



When I was a lad.....

- ⌘ CRRT was new
- ⌘ Only a few acolytes/desperados did it
- ⌘ Doing large non-Pharma funded randomized multicenter trials in CCN seemed unthinkable
- ⌘ In North America, IHD was king
- ⌘ Critical Care Nephrology was not in the medical dictionary

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My first CCN paper....

Bellomo R, Ernest D, Parkin G, Boyce N. Clearance of vancomycin during continuous haemodiafiltration. Crit Care Med 1990; 18: 181-183

My first International Presentations - ASAIO Meeting in Chicago - 1991

In-vivo catecholamine extraction during continuous haemodiafiltration (CHD) in inotrope-dependent patients.

Tumour necrosis factor clearances during veno-venous haemodiafiltration in the critically ill.

**In Chicago...I met this guy**



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then....in 1992...I moved to this city for 2 years...



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...and met this guy..

**John Kellum**



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But before  
getting to Pittsburgh  
I stopped here...



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Because  
I wanted to  
meet this  
guy...

Claudio Ronco



.....That was a mistake

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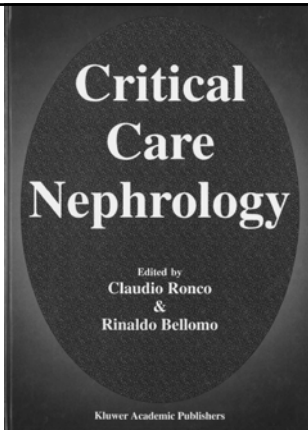
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..in 1998.....Claudio almost caused my premature death by making me help him put this together.....

Never again I said!!



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...but then John and Claudio met and ganged up...and they are the source of constant work and madness



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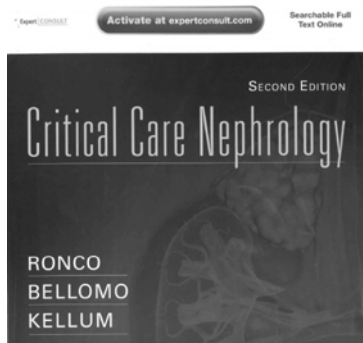
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...and forced me to do what I said I would never do again



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Other things Ravi, John and Claudio instigated..

- ⌘ The development of the Acute Dialysis Quality Initiative
- ⌘ The Yearly San Diego CRRT meeting
- ⌘ The Meeting on CCN in Vicenza every three years
- ⌘ An educational and training agenda
- ⌘ A publication agenda

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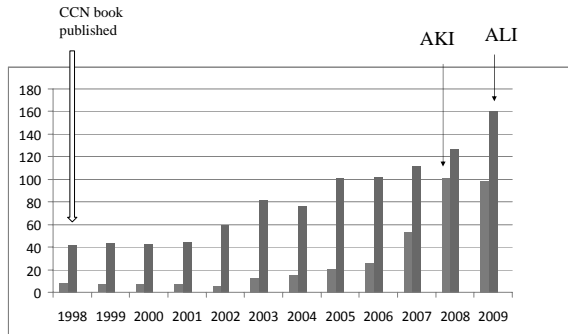
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### PubMed papers: ALI+ICU vs. AKI/ARF+ICU



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Like ALI/ARDS...it was clear that AKI/ARF needed a consensus definition

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<sup>1</sup>, Claudio Ronco<sup>2</sup>, John A Kellum<sup>3</sup>, Ravindra L Mehta<sup>4</sup>, Paul Palevsky<sup>5</sup> and the ADQI workgroup<sup>6</sup>

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

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

Received: 27 March 2004

Critical Care 2004, 8:R204-R212 (DOI 10.1186/cc2872)

