LESSONS FROM EVIDENCE BASED MEDICINE IN THE CARE OF ARF AND ESRD

Prof. Dr. Adrian Covic
University of Medicine “Gr. T. Popa”, Iași

2008
Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients

Metnitz PG et al.


- ARF associated with four-fold increased mortality
- Mortality significantly higher in ARF patients (62.8 vs. 38.5%)
Myth 1 – mortality in ARF remains unchanged?

1974-1979

Mortality 54%

85%

Sf Ioan BOTEZATORUL

Ricci, Ronco Crit Care Clin 21
Proportion of old pts. (> 80 yrs.) with ARF in ICU

Procent de varstnici din numarul total IRA

Ani

Akposso et al Intens Care Med 26:400-406, 2000
Novel Markers of Renal Injury

- Kidney injury molecule-1 (KIM-1)
- Neutrophil
- Cysteine-rich 61 protein of kidney (CRTK)
- Na⁺/H⁺ exchanger (NHE3)
- N-acetylcysteine
- γ-Glutamyltransferase
- α- and β- globulins

KIM-1 in Ischemic ATN

Western Blot Analysis of Urine NGAL post Cardiac Surgery

FIRST “CONCLUSION”: WE TREAT BETTER AND RESULTS WILL PROBABLY SHOW UP
MYTH 2
Who is responsible for the RRT?

Gambro Dialysis Opinions 2005

N= 5887

- Nephrology
- Intensivist

Nephrologist
Intensivist
Both
A SIMPLE EXPLANATION...

...Intensivists are intensively managing many things at the time....
WHILE A NEPHROLOGIST IS THINKING…
Nephrology Consultation in ARF: Does Timing Matter?

- 215 patients with ARF in 4 U.S. academic centers

- In 67 patients, consultation of nephrologist only after > 48 h (median 4 days)

- In this group, mortality was significantly higher:
  74% vs. 49% (p=0.006) in patients with RRT
  53% vs. 22% (p=0.01) in patients without RRT

- Likewise, ICU and hospital length of stay significantly longer

Severe acute renal failure in adults: place of care, incidence and outcomes

J. HEGARTY¹, R.J. MIDDLETON¹, M. KREBS¹, H. HUSSAIN¹, C. CHEUNG¹, T. LEDSON¹, A.J. HUTCHISON², P.A. KALRA¹, H.C. RAYNER³, P.E. STEVENS⁴ and D.J. O’DONOOGHUE¹

From the ¹Department of Renal Medicine, Hope Hospital, Salford, ²Manchester Institute of Nephrology and Transplantation, Central Manchester and Manchester Childrens’ Hospital, Manchester, ³Department of Renal Medicine, Birmingham Heartlands Hospital, Birmingham, and ⁴Department of Renal Medicine, Kent & Canterbury Hospital, Canterbury, UK

Received 21 December 2004 and in revised form 31 May 2005

Ident renal function. In 13 (46%) cases there was an unacceptable delay in patient transfer and in 7 (25%), delays in assessment or commencement of RRT may have adversely affected patient outcome.

Discussion. The incidence of ARE treated with RRT
**WHY?**

Early goal-directed therapy in the treatment of severe sepsis and septic shock  

<table>
<thead>
<tr>
<th></th>
<th>Early goal therapy (n = 130)</th>
<th>Standard therapy (n = 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MODS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7.6 ± 3.1</td>
<td>7.3 ± 3.1</td>
</tr>
<tr>
<td>6 h</td>
<td>5.9 ± 3.7</td>
<td>6.3 ± 3.7, p &lt; 0.001</td>
</tr>
<tr>
<td>72 h</td>
<td>5.1 ± 3.9</td>
<td>6.4 ± 4, p &lt; 0.001</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>30.5 %</td>
<td>46.5 %, p &lt; 0.01</td>
</tr>
</tbody>
</table>
2-nd CONCLUSION: TEAMWORK, BUT, NEPHROLOGIST FROM THE VERY START
Myth 3

“Renal-dose” Dopamine
Or
“IDEAL” vssopressor agent
Use of dopamine in ARF: a meta-analysis

Kellum and Decker Crit Care Med 29:1526-1531, 2001


'Low-dose' dopamine worsens renal perfusion in patients with acute renal failure

A Lauschke et al
Potential solutions:
Fenoldopam-risk of AKI in critically ill

Fenoldopam – dopamine A-1 receptor agonist

Systematic review of RCTs in ICU or major surgery
16 studies, 1290 patients

**Reduced risk of acute kidney injury** – OR 0.43 (0.32-0.59)
**Reduced need for RRT** – OR 0.54 (0.34-0.84)
**Reduced in hospital death** – OR 0.64 (0.45-0.91)
Figure 2. Histogram illustrating the effect of different doses (0–0.4 μg/kg/min) of norepinephrine on mean arterial pressure (MAP), renal blood flow (RBF), renal vascular resistance (RVR), and glomerular filtration rate (GFR) in the conscious dog. Flow is presented as a percentage, with 100% being flow in control dogs receiving placebo. Both MAP and GFR are significantly increased by norepinephrine at clinically relevant doses.

