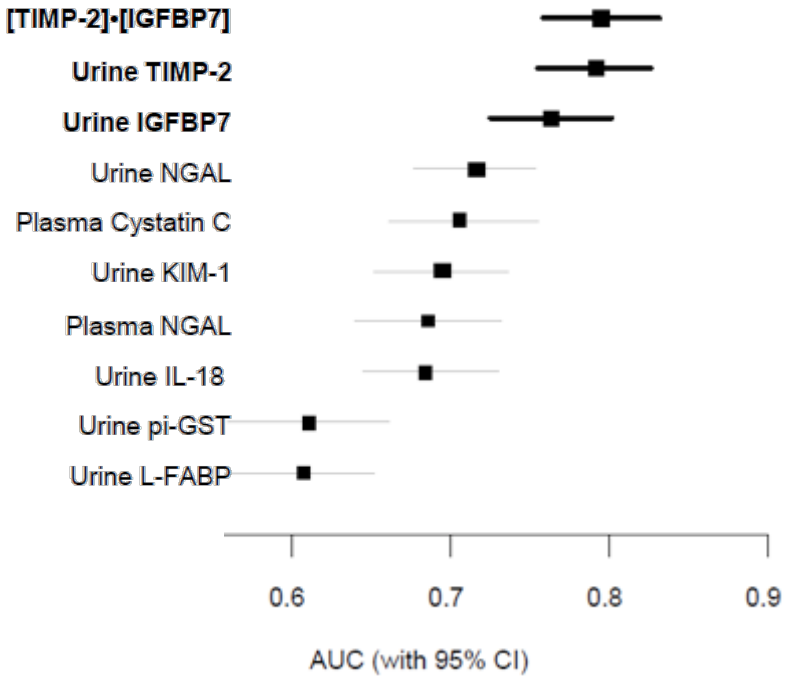
NGAL



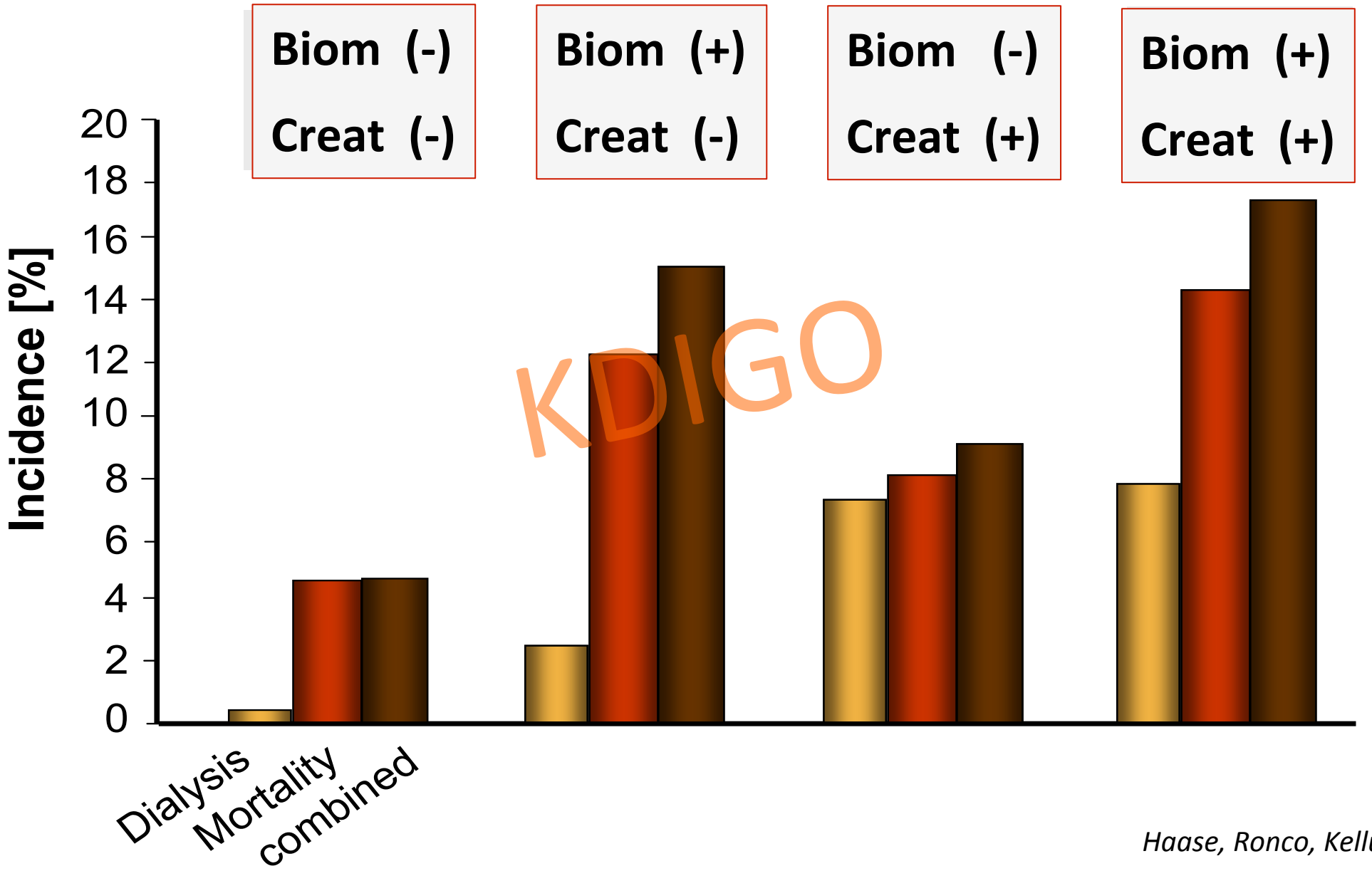
KIM - 1



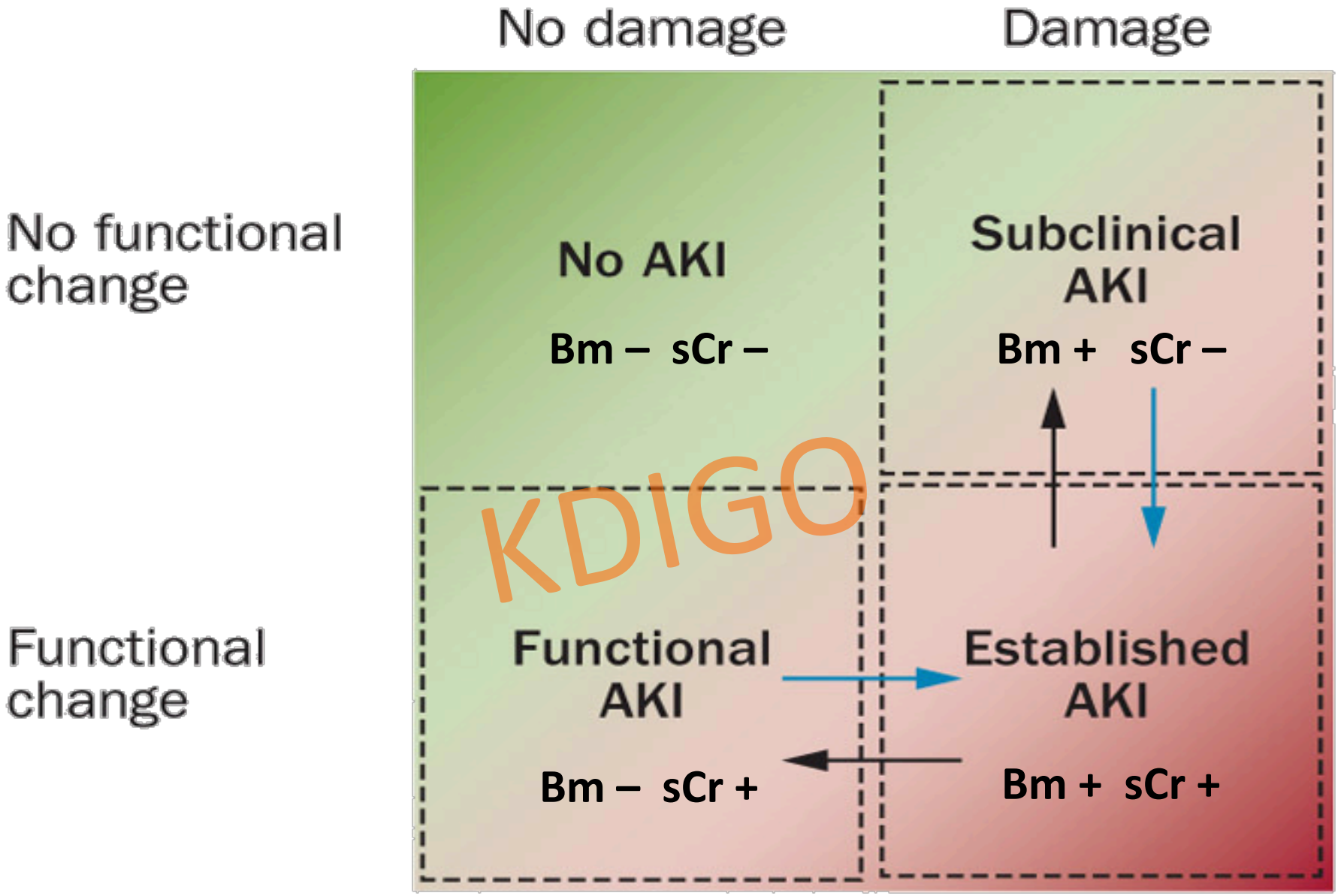
Nephrocheck



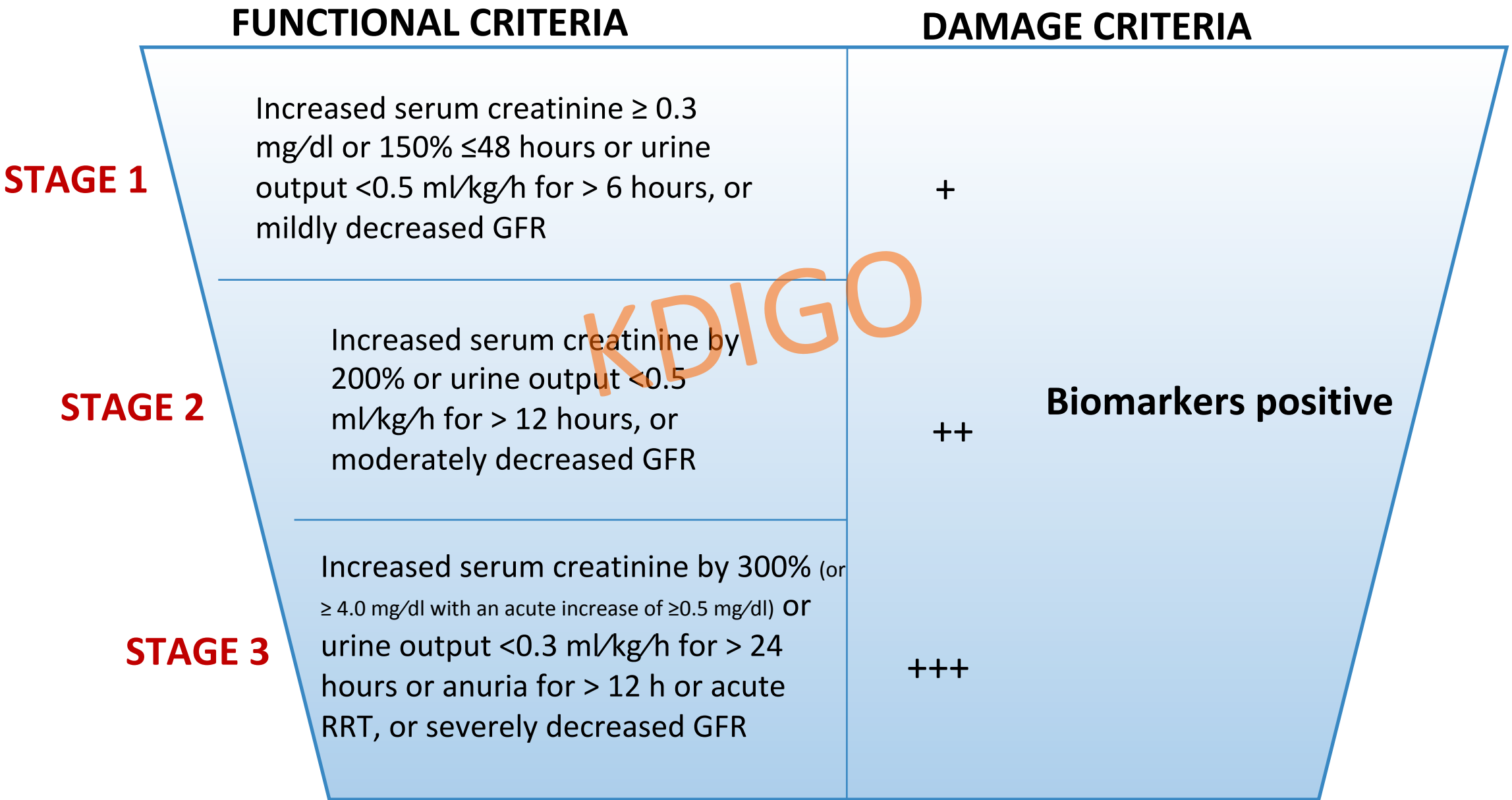
Creatinine, Biomarkers and AKI outcomes

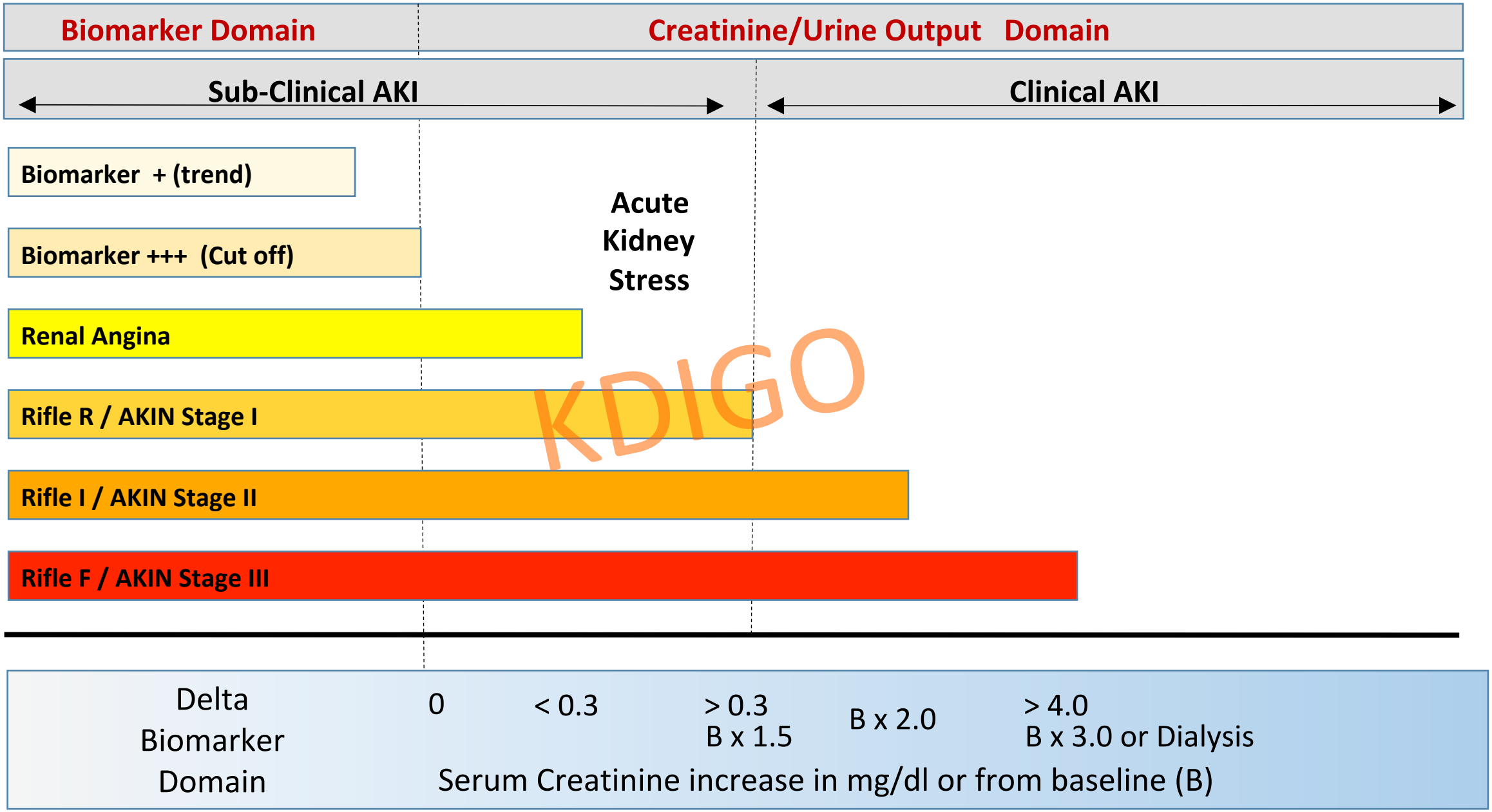


Haase, Ronco, Kellum: JACC 2012


No damage
Damage
No functional change
Functional change
No AKI
Bm – sCr –
Subclinical AKI
Bm + sCr –
Functional AKI
Bm – sCr +
Established AKI
Bm + sCr +
KDIGO
Progression
Resolution

New diagnostic criteria for AKI ?




Biomarker Domain
Creatinine/Urine Output Domain
Sub-Clinical AKI
Clinical AKI
Biomarker + (trend)
Biomarker +++ (Cut off)
Renal Angina
Rifle R / AKIN Stage I
Rifle I / AKIN Stage II
Rifle F / AKIN Stage III
Acute Kidney Stress
KDIGO
Delta Biomarker Domain
0
< 0.3
> 0.3
B x 1.5
B x 2.0
> 4.0
B x 3.0 or Dialysis
Serum Creatinine increase in mg/dl or from baseline (B)

Cellular and Molecular Mechanisms of AKI

Anupam Agarwal,* Zheng Dong,† Raymond Harris,‡ Patrick Murray,§ Samir M. Parikh,‖ Mitchell H. Rosner,¶ John A. Kellum,** and Claudio Ronco,††
for the Acute Dialysis Quality Initiative XIII Working Group