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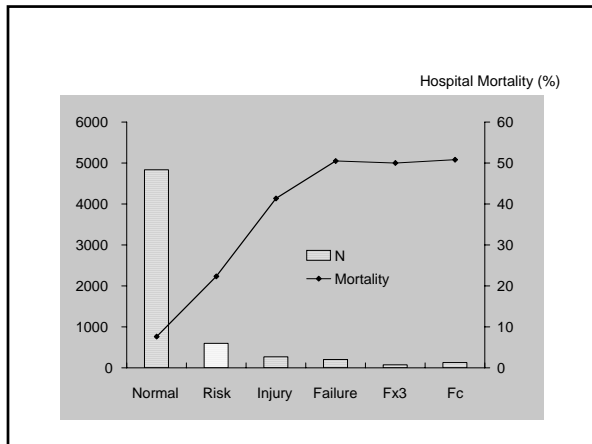
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**Table 2. Multivariate logistic regression analysis for hospital mortality in all patients**

Independent Variables	Odds Ratio (95% CI)	p Value
Age, yrs	1.037 (1.032-1.042)	<.0001
Male gender	1.180 (1.043-1.325)	.0085
Emergency admission	1.498 (1.288-1.742)	<.0001
ICU admission	2.911 (2.285-3.707)	<.0001
Mechanical ventilation	4.839 (3.695-6.338)	<.0001
Baseline creatinine, mg/dL	1.705 (1.499-1.940)	<.0001
Admission units		
General medicine	1.000 (Reference)	
Cardiology	0.380 (0.282-0.511)	<.0001
Gastroenterology	1.415 (1.010-1.984)	.044
Hematology	3.120 (2.240-4.346)	<.0001
Neurology	0.816 (0.554-1.202)	.30
Oncology	5.125 (4.229-6.222)	<.0001
Renal medicine	0.167 (0.094-0.298)	<.0001
Respiratory medicine	1.220 (0.909-1.637)	.18
Stroke unit	2.033 (1.259-2.666)	<.0001
Other medical units	0.606 (0.366-1.004)	.052
Cardiac surgery	0.087 (0.058-0.130)	<.0001
General surgery	0.512 (0.284-0.681)	<.0001
Neurosurgery	1.076 (0.732-1.585)	.71
Orthopedics	1.090 (0.732-1.579)	.65
Thoracic surgery	0.560 (0.309-0.925)	.024
Urology	0.123 (0.049-0.310)	<.0001
Vascular surgery	0.372 (0.242-0.571)	<.0001
Other surgical units	0.169 (0.065-0.438)	.0005
RIFLE criteria		
Normal	1.000 (Reference)	
Risk	2.536 (2.152-2.988)	<.0001
Injury	5.412 (4.547-6.442)	<.0001
Failure	10.124 (8.218-12.32)	<.0001

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Need to validate outside Australia.....

Research **Open Access**

**RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis**

Eric AJ Hoste<sup>1,2</sup>, Gilles Clermont<sup>1</sup>, Alexander Kersten<sup>1</sup>, Ramesh Venkataraman<sup>1</sup>, Derek C Angus<sup>1</sup>, Dirk De Bacquer<sup>3</sup> and John A Kellum<sup>1</sup>

<sup>1</sup>The Clinical Research, Investigation, and Systems Modeling of Acute Illness (CRISMA) Laboratory, Department of Critical Care Medicine, University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania, USA  
<sup>2</sup>Intensive Care Unit, Ghent University Hospital, Ghent, Belgium  
<sup>3</sup>Department of Public Health, Ghent University, Ghent, Belgium

Corresponding author: John A Kellum, kellumja@cm.upmc.edu

Received: 10 Mar 2006 Revisions requested: 27 Mar 2006 Revisions received: 1 Apr 2006 Accepted: 10 Apr 2006 Published: 12 May 2006

Critical Care 2006, 10:R73 (doi:10.1186/cc4915)  
 This article is online at: <http://ccforum.com/content/10/3/R73>  
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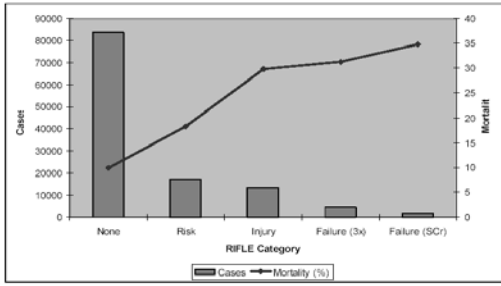
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..just as expected....

