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Abstract 1

Long Term Renal Outcomes in Critically Ill Patients with Acute Kidney Injury

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Objectives

Acute kidney injury (AKI) is common in critically ill patients. We aimed to evaluate the long term renal outcome in critically ill patients with AKI.

Methods

This was a single-center retrospective study of adult patients admitted to the Medical Intensive Care Unit (ICU) between 1st January 2010 and 31st December 2010 in our tertiary care hospital. Patients who were dialysis-dependent prior to ICU admission were excluded. AKI was defined by increment in serum creatinine >0.3 mg/dL. The outcome was progressive chronic kidney disease (CKD) defined by doubling of serum creatinine or end stage renal disease (ESRD).

Results

We evaluated 421 patients [median age 59.4 (IQR 46.4, 71.1) years, male 61.8%]. Median premorbid serum creatinine was 87 (66, 115) μmol/L. Most patients required mechanical ventilation (74.6%) and 141 patients (33.5%) required vasopressors. AKI occurred in 209 patients (49.6%) at ICU admission: 80 had AKIN Stage 1, 38 had Stage 2 and 91 had Stage 3 AKI. Eighty-eight patients (20.9%) received acute dialysis during their ICU stay. One hundred and three patients (41.1%) died during the hospitalization. Median follow-up was 27.7 (3.7, 34.4) months.

Among 248 survivors, 28 patients (11.3%) developed progressive CKD. ESRD occurred in 13 patients at median 9.8 (0, 14.5) months. In uni-variate analysis, patients with progressive CKD were more likely to have AKI (67.9% vs. 41.4%, p=0.008) and dialysis (46.4% vs 15.0%, p<0.001). In multi-variate analysis, acute dialysis was independently associated with progressive CKD [OR 3.21 (95% CI 1.21, 8.49), p=0.02].

Conclusion

Severe AKI requiring acute dialysis was associated with progressive CKD.

Abstract 2

A Systematic Review Of Health-Related Quality-Of-Life Among Critically Ill Survivors Of Acute Kidney Injury

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Purpose
Health-related quality-of-life (HQRL) is increasingly recognized as an important patient-centered outcome following acute illness. Among critically ill survivors suffering an episode of acute kidney injury (AKI), HRQL has been variably described. In this systematic review we summarize understanding on long-term HRQL among survivors of AKI in the intensive care unit.

Methods
We performed a systematic review and evidence synthesis. We included studies reporting original data that described HRQL using validated tools. The comprehensive literature search, study selection and data abstraction were performed in duplicate. Study quality was appraised. Data are primarily narratively described due to significant study heterogeneity.

Results
Our search yielded 2193 articles of which 18 fulfilled eligibility. Study quality was assessed as moderate to good. Six unique HRQL instruments were utilized. Follow up duration to ascertain HRQL was variable, ranging between 2 months to 15 years. HRQL among AKI survivors was significantly impaired to age/sex-matched normative population data. HRQL compared between survivors with and without AKI was similar beyond 6 months. Physical component domains were consistently more impaired compared with mental component domains. Limitations in activities of daily living, disability, and inability to return to work were common. Despite impaired HRQL, most survivors would receive similar treatment again, including renal replacement therapy if necessary.

Conclusion
Among critically ill survivors whose course was complicated by AKI, HRQL was universally impaired when referenced to population norms; however, was comparable to those without AKI. Physical limitations and disabilities were commonly described by patients compared with psycho-social limitations. Despite this, most survivors perceived their HRQL as acceptable and would undergo similar therapy again.

3

Epidemiology of AKI Requiring Dialysis in Critically Ill Children

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Introduction: Previous pediatric studies on dialysis in acute kidney injury (AKI) suggest that the mortality rate is mainly related to the underlying diagnosis or multiple organ failure rather than to a specific dialysis modality or other risk factors. Fluid overload before dialysis also seems to influence mortality. Our objective was to identify the most important risk factors of 28-day mortality at dialysis initiation.

Methods: We conducted a retrospective cohort study in a tertiary care pediatric center. All critically ill children who underwent acute continuous renal replacement therapy (CRRT) or intermittent hemodialysis for AKI between 1998 and 2008 were included, excluding those with chronic kidney disease. A case report form was developed and specific risk factors were identified using an item generation–item selection modality.

Results: We enrolled 70 consecutive patients. The main ICU admission reasons were respiratory failure (34%), septic shock (29%), AKI (24%) and post-operative (21%). The most frequent underlying diseases were bone marrow transplant (24%) and solid organ transplant (17%). The majority of patients received CRRT only. Thirty-three patients (47%) died within 28 days after ICU admission. The median age (8.9 years [IQR 1.9-14.2]), weight (28 kg [8-45]), PEdiatric Logistic Organ Dysfunction score (PELOD) (21 [20-32]), Pediatric Index of Mortality 2 (PIM 2) (8 [7-29]), creatinine (102 umol/l [70-155]), vasoactive score (3 [0-47]) and oxygenation index (7 [4-19]) at ICU admission were similar between survivors and non-survivors. We identified these risk factors of mortality in univariate analyses: hematological underlying disease and factors at dialysis initiation including: fluid overload ≥20%, PELOD score ≥20 and higher creatinine. Of these, only PELOD score ≥20 was significant in the multivariate logistic regression analysis (OR 4.5;95%CI 1.4-14.1;p=0.01). After ICU discharge, 12 out of 35 survivors needed dialysis. Among 31 survivors at hospital discharge, 3 required dialysis.

Discussion: Despite improvement in patient care, almost half of our patients with AKI requiring dialysis died within 28 days. Our data suggest that a higher severity of illness is the most important risk factor of mortality in AKI requiring dialysis.

Conclusion: In our pediatric study, only the severity of illness, as measured by the PELOD score before initiation of dialysis, was independently associated with an increased risk of mortality.

4

A Multicenter Population-based Epidemiological Study of Intensive Care Unit (ICU) Acquired Acute Kidney Injury (AKI) in a Brazilian Amazon Region

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Purpose of the study: Prospective epidemiological data on AKI in developing countries is scarce. This study was designed to assess the incidence of ICU-acquired AKI in the Amazon Region in Brazil.

Methods used: Prospective data on all adult patients admitted in all ICUs of the Western Amazon region (600 square kilometers and 800,000 inhabitants) were collected for 11 months during 2014 and 2015. Patients < 18 years old, chronic kidney disease stage 5, kidney transplant or ICU stay < 48 h were excluded. AKI was diagnosed by KDIGO criteria and mortality was assessed 30 and 180 days after ICU discharge.