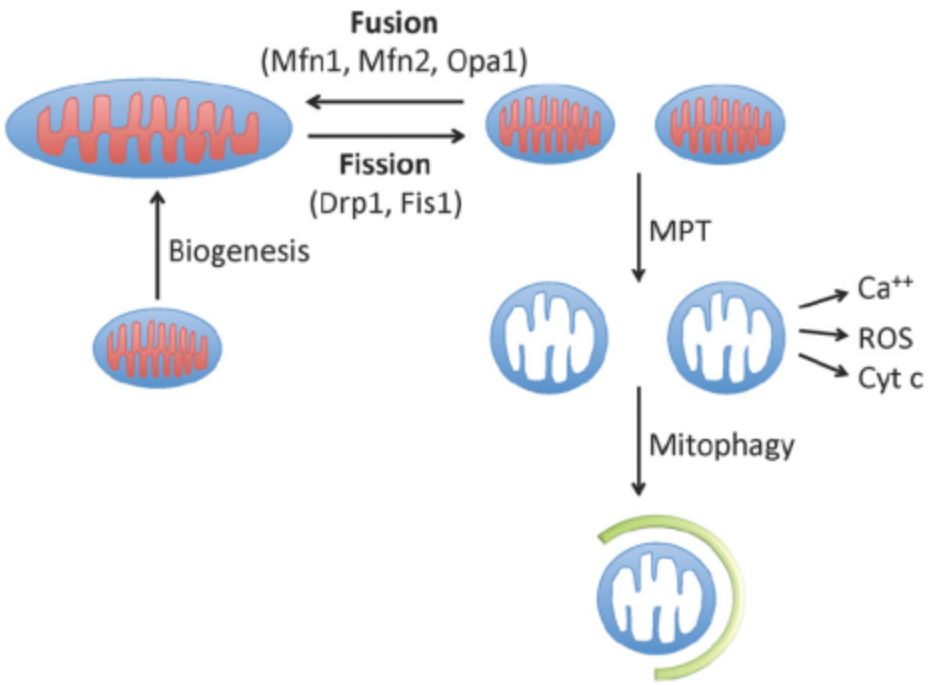
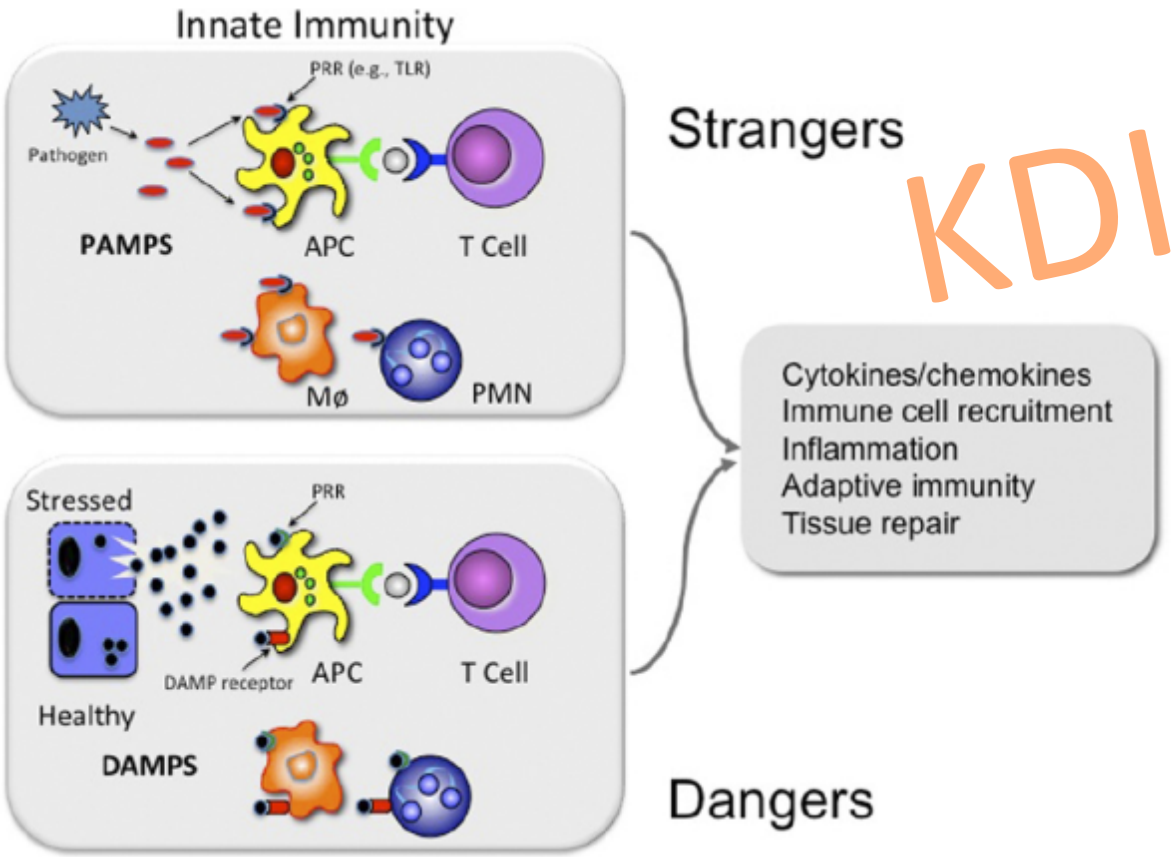