Figure 2



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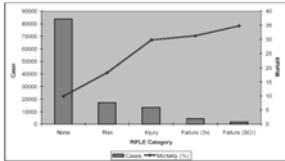
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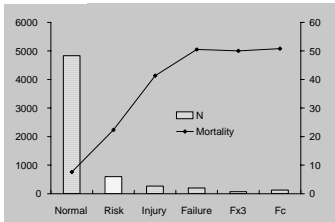
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Figure 2



ICU patients in ANZ

Hospital patients at Austin



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Now we can understand the epidemiology over time....

Research

Open Access

### Changes in the incidence and outcome for early acute kidney injury in a cohort of Australian intensive care units

Sean M Bagshaw<sup>1,2</sup>, Carol George<sup>3</sup>, Rinaldo Bellomo<sup>2,4</sup> for the ANZICS Database Management Committee

<sup>1</sup>Division of Critical Care Medicine, University of Alberta Hospital, Edmonton, Canada  
<sup>2</sup>Department of Intensive Care, Austin Hospital, Melbourne, Australia  
<sup>3</sup>Physio Manager, ANZICS APD, Melbourne, Australia  
<sup>4</sup>Department of Medicine, Melbourne University, Melbourne, Australia

Corresponding author: Sean M Bagshaw, bagshaw@ualberta.ca

Received: 23 Mar 2007 Revisions requested: 4 May 2007 Revisions received: 15 May 2007 Accepted: 25 Jun 2007 Published: 25 Jun 2007

Critical Care 2007, 11:R68 (doi:10.1186/cc5948)

This article is online at: <http://ccforum.com/content/11/3/R68>

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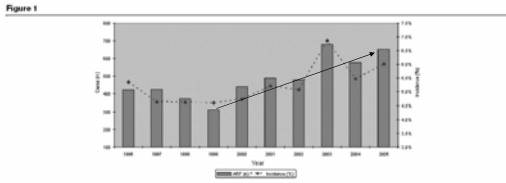
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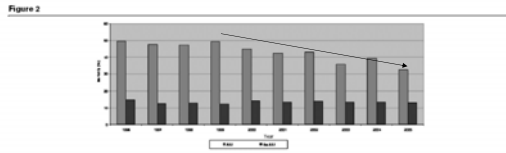
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More of it...but better survival by about 1% per year



Summary of cases of acute kidney injury and incidence from the Australia New Zealand Intensive Care Society Adult Patient Database, 1996-2005. ARF, acute renal failure.



Summary of crude mortality for patients with and without acute kidney injury from the Australia New Zealand Intensive Care Society Adult Patient Database, 1996-2005. ARF, acute renal failure.

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## Conclusion

- ⌘ Defining and classifying ARF is important
- ⌘ We used logical principles and have developed a consensus definition and classification system
- ⌘ We have now validated it in close to 300,000 patients

**Another item on the agenda:  
epidemiology of RRT practice**

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## The B.E.S.T. Kidney study

- Beginning and Ending Supportive Therapy for the Kidney
- Epidemiological study in response to issues raised by first Acute Dialysis Quality Initiative meeting (New York Aug. 2000)
- Major question: what is current worldwide practice with regard to ARF in ICU?

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## Materials and Methods

- Conducted in 54 volunteering centers in 23 countries, from September 2000 to December 2001.
- Average observation period: 182 ± 72 days
- These centers were divided into 5 center-clusters (9 centers in Asia, 6 in Australia, 26 in Europe, 8 in North America and 5 in South America).

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JAMA 2005

CARING FOR THE  
CRITICALLY ILL PATIENT

### Acute Renal Failure in Critically Ill Patients A Multinational, Multicenter Study

Shigehiko Uchino, MD

John A. Kellum, MD

Rinaldo Bellomo, MD

Gordon S. D'Ag, PhD

Hiroshi Morimatsu, MD

Nandino Margara, MD

Mart Schetz, MD

Lin Tan, MD

Catherine Bosman, MD

Eliene Macedo, MD

Noel Gilroy, MD

Ashita Tolwani, MD

Claudio Basson, MD

for the Beginning and Ending  
Supportive Therapy for the Kidney  
(BEST Kidney) Investigators

**Context** Although acute renal failure (ARF) is believed to be common in the setting of critical illness and is associated with a high risk of death, little is known about its epidemiology and outcome or how these vary in different regions of the world.