Bellomo et al, Crit Care Med, 2008
NOREPINEPHRINE in patients with AKI

Figure 3. Histogram showing the effect of norepinephrine infusion on urine output in septic sheep compared with placebo (septic control). Norepinephrine infusion nearly doubled urine output.
Survival of septic shock patients treated with vasopressors

**Vasopressin:**
- Strong splanchnic vasoconstriction
- Efferent glomerular vasoconstriction
- Deficient in many shock patients
3-rd CONCLUSION: NOREPINEPHRINE AND NOT DOPAMINE

<table>
<thead>
<tr>
<th>Norepinephrine dose (mg/kg/min)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.1</td>
<td>20</td>
</tr>
<tr>
<td>0.1-0.3</td>
<td>24</td>
</tr>
<tr>
<td>&gt;0.3</td>
<td>76</td>
</tr>
</tbody>
</table>
Myth 4

“FILLING”
MOST IMPORTANTLY
“IDEAL” SOLUTION
Use of Pulmonary artery Catheter

NEJM, 2006, 354, 2213

Proportion of Patients

Alive, PAC group
Alive, CVC group
Unassisted breathing, CVC group
Unassisted breathing, PAC group

% of cases

need for RRT
catheter complications

PAC CVC

NEJM, 2006, 354, 2213
Clinical evaluation of intravascular filling status

N=71, non-spontaneous breathing patients

Monnet et al, Critical Care Medicine, 2006
Conservative vs liberal fluid loading in ARDS patients – POSSIBLY BETTER FOR THE LUNGS

Figure 3. Probability of Survival to Hospital Discharge and of Breathing without Assistance during the First 60 Days after Randomization.

NEJM 2006, 354, 2564
SURVIVAL: albumin VS saline

Global mortality risk in the «SAFE» study in critically ill patients (albumin vs isotonic saline)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Albumin Group</th>
<th>Saline Group</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>726/3473</td>
<td>729/3460</td>
<td>0.99 (0.91–1.09)</td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>81/596</td>
<td>59/590</td>
<td>1.36 (0.99–1.86)</td>
</tr>
<tr>
<td>No</td>
<td>641/2831</td>
<td>666/2830</td>
<td>0.96 (0.88–1.06)</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>185/603</td>
<td>217/615</td>
<td>0.87 (0.74–1.02)</td>
</tr>
<tr>
<td>No</td>
<td>518/2734</td>
<td>492/2720</td>
<td>1.05 (0.94–1.17)</td>
</tr>
<tr>
<td>ARDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24/61</td>
<td>28/66</td>
<td>0.93 (0.61–1.41)</td>
</tr>
<tr>
<td>No</td>
<td>697/3365</td>
<td>697/3354</td>
<td>1.00 (0.91–1.09)</td>
</tr>
</tbody>
</table>

Fluids in ICU
Cochrane survey march 2007

- Albumin vs HES (24 trials): RR 1.14 (0.91-1.43)
- Albumin vs gelatine (7 trials): RR: 0.97 (0.68-1.39)
- Albumin vs Dextran (4 trials): RR: 3.75 (0.4-33.4)
- Gelatin vs HES: (18 trials): RR: 1.0 (0.8-1.25)

Conclusion: no difference!!

Bunn et al, Cochrane database, 2008
Fluid type and outcome

Brunkhorst et al, NEJM 2008
A Renal-Replacement Therapy

Proportion of Patients (%)

Cumulative Dose of Study Fluid (ml/kg)

- Ringer’s lactate
- HES

Brunkhorst et al, NEJM 2008
B  Death at 90 Days

Proportion of Patients (%)

Cumulative Dose of Study Fluid (ml/kg)

N=38  N=70

N=35  N=61

N=46  N=58

N=48  N=46

N=94  N=14

Ringer’s lactate  HES

Brunkhorst et al, NEJM 2008
Timing of correction of tissue perfusion on outcome

Figure 1

Odds ratio and 95% confidence interval for studies (total of 1031 patients) attempting to improve tissue perfusion after onset of tissue hypoxic can be expected. No beneficial effect on mortality was seen. (Modified from [30].)