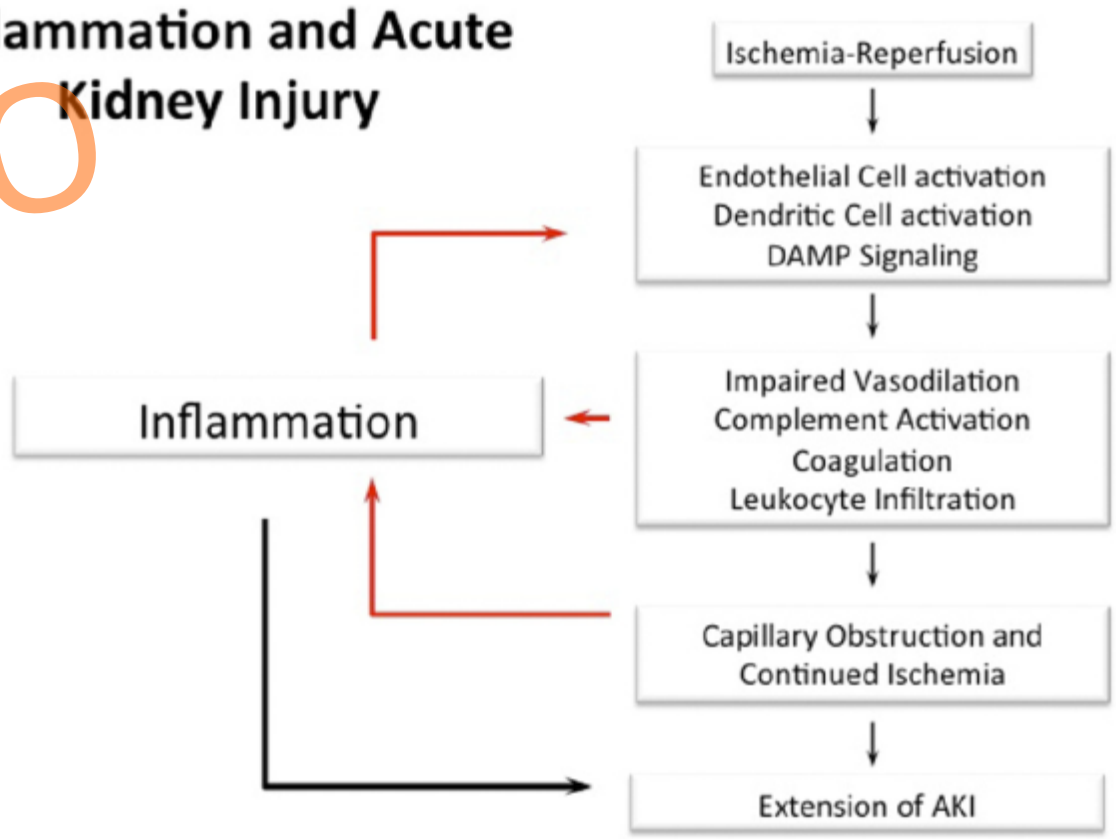
Figure 1. Involvement of mitochondria in ischemic AKI: Healthy mitochondria generate the ATP necessary for cellular health and, in the renal tubule, the energy needed for the movement of solute and water against gradients. Ischemia-reperfusion injury leads to rapid fragmentation of mitochondrial networks through a dynamic process termed fission regulated by proteins such as dynamin-related protein 1 (Drp1) and mitochondrial fission 1 protein (Fis1). The mitochondrial fusion machinery includes mitofusin 1 (Mfn1), Mfn2 and optic atrophy 1. Fragmented mitochondria appear to be a less efficient source of ATP and can undergo the MPT. MPT results in mitochondrial swelling from the influx of water, and it promotes cell death through the release of calcium (Ca^{++}), cytochrome c (Cyt c), and other proapoptotic proteins. Damaged mitochondria can be cleared and recycled through mitophagy, the first step of which is envelopment of the injured mitochondrion by a double-membrane structure termed the autophagosome (shown in green). Finally, in surviving cells, mitochondrial biogenesis results in an expansion of mitochondrial mass through regulated gene expression of structural and enzymatic components of mitochondria. Reprinted from www.adqi.net, with permission.

J Am Soc Nephrol 27: ●●●–●●●, 2016. doi: 10.1681/ASN.2015070740

The Role of Inflammation in the Cardio-Renal Syndrome: A Focus on Cytokines and Inflammatory Mediators