**Objectives** To determine the period prevalence of ARF in intensive care unit (ICU) patients in multiple countries; to characterize differences in etiology, illness severity, and clinical practice; and to determine the impact of these differences on patient outcomes.

**Design, Setting, and Patients** Prospective observational study of ICU patients who either were treated with renal replacement therapy (RRT) or fulfilled at least 1 of the predefined criteria for ARF from September 2000 to December 2001 at 54 hospitals in 23 countries.

**Main Outcome Measures** Occurrence of ARF, factors contributing to etiology, illness severity, treatment, need for renal support after hospital discharge, and hospital mortality.

**Results** Of 29,269 critically ill patients admitted during the study period, 1738 (5.7%; 95% confidence interval [CI], 5.5%-6.0%) had ARF during their ICU stay, including 1260 who were treated with RRT. The most common contributing factor to ARF was septic shock (47.5%; 95% CI, 45.2%-49.5%). Approximately 30% of patients had preadmission renal dysfunction. Overall hospital mortality was 60.3% (95% CI, 58.0%-

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## 1: Demographics of ARF

- ICU admissions: 29,269
- ARF but no RRT: 498
- ARF with RRT: 1,260
- Total: 1,758
- Incidence of RRT: 4.2%

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## Demographics

- Number of patients: 1758
- Gender (M/F): 63.7 / 36.3%
- Age: 67 years (53-75)
- SAPS-II score: 48 (38-61)
- Chronic renal dysfunction: 29.5%

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## Contributing Factors

1. Medical/Surgical: 58.8 vs. 41.2%
2. **Sepsis: 47.4%** How little do we know about this!
3. Major surgery: 34.4%
4. Low cardiac output: 26.9%
5. Hypovolemia: 25.5%
6. Drugs: 19.0% How does this happen?
7. Hepatorenal syndrome: 5.7%

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## Overall Outcomes

- ICU stay: 9 days (4-21)
- Hospital stay: 22 days (11-44)
- ICU mortality: 51.7%
- Hospital mortality: 60.2%
- Hospital discharge with RRT: 5.4%

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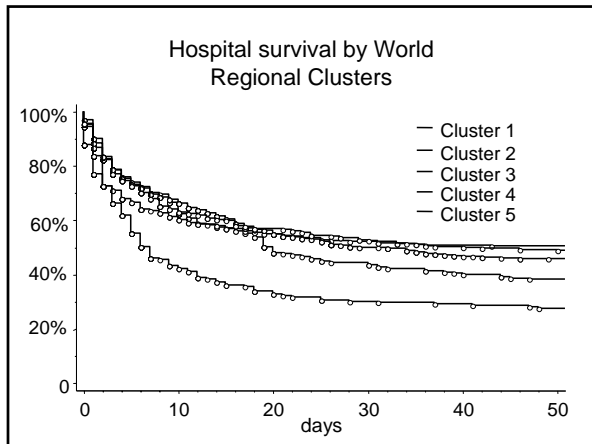
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Multivariate logistic regression analysis for hospital mortality

Cluster	Centers	Odds Ratio (95% CI)
Cluster 1	6	1.000 (referent)
Cluster 2	25	1.247 (0.908 - 1.715)
Cluster 3	8	0.888 (0.608 - 1.299)
Cluster 4	5	3.489 (2.157 - 5.646)
Cluster 5	9	1.939 (1.268 - 2.963)

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- Summary**
- Multinational, multicenter, prospective, epidemiological study of ARF, the largest conducted so far.
  - Differences in local health care processes and interventions affected survival.
  - Useful for the statistical powering and design of future international interventional trials.

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What about diuretics...are they toxic or do they help?