Summary of the results: During the study period, 824 patients were ICU admitted and 642 fulfilled selection criteria. AKI incidence was 38% and was associated with age (OR 1.11 for each 5 year increase, $p < 0.001$) previous fluid balance > 1,500 ml/24h (OR 2.3, $p = 0.017$), mechanical ventilation (OR 1.7, $p = 0.018$) and surgery (OR 0.38, $p = 0.017$). The main reasons for ICU admission in patients who developed AKI were hemodynamic instability (22.3%), respiratory failure (18.6%), surgery (17.8%), neurological diseases (14.2%), and sepsis (9.3%). Only 2.3% had tropical diseases. There were significant association between AKI and mortality during ICU stay (42% vs 27%, $p<0.001$) and mortality within 30 days after ICU discharge (10% vs 6%, $p=0.046$). AKI mortality during ICU stay was associated with mechanical ventilation (OR 3.5, $p < 0.001$), use of vasoactive drugs (OR 2.6, $p < 0.001$), age (OR 1.07for each 5 years increase, $p = 0.017$) and surgery (OR 0.54 , $p = 0.017$).

Conclusion reached: AKI has a high incidence and mortality rate in ICU patients of the Western Amazon area. Causes of ICU admission and risk factors for AKI in this study did not differ from those seen in developed countries. The lack of tropical diseases-associated AKI might be due the particular conditions of the Amazon area, with rivers not navigable most of the year, long rain period making difficulty access to larger cities and poor health services infrastructure in remote areas.

5

Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates (AWAKEN): Incidence and Outcomes from an International Multi-center Cohort Study

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On behalf of the Neonatal Kidney Collaborative
Background: Single center studies report neonatal acute kidney injury (AKI) incidence 12-70%; neonates with AKI appear to have worse outcomes. These findings prompted the formation of the Neonatal Kidney Collaborative (NKC) to improve our understanding of neonatal AKI.
Objective: Assess the incidence of neonatal AKI and its association with outcomes in a large, multi-center cohort.
Design/Methods: NKC includes 24 institutions from 4 countries (USA, Canada, Australia and India). NICU admissions from Jan 1, 2014 to Mar 31, 2014 were screened; data from 20 centers are presented. Inclusion criteria: 1) admission during the study period, 2) need for intravenous fluids ≥48 hrs. Exclusion criteria: 1) admission at > 2 weeks of age, 2) congenital heart disease requiring surgical repair at < 7 days of age, 3) lethal chromosomal anomaly, 4) death within 48 hours of admission. AKI was defined using the KDIGO SCr based definition: a rise in SCr of 0.3 mg/dl or a 50% rise from baseline = stage 1; 100% rise = stage 2, and 200% rise = stage 3. Baseline SCr = lowest previous value.
Results: Of 3397 screened neonates, 1742 (51%) met study criteria. Of these, 960 (55%) had at least 2 SCr measured and were included in the analyses. 192/960 (20%) developed AKI: stage 1 =22%; stage 2 = 28%, stage 3 =50%. Compared with patients without AKI, those with AKI were more likely to die, have neurologic, cardiovascular, pulmonary, infectious, and renal diagnoses, and be hospitalized ≥120 days (Table). 10% (N=20) of those with AKI received renal replacement therapy.
Conclusions: The AWAKEN study demonstrated an AKI incidence of 20%. Those with AKI are at risk for significant clinical outcomes. Further analysis of this robust database is underway.

Outcomes by AKI stage	AKI 0 (n=768)	AKI 1 (n=41)	AKI 2 (n=54)	AKI 3 (n=97)	p-value
Status at <120 days					<0.0001*
Home	609 (80%)	22 (54%)	30 (56%)	44 (45%)	
Still in NICU	26 (3%)	1 (2%)	13 (24%)	21 (23%)	
Transferred Convalescent Care	87 (11%)	5 (12%)	4 (7%)	17 (18%)	
Transferred Escalation of Care	13 (2%)	2 (5%)	4 (7%)	3 (3%)	
Died	31 (4%)	11 (27%)	3 (6%)	12 (12%)	
Discharge Diagnoses					
Cardiovascular	144 (19%)	18 (44%)	33 (61%)	44 (45%)	<0.0001*
Pulmonary	82 (11%)	12 (29%)	25 (46%)	41 (42%)	<0.0001*
Neurological	144 (19%)	16 (39%)	18 (33%)	28 (29%)	<0.0004*
Renal	62 (8%)	15 (34%)	21 (39%)	47 (49%)	<0.0001*
Infection	181 (24%)	16 (39%)	22 (41%)	33 (34%)	0.0018*

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Risk factors for Neonatal Acute Kidney Injury: Results from the Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) Study

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On behalf of the Neonatal Kidney Collaborative

Background: The risk of neonatal acute kidney injury (AKI) is as high as 70% in select subpopulations. However most reports are from single-center studies, making generalizability difficult.
Objective: The aim of this study was to determine the risk factors for neonatal AKI using the largest multi-center international cohort of neonates derived from 20 institutions participating in the AWAKEN study conducted by the Neonatal Kidney Collaborative.
Design/Methods: AWAKEN is a retrospective cohort study of all neonates who were admitted to the NICU from January 1- March 31, 2014 requiring intravenous fluids for > 48 hours and who met the inclusion and exclusion criteria. AKI was defined according to the neonatal KDIGO definition limited to serum creatinine.
Results: Of the 3397 neonates screened, 1742 met the inclusion criteria and 960 had >1 serum creatinine measurement. AKI (stages 1-3) was identified in 192 neonates. Maternal and neonatal risk factors that separated neonates with and without AKI are listed in the Table.
Conclusions: This is the first multi-center international study to evaluate the risk factors associated with neonatal AKI. Many of these results are consistent with the single-centre studies reported in the literature. The data will require further stratification tailoring the risk factor analyses for subpopulations of neonates. Using the AWAKEN cohort, we plan to develop and validate risk stratification models which can be used in future prospective studies to aid in the early identification of neonatal AKI.