Figure 2

Odds ratio and 95% confidence interval for studies (total of 662 patients) attempting to improve tissue perfusion before onset of tissue hypoxic can be expected. Beneficial effect on mortality were seen. (Modified from [30].)
4-th CONCLUSION: SALINE, CVP + GOOD CLINICAL PRACTICE, POSIBIL RINGER MACROMOLECULAR SOLUTIONS
MYTH 5

FUROSEMID

COMPULSORY?
Loop Diuretics and ARF: double-blind, randomized trial

## Loop Diuretics and ARF: double-blind, randomized trial

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>OR (95% CI) Covariate adjusted</th>
<th>Covariate and propensity score adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td>1.37 (0.97-1.92)</td>
<td>1.65 (1.05- 2.58)</td>
<td>1.68 (1.06-2.64)</td>
</tr>
<tr>
<td>Nonrecovery of renal function</td>
<td>1.53 (1.08-2.15)</td>
<td>1.70 (1.14-2.53)</td>
<td>1.79 (1.19-2.68)</td>
</tr>
<tr>
<td>Death or nonrecovery</td>
<td>1.48 (1.02-2.12)</td>
<td>1.74 (1.12-2.68)</td>
<td>1.77 (1.14-2.76)</td>
</tr>
</tbody>
</table>

Mehta et al JAMA 288: 2547-2553, 2002
Diuretics and outcome of AKI - metaanalysis

Figure 1. Forest plot showing effect of randomized and nonrandomized studies on mortality treatment effect as risk ratio. Small solid squares, study estimates; vertically capped horizontal lines, 95% credible intervals (CI); vertical lines within vertically capped diamond-shaped boxes, subgroup and overall point estimates and 95% CI; vertical straight line, the null effect.

Sampath et al, Crit Care Med, 2007
5-th CONCLUSION: FUROSEMID – PROBABLY, but AFTER CORRECT FILLING (!)
PROMISSES OR CERTITUDES?

1. Insulin – intensive glycaemic control
2. EPO
3. Activated Protein C
4. Steroids
5. Atrial Natriuretic Factor - ANF

6. Growth factors - IGF I; Endothelin antagonist receptors; Tyroxin; PGE₁
1) Effect of control of mean blood glucose in ICU patients

Percentage of risk for several complications in ICU patients with stay > 5 days

Cumulative risk of hospital death in ICU patients with stay > 5 days


% risk

- Death in ICU
- CI polyneuropathy
- Bacteremia
- Inflammation
- >2 red cell transfusions
- Acute renal failure

Cumulative Hazard (% in hospital death)

Days after inclusion

- > 150
- 110-150
- < 110
Survival: intensive insulin therapy or conventional insulin therapy in severe sepsis

2) EPO: Cumulative patient survival in critically ill patients

EPO: n 733
Control: n 722

EFFICACY AND SAFETY OF RECOMBINANT HUMAN ACTIVATED PROTEIN C FOR SEVERE SEPSIS

JORDON R. BERNARD, M.D., JEAN-LOUIS VINCENT, M.D., PH.D., PIERRE-FRANCOIS LATERRRE, M.D., STEVEN P. LAROSA, M.D., JEAN-FRANCOIS DHAINAUT, M.D., PH.D., ANGEL LOPEZ-RODRIGUEZ, M.D., JAY S. STEINGRUB, M.D., GARY E. GARBER, M.D., JEFFREY D. HELTERBRAND, PH.D., E. WESLEY ELY, M.D., M.P.H., AND CHARLES J. FISHER, JR., M.D., FOR THE RECOMBINANT HUMAN ACTIVATED PROTEIN C WORLDWIDE EVALUATION IN SEVERE SEPSIS (PROWESS) STUDY GROUP*
Coagulation

Anticoagulant  Procoagulant

COAGULATION

TM - thrombin

PC  APC + PS  Degrades Va, VIIIa (-)

ATIII  T-ATIII complexes (-)

TFPI

Thrombin

Xa  X  VIIa  TF

IXa  IX  Prothrombin
APC Therapy for Patients with Septic Shock

Days after the Start of the Infusion

Survival (%)

P = 0.006

24.7% †
30.8% †
19.4% relative red’n

NO. AT RISK

Drotrecogin alfa activated
Placebo

850 737 684 857 640
840 705 639 802 581
Hydrocortisone Therapy for Patients with Septic Shock

Kaplan–Meier Curves for Survival at 28 Days.

**Anaritide:**
21-Day Dialysis-Free Survivorship.

* p=0.005 A vs. P

Lewis et al, AJKD 2000
When to initiate acute dialysis?
Generally accepted indications

- Acute (life-threatening) hyperkalemia
- Severe volume overload (pulmonary edema)
- Severe metabolic acidosis
- Uremic organ complications (e.g. pericarditis)

'Prophylactic' dialysis:
- Creatinine clearance, e.g. 0.1-0.15 ml/kg/min?
- Serum urea concentrations, e.g. 150, 200, ... mg/dl?
• Retrospective analysis (100 trauma patients, 1989-97)

• „Early“: BUN<60 mg/dl; „late“: BUN> 60 mg/dl

• „Early“ starters had significantly better survival compared to „late“ starters: 39% vs. 20.3% (p=0.041)
### Timing of initiation of RRT and prognosis in AKI-PICARD group