### Diuretics and mortality in acute renal failure\*

Shigehiko Uchino, MD; Gordon S. Doig, PhD; Rinaldo Bellomo, MD; Hiroshi Morimatsu, MD; Stanislao Morgera, MD; Miet Schetz, MD; Ian Tan, MD; Catherine Bouman, MD; Etienne Macedo, MD; Noel Gibney, MD; Ashita Tolwani, MD; Claudio Ronco, MD; John A. Kellum, MD; for the Beginning and Ending Supportive Therapy for the Kidney (B.E.S.T. Kidney) Investigators

**Objective:** According to recent research, diuretics may increase mortality in acute renal failure patients. The administration of diuretics in such patients has been discouraged. Our objective was to determine the impact of diuretics on the mortality rate of critically ill patients with acute renal failure.

**Design:** Prospective, multiple-center, multinational epidemiologic study.

**Setting:** Intensive care units from 64 centers and 23 countries.

**Patients:** Patients were 1,743 consecutive patients who either were treated with renal replacement therapy or fulfilled pre-defined criteria for acute renal failure.

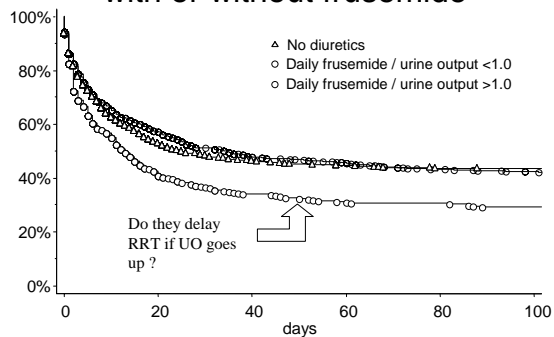
**Interventions:** Three distinct multivariate models were developed to assess the relationship between diuretic use and subsequent mortality: a) a propensity score adjusted multivariate model containing terms previously identified to be important predictors of outcome; b) a new propensity score adjusted multivariate model; and c) a multivariate model developed using standard methods, compensating for collinearity.

**Measurements and Main Results:** Approximately 79% of patients were treated with diuretics at study inclusion. Mean age was 68 and mean Simplified Acute Physiology Score II was 47. Severe sepsis/septic shock (42.8%), major surgery (39.1), low cardiac output (29.7), and hypovolemia (28.2%) were the most common conditions associated with the development of acute renal failure. Furosemide was the most common diuretic used (98.3%). Combination therapy was used in 98 patients only. In all three models, diuretic use was not associated with a significantly increased risk of mortality.

**Conclusions:** Diuretics are commonly prescribed in critically ill patients with acute renal failure, and their use is not associated with higher mortality. There is full equipoise for a randomized controlled trial of diuretics in critically ill patients with renal dysfunction. (Crit Care Med 2004; 32:1669-1677)

**Key Words:** acute kidney failure; critical illness; furosemide; diuretics; epidemiology; renal replacement therapy; logistic regression modeling; multicollinearity; propensity scores

### Hospital survival for patients with or without frusemide



### Comprehensive statistical analyses with BEST kidney

Method 1:

Confirmatory propensity adjusted mortality model

Diuretic use 1.210 (0.96-1.5)  $p=0.100$

Method 2:

New propensity adjusted mortality model

Diuretic use 1.217 (0.91-1.6)  $p=0.181$

Method 3:

Multicollinearity adjusted model

Diuretic use 1.222 (0.92-1.6)  $p=0.153$

## Summary

- In a prospective, large, multinational cohort, despite rigorous statistical analysis, diuretics were **NOT** associated with an increased risk of death.
- The use of diuretics cannot be “discouraged” in such patients.
- A clinical trial is both desirable and logistically possible.

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## Evaluation of ARF scores

- No reliable scoring system to stratify patient selection and confirm balanced randomization.
- Accuracy of general severity scoring systems (APACHE-II, SAPS-II, MPM) have been questioned.
- Development and validation of ARF-specific scores were conducted in a small number of centers.

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Can they predict outcome and stratify for trials....