Risk Factor	no AKI, n=768 (%)	AKI, n=192 (%)	p value
MATERNAL CHARACTERISTICS			
maternal hemorrhage	19 (2)	12 (6)	0.01
antenatal steroids	290 (38)	99 (52)	0.005
assisted conception	43 (6)	22 (11)	0.01
maternal age (years)	28 (+/-6)	27 (+/-5)	0.004
oligohydramnios	36 (5)	17 (9)	0.02
PERINATAL EVENTS			
oxygen for resuscitation	367 (48)	124 (65)	<0.0001
positive pressure ventilation	397 (52)	140 (66)	<0.0001
intubation	191 (25)	119 (62)	<0.0001
chest compression	39 (5)	21 (11)	<0.0001
NEONATAL CHARACTERISTICS			
Apgar 1 min	7 (4, 8)	4 (2, 7)	<0.0001
Apgar 5 min	8 (7, 9)	7 (6, 8)	<0.0001
gestational age <35 weeks	406 (53)	136 (71)	<0.0001

birthweight <1500 g	118 (24)	116 (60)	<0.0001
length (cm)	44.4 (+/-6)	38.6 (+/-8)	<0.0001
head circumference (cm)	30.9 (+/-4)	27.1 (+/-5)	<0.0001
respiratory failure	384 (50)	140 (73)	<0.0001
congenital heart disease	30 (4)	16 (8)	0.01

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Low Pre-operative Serum Bicarbonate Levels Predict Acute Kidney Injury after Cardiac Surgery

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Purpose: Acute kidney injury (AKI) after cardiac surgery is a common and serious complication, and is associated with high mortality rates. There is evidence showing that metabolic acidosis induce decline of glomerular filtration rate (GFR) in associated with activation of intrarenal renin-angiotensin system. Whether pre-operative serum bicarbonate levels are associated with the development of AKI in patients who undergo cardiac surgery is not well known. Therefore, the aim of this study was to identify the clinical implications of pre-operative serum bicarbonate levels on AKI occurrence after cardiac surgery.
Methods: Patients who underwent coronary artery bypass or valve surgery at Yonsei University Health System from January 2013 to December 2014 were enrolled. Serum bicarbonate levels and creatinine concentrations within 96 hours before cardiac surgery were adopted for preoperative values. The patients were categorized into three groups according to preoperative serum bicarbonate levels; group 1 (n=193), <23 mEq/L; group 2 (n=226), 23-24 mEq/L; group 3 (n=456), >24 mEq/L. Primary outcome was incidence of AKI at 48 hours after cardiac surgery. AKI was defined by the Acute Kidney Injury Network criteria. Multiple logistic regression analysis was performed to find risk factors of AKI occurrence.
Results: The mean age was 60.5 years, and 518 (59.2%) patients were male. 228 patients (26.1%) developed AKI at 48 hours after cardiac surgery [stage 1, 173 (19.8%); stage 2, 28 (3.2%); stage 3, 27 (3.1%)]. Incidence of AKI was higher in group 1 (34.6%) than group 2 (26.3%) and group 3 (39.0%) ($P < 0.001$). In addition, the duration of postoperative ICU stay was longer in AKI patients [AKI patients (6.2 days) vs. non-AKI patients (2.7 days), $P<0.001$] and in the low preoperative serum bicarbonate level groups [group 1 (4.4 days), group 2 (3.6 days), group 3 (3.3 days), $P<0.001$]. In multivariate logistic regression analysis, low pre-operative serum bicarbonate levels were significantly associated with AKI even after adjusting for age, sex, history of hypertension, history of diabetes mellitus, operation type, hemoglobin levels, and GFR. [group 1 vs. group 3, odds ratio=2.36, 95% confidence interval=1.57-3.54, $P<0.001$].
Conclusion: Correction of low serum bicarbonate levels before cardiac surgery may reduce the risk of AKI development.

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A clinical risk model to predict acute kidney injury after cardiac surgery in Chinese patients

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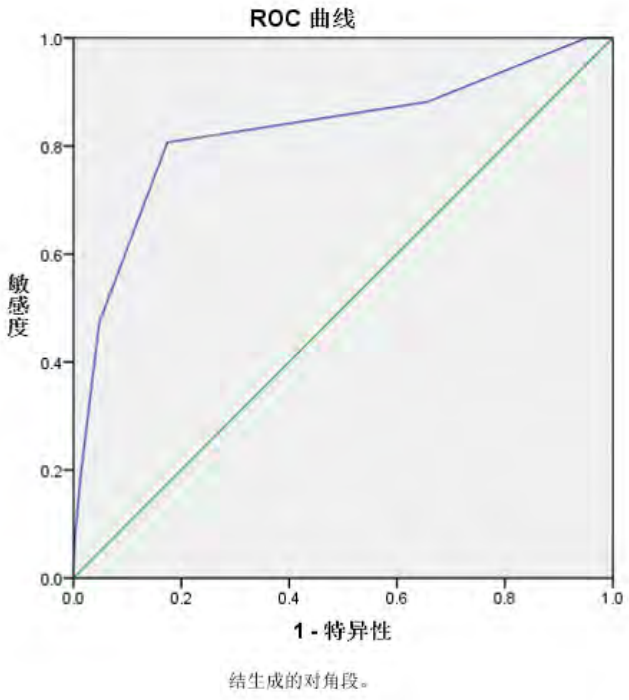
Objective: To establish and validate a risk model to predict AKI after cardiac surgery (AKICS) based in Chinese patients. Methods: 7233 patients who underwent cardiac surgery (CABG,OPCAB, valve surgery or CABG with/without valve surgery)in the department of cardiac surgery in our centre between Jan,2010 and April,2013 were included. Logistic regression was used to analyze the incidence and preoperative risk factors of AKICS among 6081 patients, and a specific number of points were assigned to each risk factor according to the odds ratio (OR) observed, the other patients were set for validation, by means of Hosmer—Lemeshow goodness-of-fit test for the calibration and receiver operation characteristic(ROC) curves with area under ROC curve(AUROC) for the discrimination. Results: The incidence of AKI and RRT after cardiac surgery in the derivation cohort were 23.8% (1446/6081) and 1.5% (93/6081) respectively. The mortality of derivation cohort was 2.8% (170/6081). According to the logistic regression: male(OR=2.277),atrial fibrillation（OR=1.766）,preoperative kidney disease(without RRT)（OR=3.904）, preoperative coronary angiography（OR=1.137）,NYHA>2（OR=1.457）, were recognized as independent risk factor for AKI after cardiac surgery. The risk model was categorized to high risk cohort (total score≤8) and low risk cohort (total score 9-12), the risk of AKI in the derivation cohort was 35.6% (low risk cohort) vs 83.4%(high risk cohort). The AUROC for AKICS of the validation cohort was 0.81,which meant a good discrimination, and Hosmer—Lemeshow goodness-of-fit test ($\chi 2$=10.13，p=0.256) showed a proper calibration. Conclusions: The risk model based upon chinese patients, with AKI being defined with the 2012 KDIGO AKI guideline is established and proper prediction value for AKICS is validated.