Mitchell H. Rosner, MD, Claudio Ronco, MD,† and Mark D. Okusa, MD**





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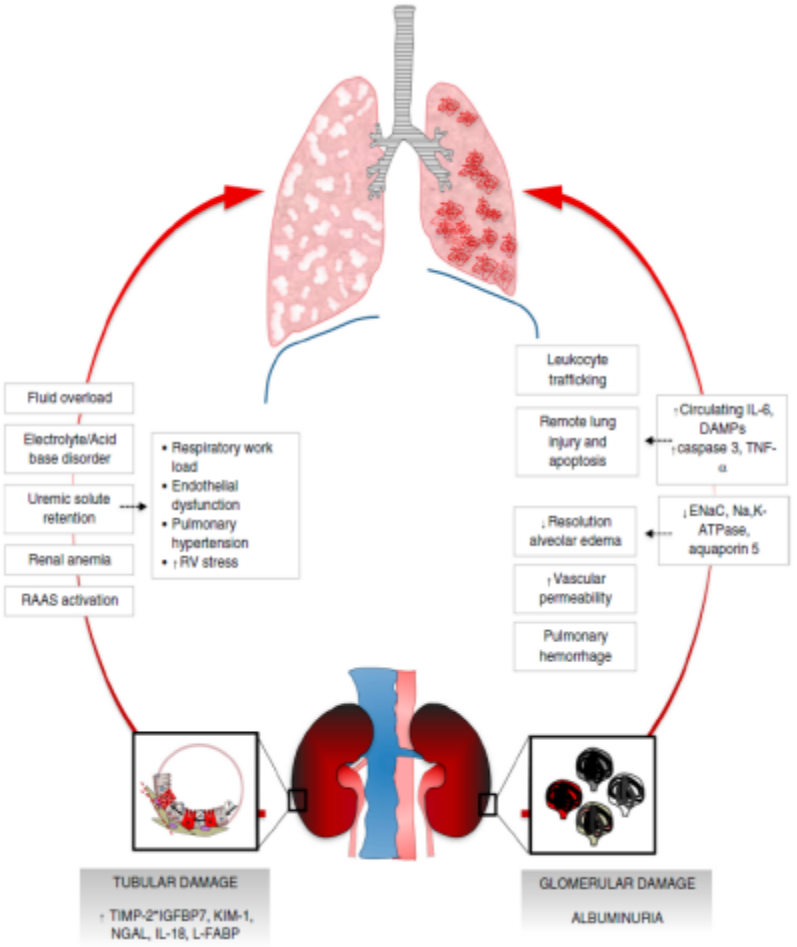
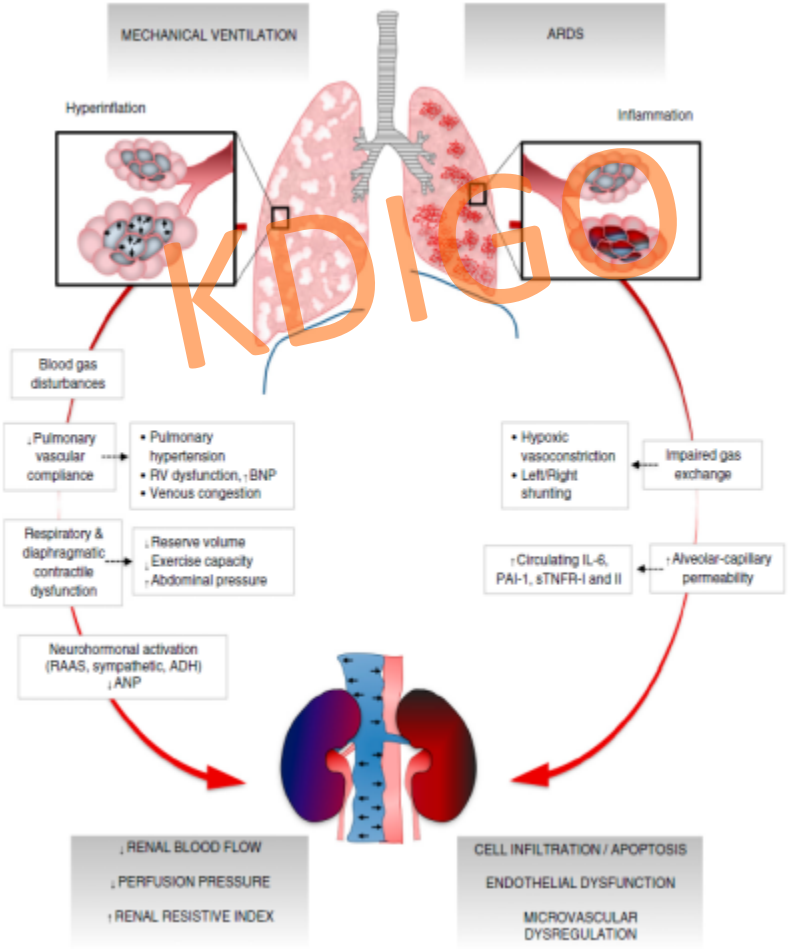
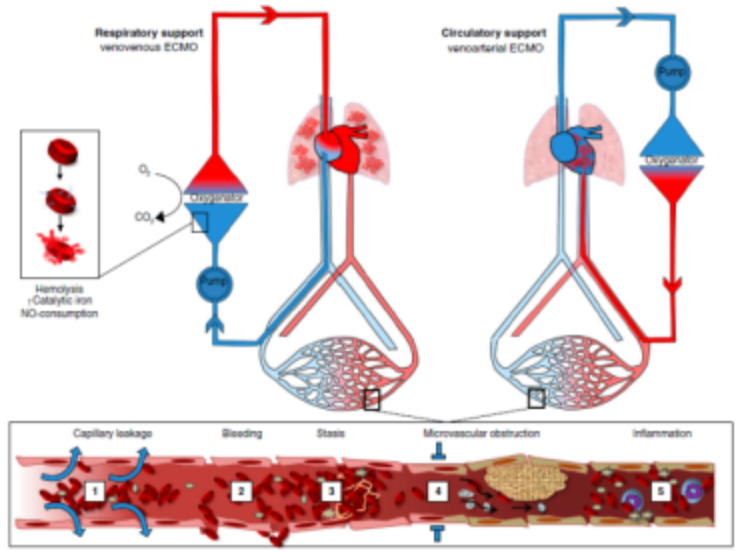
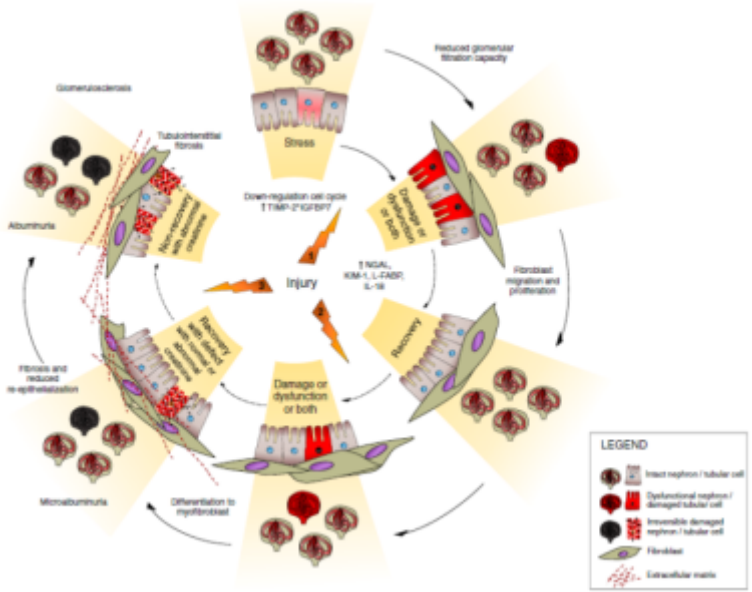
Lung–Kidney Crosstalk in the Critically Ill Patient