### External validation of severity scoring systems for acute renal failure using a multinational database

Shigehiko Uchino, MD; Rinaldo Bellomo, MD; Hiroshi Morimatsu, MD; Stanislao Mergera, MD; Milet Schetz, MD, PhD; Ian Tan, MD; Catherine Bouman, MD; Etienne Macedo, MD; Noel Gibney, MD; Ashita Tolwani, MD; Gordon S. Dalg, PhD; Heleen Oudemans van Straten, MD; Claudio Ronco, MD; John A. Kellum, MD for the Beginning and Ending Supportive Therapy for the Kidney (B.E.S.T. Kidney) Investigators

**Objective:** Several different severity scoring systems specific to acute renal failure have been proposed. However, most validation studies of these scoring systems were conducted in a single center or in a small number of centers, often the same ones used for their development. Therefore, it is not known whether such severity scoring systems may be widely applied.

**Design:** Prospective clinical investigation.

**Setting:** Intensive care units.

**Patients:** One thousand seven hundred and forty-two intensive care unit patients with acute renal failure who were either treated with renal replacement therapy or fulfilled predefined criteria.

**Interventions:** Demographic and clinical information and outcomes were measured.

**Measurements and Main Results:** Scores for four acute renal failure-specific scoring systems and two general scoring systems (Simplified Acute Physiology Score II and Sequential Organ Failure Assessment) were calculated, and their discrimination and calibration were tested with receiver operating characteristic curves

and Hosmer-Lemeshow goodness-of-fit tests. For the receiver operating characteristic curves, blood lactate levels were also used as a reference. All scores had an area under the receiver operating characteristic curve < 0.7 (Melta 0.670, Liao 0.696, Chertow 0.616, Paganini 0.643, Simplified Acute Physiology Score II 0.645, Sequential Organ Failure Assessment 0.675, lactate 0.639). For scores that can calculate predicted mortality, the Hosmer-Lemeshow goodness-of-fit test showed poor calibration.

**Conclusions:** None of the scoring systems tested had a high level of discrimination or calibration to predict mortality for patients with acute renal failure when tested in a broad cohort of patients from multiple countries. A large, multi-center database might be needed to improve the discrimination and calibration of acute renal failure scoring system. (Crit Care Med 2006; 35:1961-1967)

**Key Words:** acute kidney failure; critical illness; severity score; renal replacement therapy; hemodialysis; hemofiltration

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## ARF specific scoring systems

	Mehta	Liano	Chertow	Paganini	BEST
Published year	2002	1993	1998	1996	2004
Sample size	605	328	256	512	1742
Number of centers	4	1	48	1	54
Countries	USA	Spain	USA Canada	USA	23 countries
Place of patients	ICU	Hospital	Hospital	ICU	ICU
Mean age	56	58	62	63	67
Gender (male)	72%	68%	65%	62%	64%
Mean creatinine	326	-	405	-	329
Mean urea	23.5	-	23.6	-	26.5
Hospital mortality	52%	53%	36%	67%	61%
RRT requirement	28%	51%	42%	100%	63%

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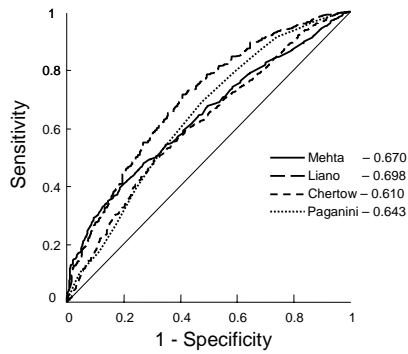
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## ROC curves for ARF scores




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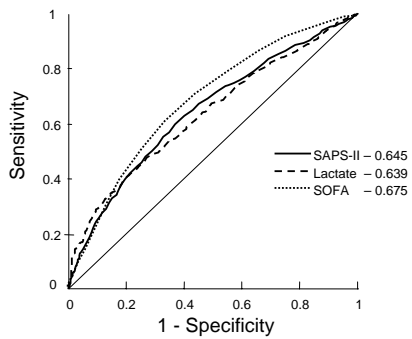
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## ROC curves for general severity scores and lactate