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Subclinical Acute Kidney Injury is an Early Stage of AKI

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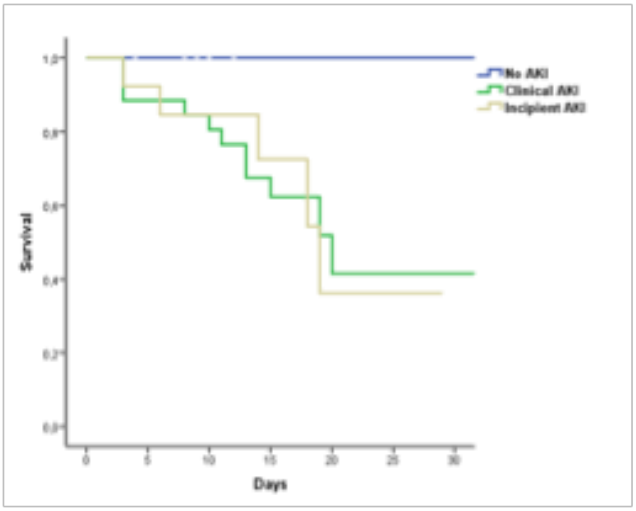
Background: A recent ADQI consensus conference on utilizing biomarkers in AKI has suggested that novel biomarkers such as NGAL, KIM-1, and IGFBP-7 can identify kidney damage prior to elevations in serum creatinine (sCr). Combining damage and functional markers can thus permit recognition of an early stage of AKI termed subclinical AKI. In this study we tested the hypothesis that a panel of damage biomarkers could detect subclinical AKI and would predict the subsequent development of clinical AKI.
Methods: We included 50 consecutive patients admitted to a Medical ICU. Daily sCr, urine albumin (uAlb) and urine β2–Microglobulin levels were measured each 24 hours for 7 consecutive days; we also evaluated urine sediment and assigned a score from 1 to 3 using Perazella et al criteria. We define subclinical AKI if any of the following criteria was reached in the absence of alterations in sCr: a) new onset of albuminuria (≥15 mg/L), or b) β2-Microglobulin (≥3.2 mg/L), or c) a urinary sediment score ≥2. Clinical AKI was defined by KDIGO sCr criteria. We analyzed the predictive value of each of these biomarkers for the subsequent development of clinical AKI as well to predict survival.
Results: Of the 50 patients, 11 (22%) did not develop AKI while 39 (78%) developed incipient AKI that progressed to clinical AKI in 26 (67%) while 13 (33%) did not have a rise in sCr. The rise in uAlb levels and β2-Microglobulin levels at 24 and 48 h. predicted the development of clinical AKI (uAlb AUC 0.753 (95% CI 0.612-0.894), p = 0.02; and β2-Microglobulin 0.770 (95% CI 0.624-0.916), p=0.010) at 24 h; and uAlb 0.707 (95% CI 0.555-0.859), p=0.012; and β2-Microglobulin 0.703 (95% IC 0.545-0.861), p=0.14 at 48 h; respectively). A urinary sediment score ≥2 at 24 and 48 h equally predicted the development of clinical AKI; AUC 0.818 (95% IC 0.638-0.998), p=0.001 and 0.773 (95% IC 0.580-0.965), p=0.006, respectively. 28 day mortality did not differ between patients with subclinical AKI who didn't developed clinical AKI and patients with subclinical AKI who developed clinical AKI.
Conclusions: Our data shows high incidence of subclinical AKI that progressed to clinical AKI. These findings support the ADQI recommendations to consider subclinical AKI based on positive damage biomarkers alone as an early phase of AKI. Identification of incipient AKI would potentially allow earlier intervention with preventive and treatment strategies to reverse kidney injury and improve recovery.



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High Level of Plasma Pro-Enkephalin (penKid) in the General Population Predicts Deterioration of Kidney Function and Incidence of Chronic Kidney Disease

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Purpose of the study:

Recently, elevated plasma Pro-Enkephalin (penKid), a stable surrogate marker for Enkephalins, has been associated with decreased estimated glomerular filtration rate (eGFR) in acute disease settings. Here we examined if penKid predicts incident chronic kidney disease (CKD) and decline of renal function in a prospective general population cohort without CKD at baseline.

Methods:

The background population for this study is the population-based Malmö Diet and Cancer Study (MDC) of which 28,098 subjects participated in the baseline examination between 1991 and 1996. In a random sample (n=2,568) of subjects without CKD (eGFR > 60 mL/min/1.73 m2) at inclusion the relationship between penKid concentration at baseline and presence of CKD at follow-up re-examination as well as the association of penKid with yearly change in eGFR, plasma creatinine and plasma Cystatin C was examined.

Results:

During a mean follow-up time of 16.6 years, 31.7% of the subjects developed CKD. Among participants in the highest versus the lowest tertile of penKid concentration at baseline the OR for CKD was 1.50 (95% CI 1.18-1.94) after adjusting for age, sex, follow-up time, and baseline levels of eGFR, fasting glucose, BMI, antihypertensive treatment and systolic blood pressure. The yearly mean decline of eGFR as well as the yearly rise of cystatin C and creatinine were significantly higher among participants with penKid levels in the highest tertile (P-trend=0.0003, 0.005 and 0.000003). Through genome-wide association analysis in 4,150 participants of the same cohort we identified one locus with 24 SNPs located up- or downstream of the PENK gene that associated with penKid concentration (P<5x10exp-8). The strongest association was observed for rs1012178 where the T minor allele associated with 0.057 pmol/L higher penKid levels per allele (P=4.666exp-21). The T-allele associated with 19% increased risk of CKD per minor allele (P=0.03).

Conclusions:

Circulating plasma concentration of penKid predicts incident CKD and may be useful in identifying subjects in need of pharmacological and non-pharmacological primary preventive regimens. In addition, the Mendelian Randomization analysis suggests that the relationship between penKid levels and incident CKD could be causal.