<table>
<thead>
<tr>
<th>Low BUN at start RRT &lt; 76 mg/dl</th>
<th>RR for death (CI)*</th>
<th>RR for death (CI)**</th>
<th>RR for death (CI)***</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>High BUN at start RRT &gt; 76 mg/dl</td>
<td>1.85 (1.16-2.96)</td>
<td>2.07 (1.30-3.29)</td>
<td>1.97 (1.21-3.20)</td>
</tr>
</tbody>
</table>

- *Adjusted for age, hepatic failure, sepsis, thrombocytopenia, and serum creatinine and stratified by site and initial dialysis modality,
- ** Adjusted for propensity score alone
- *** Adjusted for co)variates and propensity score

Treatment practices in RRT for AKI

Figure 1. Percent of patients with specified frequency of intermittent hemodialysis (IHD) treatment. Horizontal lines represent pooled data from all sites while the symbols represent data for individual sites. Data for treatment schedules less frequent than four-times per week (two-times per week, three-times per week and alternate-day treatment schedules) are pooled.

Overberger et al, cJASN,2008
### Table 3. Outcomes According to Treatment Group.*

<table>
<thead>
<tr>
<th></th>
<th>Alternate-Day Hemodialysis (N=80)</th>
<th>Daily Hemodialysis (N=80)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality — no. (%)†</td>
<td>37 (46)</td>
<td>22 (28)</td>
<td>0.01</td>
</tr>
<tr>
<td>Resolution of acute renal failure</td>
<td>16±6</td>
<td>9±2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Plus-minus values are means ± SD.

†Mortality was calculated according to the intention to treat.
Mortality in CVVH patients is related to the volume of replacement fluid

- Prospective RCT of different doses in CVVH treatment of ARF
- 425 patients
- Primary endpoint: survival @15 days after stopping CVVH

Significantly better survival with 35 or 45 ml/kg/min vs. 20 ml/kg/min

Outcome CRRT vs IHD

P = 0.02

N = 166

Mehta et al, Kidney Int, 2001, 1154-1163
Survival IHD vs CRRT
A randomised controlled trial

<table>
<thead>
<tr>
<th></th>
<th>Intermittent haemodialysis</th>
<th>Continuous venovenous haemodiafiltration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of sessions (h)</td>
<td>5.2 (5.1–5.3)</td>
<td>continuous</td>
</tr>
<tr>
<td>Blood flow (mL per min)</td>
<td>278 (273–281)</td>
<td>146 (145–147)</td>
</tr>
<tr>
<td>Dialysate flow*</td>
<td>500</td>
<td>1099 (1068–1128)</td>
</tr>
<tr>
<td>Ultrafiltration flow (mL per h)</td>
<td>1278 (1255–1301)</td>
<td></td>
</tr>
<tr>
<td>Net ultrafiltration† (mL per day)</td>
<td>2213 (2141–2285)</td>
<td>2107 (2011–2203)</td>
</tr>
<tr>
<td>Mean urea (mmol/L)</td>
<td>15.7 (7.5)</td>
<td>14.8 (9.1)</td>
</tr>
</tbody>
</table>

Data are mean (95% CI) or mean (SD). *mL per min in the intermittent haemodialysis group and mL per h in the continuous venovenous haemodiafiltration group. †Mean volume loss per day of treatment.

Table 2: Treatment modalities

Vinsonneau et al, Lancet 2006, Hemodaife
Survival IHD vs CRRT
A randomised controlled trial

![Survival Graph]

Vinsonneau et al, Lancet 2006, Hemodaife
CRRT vs IHD: The PICARD experience

Figure 1. Mortality within 60 d after acute kidney injury requiring dialysis: Continuous renal replacement therapies versus intermittent hemodialysis.

Cho et al, JASN november 2006
IHD vs CRRT: a meta analysis

Bagshaw et al, Crit Care Med, 2008
CIRCUMSTANTIAL EVIDENCE, THAT'S ALL YOU'VE GOT!

YOU CAN'T GET A FAIR TRIAL IN THIS TOWN.
Conclusion:

„These data suggest that, provided strict guidelines to improve tolerance and metabolic control are used, almost all patients with acute renal failure as part of multiple-organ dysfunction syndrome can be treated with intermittent haemodialysis“

Vinsonneau et al, Lancet 2006; 368: 379-85
Fig 2. (A) MAP, (B) heart rate, (C) CO, and (D) SVR in 20 patients treated with extended dialysis (open circles) and 19 patients treated with CVVH (closed circles). There were no significant differences between groups with respect to hemodynamic variables.
The Genius dialysis System
... What else is important:

Dialysis dose

\[
\frac{K \times t}{V}
\]

\[
\frac{M.D. \times t}{P}
\]