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### Area under the ROC curves

	Total	RRT	No RRT
Mehta	0.670	0.681	0.667
Liano	0.698	0.691	0.705
Chertow	0.610	0.588	0.638
Paganini	0.643	0.647	0.634
SAPS-II	0.645	0.622	0.680
Lactate	0.639	0.641	0.629
SOFA	0.675	0.676	0.669

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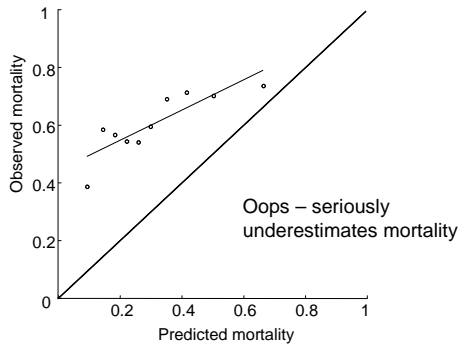
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### Calibration curves for Chertow's score




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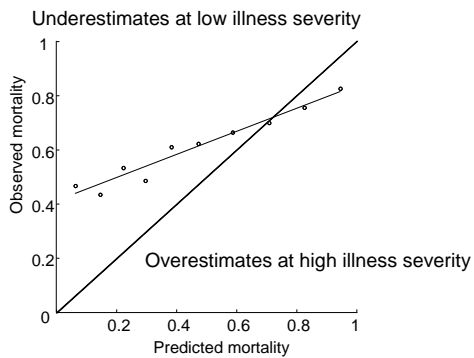
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### Calibration curves for SAPS-II score




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## Summary

- None of scoring systems we tested had adequate discrimination or calibration ability for the prediction of mortality in patients with ARF.
- A large, multicenter database is required to develop a more robust ARF-specific scoring system (an important task for a young investigator).

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## IRRT vs. CRRT

- Continuous RRT has potential physiological advantages over intermittent RRT.
- Multiple epidemiological studies and several randomized studies compared CRRT and IRRT, with controversial results.
- Renal recovery might also be affected differently by CRRT and IRRT.

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## Mode of initial RRT in BEST kidney

- CRRT : 80% (N=1006)
- IRRT : 16.9% (N=212)  
(IHD, IHDF, IHF)
- Others : 3.2%  
(PD, SCUf, SLEDD, SLEDF,  
high flow CHDF, ST-HVHF)

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### Multivariate logistic regression analysis for hospital survival

	Odds Ratio	
From hospital to ICU	0.956	$p < 0.0001$
Age	0.973	$p < 0.0001$
Platelet count	1.003	$p < 0.0001$
Gastrointestinal	0.427	$p = 0.0004$
Vasopressors	0.547	$p = 0.0005$
Low cardiac output	0.592	$p = 0.0022$
Sepsis / septic shock	0.662	$p = 0.0084$
Hematologic	0.371	$p = 0.0093$
ICU to RRT start	0.968	$p = 0.011$
SAPS-II	0.988	$p = 0.013$
Diuretics	0.508	$p = 0.013$
Mechanical ventilation	0.621	$p = 0.013$
Urine output	1.001	$p = 0.017$
<b>CRRT</b>	<b>0.743</b>	<b><math>p = 0.12</math></b>

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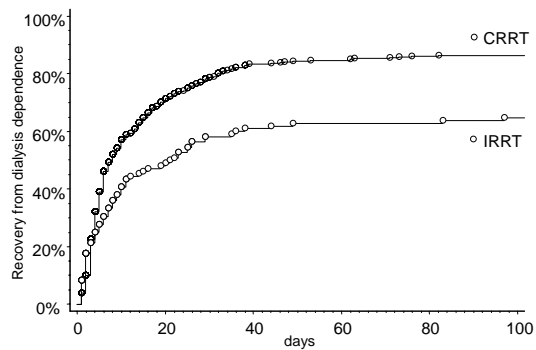
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### Recovery from dialysis dependence