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A Worldwide Multicentre Evaluation of Acute Kidney Injury in Septic and Non-septic Critically Ill Patients: The Intensive Care Over Nations (ICON) Audit

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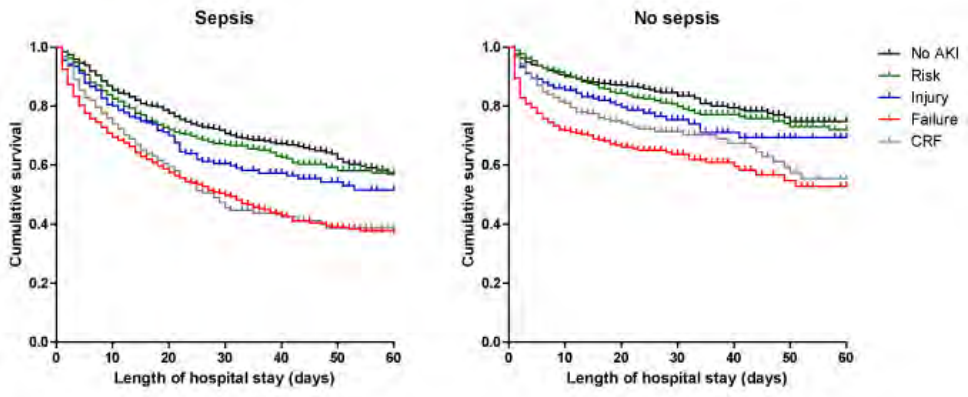
Introduction: Acute Kidney Injury (AKI) is a serious complication in hospitalized patients, particularly in the critically ill, in whom AKI is independently associated with poor prognosis and outcome. Sepsis is the most important cause of AKI and its pathogenesis is clearly distinct from non-septic AKI. Here, we compared the clinical course and outcome in septic and non-septic critically ill patients worldwide.
Methods: Intensive Care Units (ICUs) were invited to participate voluntarily in the Intensive Care Over Nations (ICON) audit. In participating centers, data was prospectively collected from all adult patients (>16 years) admitted to the ICU during a 10-day period. Patients admitted for less than 24h for routine postoperative surveillance were excluded. Data was collected daily during the ICU stay up to 28 days, with a follow-up for outcome data until hospital discharge or death. AKI was defined according to the Risk, Injury, Failure, Loss and End-Stage (RIFLE) classification and was diagnosed during the first 48h after ICU admission. Patients with pre-existent chronic renal failure (CRF) were analyzed as a separate subgroup.
Results: The study population comprised 9579 patients. At admission, 30% of patients fulfilled sepsis criteria of which 67% developed AKI, compared to 57% in the non-septic population ($p<0.0001$). AKI was more severe in septic patients and these patients were less likely to recover to a lower RILFE category compared to non-septic patients (improvement between day 3 and day 7 in 22 vs. 32%, $p<0.0001$). Dialysis incidence was higher in septic patients compared to non-septic patients (21% vs. 5%, $p<0.0001$). Also in-hospital mortality rates were higher (33% vs. 14%, $p<0.0001$), which increased to 51% in septic and 35% in non-septic AKI-F patients. Hospital mortality of septic AKI-F patients was similar compared to septic patients with pre-existent CRF (HR 1.6, 95%CI 1.3-2.0 compared to 1.8, 95%CI 1.5-2.1 in septic AKI-F patients). Septic patients with AKI-R or AKI-I that improved between day 3 and day 7 after admission showed a similar mortality compared to septic patients who did not develop AKI, while mortality remained elevated in AKI-F patients that improved between day 3 and 7. Cumulative survival curves are presented in Figure 1.
Conclusion: AKI in sepsis is more severe, less likely to recover and associated with a higher mortality, compared to non-septic AKI.



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Progression of Chronic Kidney Disease and Cardiovascular Outcomes After Cardiac Catheterization Associated-Acute Kidney Injury and Comparison with Population Controls

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Purpose of the study: Studies of chronic kidney disease (CKD) progression following Acute Kidney Injury (AKI) have largely relied on administrative data. We investigated the association between AKI and CKD progression using laboratory data and long-term endpoints in a national U.S. cohort with matched population controls. We hypothesized there is an association between AKI and CKD progression.

Methods: All Veterans Affairs (VA) patients undergoing percutaneous coronary intervention (PCI) in the VA Clinical Assessment, Reporting, and Tracking Program between 2005-2010 were studied. A matched control group was derived from patients unexposed to cardiac catheterization during the same time period. AKI was defined as an absolute (0.5 mg/dL) or relative (25%) increase in serum creatinine or dialysis within 7-days. CKD progression was defined as an increase in CKD stage by two independent laboratory measures at least 90-days apart, or new onset of dialysis or hospitalization for renal failure. Time to event analyses were conducted using Kaplan-Meier and Cox proportional hazards modeling.

Results: There were 21,254 PCI patients and 96,660 controls. AKI developed in 13% of PCI patients. Patients developing AKI, not developing AKI, and controls had a CKD progression incidence 28.72 (per 100 person years), 11.14, and 6.58, respectively. Compared to controls, PCI patients with or without AKI were more likely have CKD progression in adjusted analyses (AKI: 4.14 95%CI 3.88, 4.42, $p < 0.001$; No AKI: 1.74 95%CI 1.68, 1.80, $p < 0.001$). Among patients with CKD prior to PCI, AKI was associated with a 11-fold (9.36, 12.18) increased likelihood of progression of CKD over controls. Similar results were observed for other post-discharge events, including dialysis, AMI, and all-cause mortality.

Conclusions: Patients developing AKI following PCI exhibited more rapid CKD progression, dialysis, AMI, and mortality outcomes than both PCI patients without AKI and matched controls.

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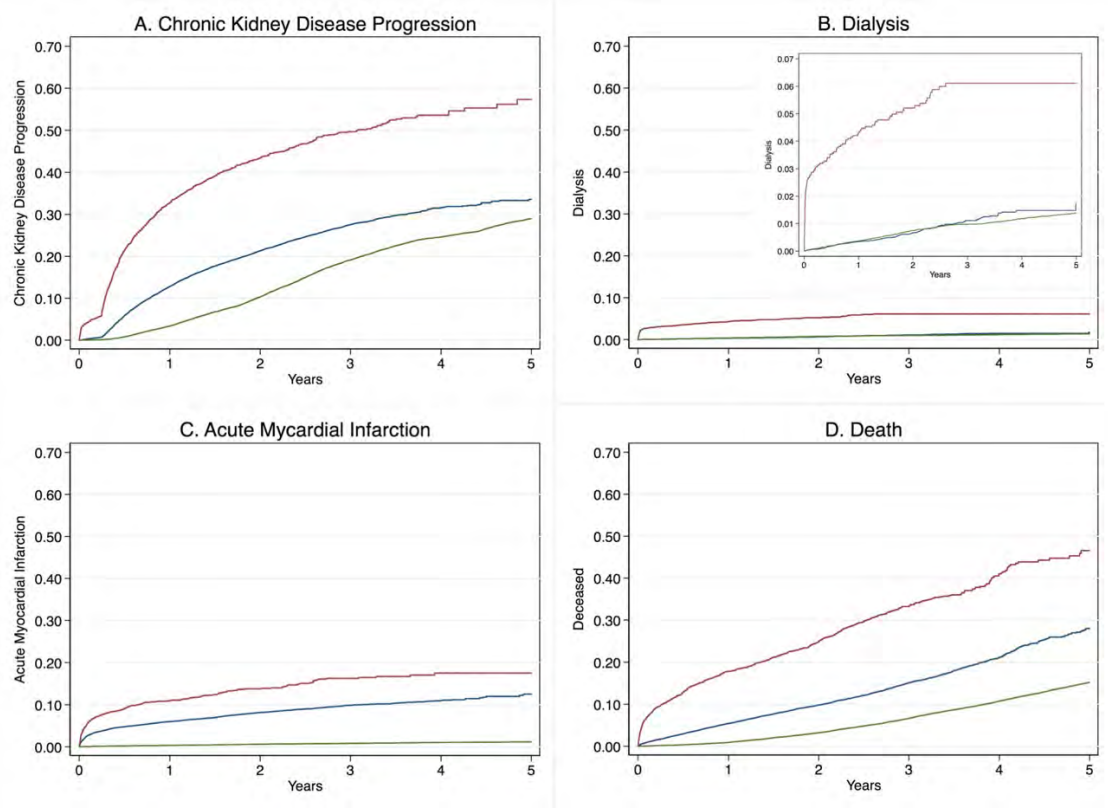