Faeq Husain-Syed[1,2], Arthur S. Slutsky[3,4], and Claudio Ronco[1]





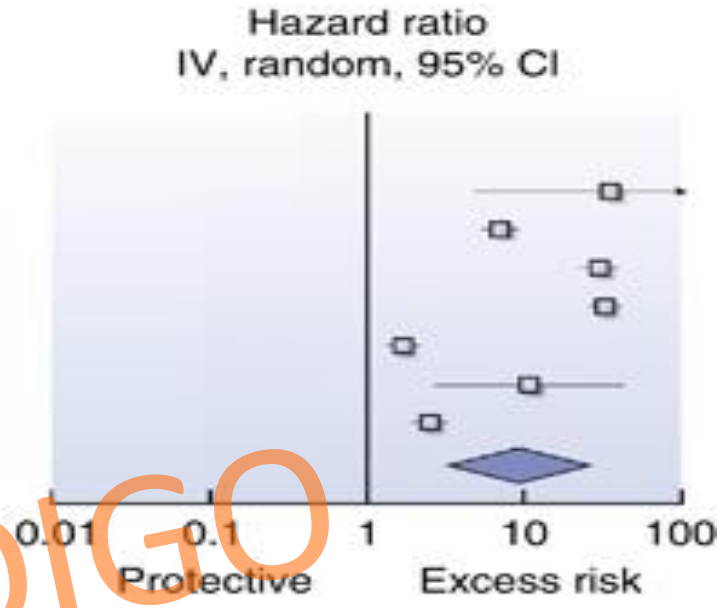




CKD and ESRD after AKI

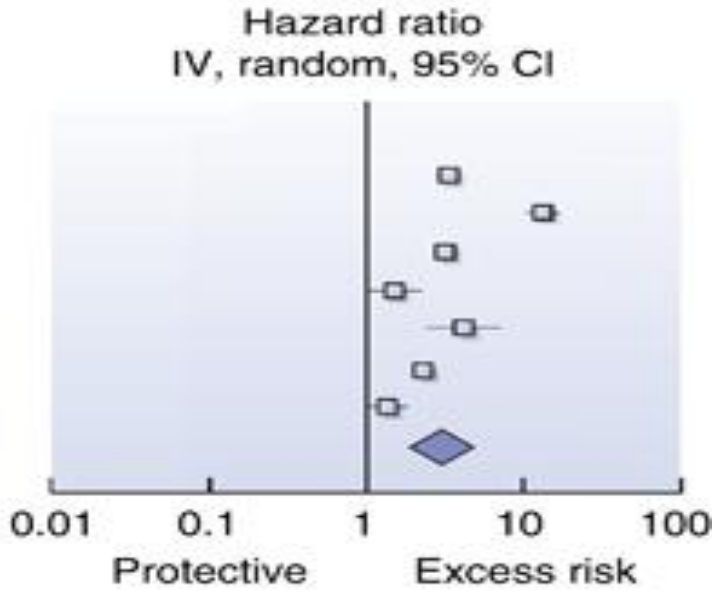
AKI to CKD

HR = 8.8
(95%CI 3.1-25.5)



AKI to ESRD

HR = 3.1
(95%CI 1.9-5.0)



Coca, et al.
Kidney Int 2012

nature REVIEWS
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Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup

Lakhmir S. Chawla[1], Rinaldo Bellomo[2], Azra Bihorac[3], Stuart L. Goldstein[4], Edward D. Siew[5], Sean M. Bagshaw[6], David Bittleman[7], Dinna Cruz[8], Zoltan Endre[9], Robert L. Fitzgerald[7], Lui Forni[10], Sandra L. Kane-Gill[11], Eric Hoste[12], Jay Koyner[13], Kathleen D. Liu[14], Etienne Macedo[8], Ravindra Mehta[8], Patrick Murray[15], Mitra Nadim[16], Marlies Ostermann[17], Paul M. Palevsky[18,19], Neesh Pannu[20], Mitchell Rosner[21], Ron Wald[22], Alexander Zarbock[23], Claudio Ronco[24] and John A. Kellum[25] on behalf of the Acute Disease Quality Initiative Workgroup 16.