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### Multivariate logistic regression analysis for recovery from dialysis dependence

	Odds Ratio	
Chronic renal dysfunction	0.277	$p < 0.0001$
<b>CRRT</b>	<b>3.333</b>	<b><math>p &lt; 0.0001</math></b>
Trigger: Dx unspecified	0.400	$p = 0.0065$
Gender (Male)	1.905	$p = 0.0321$
High urea/creatinine	0.476	$p = 0.033$

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## 4: Summary

- Modality of RRT was not a significant independent predictor of hospital mortality.
- CRRT was strongly associated with a higher incidence of renal recovery compared to IRRT.
- This information is vital for the design of future international interventional trials.

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## Other targets.....

- ⌘ RCTs in CPB-associated AKI (beginning)
- ⌘ New techniques of CRRT (early work)
- ⌘ Acid-base physiology (huge changes with Stewart's approach)
- ⌘ Understanding the pathogenesis of septic AKI (in its infancy – so much to do!)
- ⌘ Diuretics – the need for appropriate DB RCTs (SPARK has started)

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## More targets....

- ⌘ Choice of fluids and AKI (CHEST trial of starch vs. saline – n=7,000 to start in 2 weeks)
- ⌘ Fluid balance and AKI (**Ravi** has started)
- ⌘ Biomarkers (huge!! –Listen to **Prasad**)
- ⌘ Intensity of RRT and outcome (big trials)
- ⌘ Understanding the pathogenesis of CPB-associated AKI (a bit of progress?)

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..and more targets...

- ⌘ Understanding the histology of AKI (trying with Sean – hard work!)
- ⌘ Attacking dogma: pre-renal azotemia ? ATN? Urinalysis? (have started – need to do more)
- ⌘ Understanding the role of vasoactive drugs (slowly getting there)
- ⌘ Understanding the role of blood pressure in ward patients who develop AKI (early efforts)
- ⌘ Understanding the meaning of urine output (first study soon to appear)

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### The Landscape of CCN- Conclusions

The landscape has changed a great deal over 20 years

“When I started, baseball was played by nine tough competitors, on grass, in graceful ballparks. By the time I finished, there were ten men on a side, the game was played indoors on plastic and I spent my time watching out for a man dressed in chicken suit who kept trying to kiss me”

Ron Luciano (Baseball Umpire)

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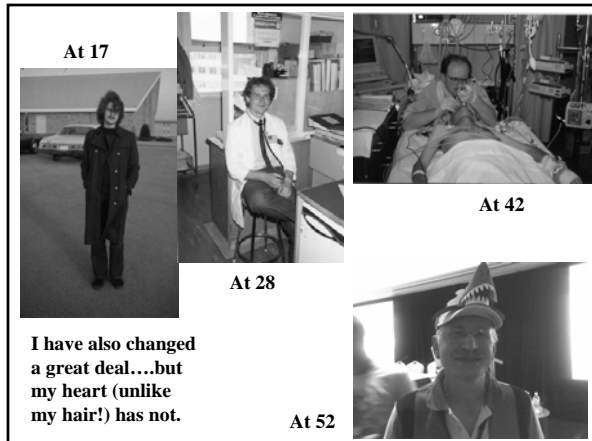
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So... why did I participate in all these changes? My two simple goals

⌘ Decrease the number of patients who receive random medicine and increase those who receive randomized medicine

⌘ Decrease the number of patients who receive eminence-based medicine and increase those who receive evidence-based medicine

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Although we have gone a long way.....

The NEW ENGLAND  
JOURNAL of MEDICINE

Intensity of Renal Support in Critically Ill Patients  
with Acute Kidney Injury

The VA/NIH Acute Renal Failure Trial Network\*

The NEW ENGLAND  
JOURNAL of MEDICINE

ESTABLISHED IN 1827      OCTOBER 22, 2009      VOL. 363      NO. 17

There are many things we do not know that need open-minded approaches and endless research.

Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

The RENAL Replacement Therapy Study Investigators\*

The fight against random eminence-based medicine goes on!

**This is now the task of a new group of young CCN researchers !!**

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