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Plasma Pro-Enkephalin and Poor Long-Term Outcome in Renal Transplant Recipients

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Purpose of the study:

Enkephalins are well-known endogenous opioid peptides. Recent evidence indicates that they are not only involved in regulation of pain, but also in homeostasis of the immune system and the circulation. Pro-Enkephalin (penKid) is stable in plasma and has been established as reliable surrogate marker for the unstable enkephalins. Recent studies found associations of penKid with acute kidney injury and prognosis after myocardial infarction. We aimed to investigate whether plasma penKid could be linked to chronic kidney disease and poor long-term outcome in renal transplant recipients (RTR).

Methods:

We included 664 RTR who were 8.1±7.6 years after transplantation. Plasma levels of penKid were measured with a double monoclonal sandwich immunoassay.

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Results:

Mean age was 53±13 years, 56% were male, estimated glomerular filtration rate (eGFR) was 49 mL/min/1.73m2 (interquartile range [IQR]: 37-64 mL/min/1.73m2) and urinary albumin excretion (UAE) was 40 mg/24h (IQR: 10-196 mg/24h). Median penKid was 110 pmol/L (IQR: 85-148 pmol/L). penKid was correlated with both eGFR (r=-0.73, P<0.001) and UAE (r=0.35, P<0.001). During a median follow-up of 3.1 years (IQR: 2.7-3.9 years), 45 RTR developed graft failure and 76 died. penKid was both associated with increased risk of graft failure (hazard ratio per standard deviation increment of the logarithm of penKid, 2.76; 95% CI, 1.69-4.53) and all-cause mortality (HR=1.83; 95%CI, 1.24-2.69), independent of age, sex, eGFR, and UAE. These associations remained materially unchanged after additional adjustment for body mass index, alcohol consumption, smoking, systolic blood pressure, antihypertensive drug use, use of calcineurin inhibitors, and high-density lipoprotein. penKid also predicted the composite outcome graft failure and mortality (HR=2.24; 95% CI, 1.61-3.11), independent of age, sex, eGFR, and UAE.

Conclusions:

High concentrations of penKid are linked to chronic kidney disease as reflected by correlations with eGFR and UAE. In addition, penKid was independently associated with increased risk of graft failure and mortality in RTR. Plasma penKid is an interesting new biomarker which may aid in early identification of RTR at risk for late graft failure and premature mortality.

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Hospital Re-admission and Post-discharge Mortality in Critically Ill patients with Acute Kidney Injury

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Introduction

Acute kidney injury (AKI) in critically ill patients is associated with increased in-hospital mortality. We aimed to evaluate its impact on post-discharge mortality and hospital re-admission rates.

Methods

Retrospective cohort study of adults admitted to the medical intensive care unit (MICU) in a tertiary care hospital between 1 January 2010 and 31 December 2010. Patients were excluded if they were dialysis-dependent prior to MICU admission.

Patients' demographic, co-morbidity and laboratory data were obtained from electronic medical records. AKI was present if serum creatinine increased >0.3 mg/dL (26.4 mcmol/L) from baseline. Outcomes studied were hospital re-admission and post- discharge mortality.

Results

We studied 421 patients: median age 59.4 years (IQR: 46.4, 71.1 years), male 61.8%.Comorbidities included diabetes mellitus (DM) 26.8%, hypertension 39.7%, ischemic heart disease (IHD) 20.9%, chronic liver disease or cirrhosis 5.7% and active malignancy 27.1%. Premorbid MDRD eGFR was 72.9 (47.7, 102.2) ml/min/1.73

m2. AKI was present in 209 patients (49.6%) at ICU admission (91 patients with Acute Kidney Injury Network Stage 3 AKI) and 173 (41.1%) died.

Median follow up for the 248 survivors was 27.7 (3.7 to 34.4) months. 155 patients (62.5%) had a hospital re-admission at median 2 (1, 7) months after discharge. After adjusting for age, gender, DM, hypertension, IHD, liver cirrhosis, chronic lung disease, active malignancy, premorbid serum creatinine, need for mechanical ventilation and vasopressor at ICU admission and AKI, only age was independently associated with hospital readmission [adjusted OR 1.03, 95% CI (1.01, 1.05), p=0.009].

Fifty-two patients (21.0%) died at 7 (2 to 21) months after discharge. Male gender [adjusted OR 2.64, 95% CI (1.18, 5.90), p=0.02] and active malignancy [2.55 (1.16, 5.61), p=0.02] were independently associated with post-discharge death.

AKI at ICU admission was not different between patients with (45.8%) and without hospital readmissions (41.9%), p=0.59; nor between patients with (32.7%) and without post discharge mortality (47.4%), p=0.06.

Conclusion

AKI was not associated with hospital re-admission and post-discharge death in this cohort of critically ill patients.

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The Association of Plasma Pro-Enkephalin with Renal Function Decline

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Purpose of the study:

Enkephalins are well-known as small endogenous opioid peptides. Recent evidence indicates that they are not only involved in regulation of pain, but also play roles in the periphery in homeostasis of the immune system and the circulation. Pro-Enkephalin (penKid) is stable in plasma and has been established as reliable surrogate marker for unstable enkephalins. Observational studies found associations of penKid with acute kidney injury and chronic renal failure. We therefore aimed to prospectively examine the association of penKid with renal function decline in a population-based cohort.

Methods:

We studied 5,544 subjects of the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study, a prospective, population-based cohort of Dutch men and women aged 28-75 years. Plasma levels of penKid at baseline were measured with a double monoclonal sandwich immunoassay. Estimated glomerular filtration rate (eGFR) was measured at baseline, after 2.3±0.3 years, 5.1±0.6 years, and 7.7±0.9 years, and were LN-transformed. Linear mixed models were used to define individual eGFR slopes. Next, multivariable linear regression of penKid was performed with the individual eGFR slopes as outcome, with adjustment for potential confounders.

Results:

At baseline, mean age was 53±13 years, 50.4% were male, and eGFR was 94 mL/min/1.73m2 (interquartile range [IQR]: 82-105 mL/min/1.73m2). Baseline median penKid was 52 pmol/L (IQR: 45-62 pmol/L). penKid was correlated with baseline eGFR (r=-0.44, P<0.001). The geometric mean of individual eGFR slopes was -1.13±0.95 mL/min/1.73m2 per year. Log-transformed penKid was significantly associated with annual decline in eGFR (st.β=-0.133; P<0.001; R2=0.02). This association remained significant after adjustment for age, sex, baseline eGFR, smoking, alcohol consumption, high-density lipoprotein, systolic blood pressure, and urinary creatinine and albumin excretion (st.β=-0.032; P=0.04; R2=0.25).

Conclusion:

In this population-based cohort, penKid was significantly associated with renal function decline. This association was independent of potential confounders. Measurement of penKid could be a helpful tool to guide measure preventing renal function decline.

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Furosemide Stress Test, Renal Angina Index, and Urinary Sediment: Which I Should Use to Predict AKI?

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Background: In recent years several approaches for identifying patients at risk of AKI were used; among them two have been of increasing interest: the furosemide stress test (FST) and the renal angina index (RAI). We recently used Perazella et al urinary sediment score (USS) to predict subsequent development of clinical AKI. All of these approaches aim to delineate patients at risk for subsequent severe AKI (AKI beyond the period of functional injury) versus those at low risk. We aimed to assess the performance of these three different ways to identify patients at risk of subsequent severe AKI in an ongoing cohort of adult critically ill patients at risk of AKI.
Methods: We analyzed data from 30 hospitalized patients admitted to our Medical ICU. We measured serum creatinine (sCr) every 24 hours for 7 consecutive days following ICU admission, and urinary volume was assessed hourly each 24 hours. At admission (day 0) and 24 hours after (day 1): a) the RAI was calculated at ICU using the following formula: Risk level (presence of sepsis (yes or no), use of vasopressors and use of invasive mechanical ventilation, and presence of diabetes mellitus, and) x Injury level (changes in kidney function based on eGFR); b) we evaluate the USS (Perazella et al); and c) we applied the FST (as describe by Chawla et al in Crit Care 2013 Sep 20; 17(5):R207) at ICU admission (day 0). We assessed the performance of these 3 tests to predict the subsequent development of AKI using KDIGO sCr and urinary volume criteria.
Results: Of the 30 patients included in this study, 4 (13.3%) patients met the primary end point of AKI diagnosis (using sCr KDIGO criteria). The performance of the two different scores and the test were as follows: RAI had the best performance with a ROC AUC of 1.00(p = 0.002); followed by FST with a ROC AUC of 0.990 (p = 0.002) but we consider a cut-off point of <600 cc of urine at 2 hours since none of the patients who developed AKI had <200 cc of urine as the original cut-off value proposed by Chawla et al; finally the use of USS (≥ 2) had a ROC AUC of 0.981 (p = 0.002). The sensitivity, specificity, PPV and NPV of the 3 tests used

are shown on table 1.
Conclusions: The 2 scores (RAI and USS) and the furosemide stress test have robust predictive capacity to identify critically ill patients at high risk of developing AKI before a rise in serum creatinine occurs. These preliminary data of our ongoing study warrants future studies to validate these findings.

	Furosenide Stress Test	Renal Angina Index	Urinary Sediment Score
Sensitivity (%)	75	100	100
Specificity (%)	100	100	92
PPV (%)	100	100	67
NPV (%)	96	100	100

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The Role of Bioimpedance Analysis as a Predictor of Outcomes in Acute Kidney Injury Patients Requiring Renal Replacement Therapy

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Background: Fluid overload is one of the independent risk factor for mortality in acute kidney injury (AKI) patients. Bioimpedance analysis (BIA) is a promising tool for quantifying volume status in end stage renal disease. However, the role of BIA in estimation fluid balance and predictor outcome in acute kidney injury (AKI) is still unclear. This prospective cohort study aims to investigate the role of BIA as a predictor of mortality in AKI patients.
Methods: We enrolled adult patients with severe AKI who underwent continuous renal replacement therapy (CRRT) or sustained low-efficiency dialysis (SLED) admitted in intensive care units (ICUs) of King Chulalongkorn Memorial Hospital from October 2013 to February 2015. Baseline characteristics including actual body weight were recorded. Volume status was estimated by fluid accumulation from admission to study date (a total input fluid minus total output fluid). We tested multi-frequency BIA within 24 hours after RRT initiation. The primary outcome was 28-day mortality.
Results: A total of 41 critically ill patients were included in this study (49% are male). Mean body weight at admission was 60.2 kg. Twenty-three patients (56%) were dead within 28 days. Mean body fluid accumulation was 3.98 ± 3.88 and 4.67 ± 5.73 liters (7.10% ± 7.09% and 7.45% ± 8.68% compared to body weight at admission) in survival and non-survival group, respectively (p=0.663), while mean excess fluid from BIA was 4.73 ± 3.12 and 5.50 ± 6.27 liters (p=0.637). The correlation (r) between body fluid accumulation and excess fluid from BIA is 0.756 (p<0.001). The ROC curve of fluid accumulation and excess fluid by BIA for predict 28-day mortality were 0.534 and 0.499, respectively.
Conclusions: Fluid accumulation and excess fluid from BIA has a good correlation in AKI patients requiring RRT. However, this two methods of volume status estimation are poor predictor for 28-day mortality in these patients.

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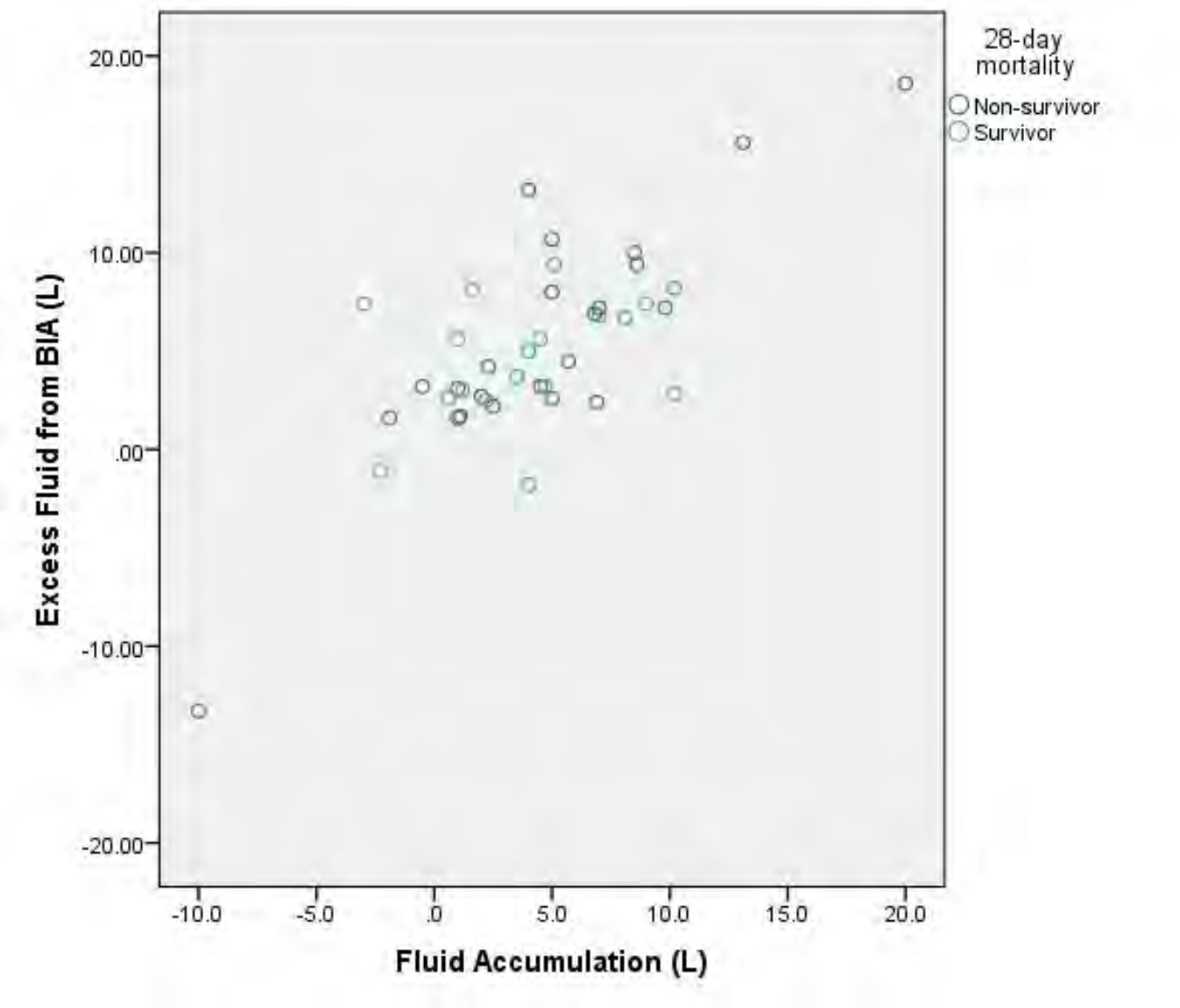

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Evolution of AKI Treatment in ICU in 2 Hospitals of Piedmont (Italy) in The Last 15 Years: Analysis of Outcome, Progression Toward CKD and RRT Modality.

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AKI is one of the most common complications in patients (pts) admitted to ICU leading to an increased risk of multiple organ failure (MOF) and death. We report a 15-year retrospective analysis of AKI incidence in 2

different hospitals in the Piedmont region in Italy with the aim to evaluate the clinical impact of AKI on outcome and progression toward chronic kidney disease (CKD). In addition, we analyzed the evolution of RRT modality in our centers.
We analyzed all pts admitted to ICU and treated by renal replacement therapies (RRT) for AKI in the period 2001-2015. RIFLE, SOFA and ATN_ISS scores were calculated. Diagnosis of sepsis/septic shock was performed according to published criteria. We evaluated ICU mortality and renal function in survivors at ICU discharge. Statistical analysis was performed using the Hemer-Lemeshow test.
We treated by RRT 2836 pts for a total of 16165 RRT sessions performed. Pts characteristics were: 68.9% males; age 68.2±12.3 years; serum creatinine (sCr) at the start of RRT 4.3±2.2 mg/dl; RIFLE Failure 62.5%, Injury 28.5%, Risk 9%; SOFA 10.3±1.2; number of organ failures: 3.7±1.4; ATN_ISS 0.825±0.198. ICU mortality was 1560/2836 (55%): the observed mortality was significantly lower than that expected by the ATN_ISS score (61.5%). Sepsis (31.4%) and ischemia-reperfusion injury after major cardiac surgery (24.6%) were the main causes of AKI. Mortality in septic pts (64.3%) was significantly higher than in the non-septic AKI population (45.7%) ($p<0.05$). At ICU discharge, survivors presented elevated levels of sCr (2.4±0.9 mg/dl). In the period 2001-2012, prolonged intermittent RRT was the preferred modality of treatment. In the last 3 years, hemodynamic instability associated with intense fluid overload lead to an increased use of CRRT with regional citrate anticoagulation. Since sepsis is the main cause of AKI associated with a worse outcome, the use of high cut-off or adsorptive membranes was also increased.
In conclusion, this 15-year retrospective analysis showed a persistent increase of AKI incidence in ICU usually in association with MOF and high mortality rates. Sepsis was the main cause of AKI and represented a further risk factor for a worse outcome. Since 2013, CRRT using citrate anticoagulation was the preferred modality in consideration of the clinical complexity of these patients. Survivors presented high levels of sCr, suggesting the potential progression toward CKD and the need of nephrological follow-up.

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Acute Kidney Injury In Non Renal Solid Organ Transplantation: a rising clinical problem

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Only few studies evaluated Acute Kidney Injury (AKI) incidence in non renal solid organ transplant (NRSOT) recipients. The aims of the present study were: 1) a 15-year analysis of AKI incidence in NRSOT in a 1000-bed University Hospital; 2) to identify the clinical impact of AKI on outcome and progression toward chronic kidney disease (CKD) in this selected population.

We retrospectively analyzed (2000-2015) the percentage of NRSOT in the whole AKI population treated by renal replacement therapies (RRT) in our centre. For each NRSOT recipient, we evaluated RIFLE and SOFA scores and the severity index ATN_ISS at the start of RRT. The percentage of AKI requiring dialysis in the whole NRSOT population and for single transplanted organ (liver, heart or lung graft) was also studied. Renal function was evaluated at the end of the observation period (30 days). Hemer-Lemeshow statistical test was performed.

In the period 2000-2015, we treated 2756 critically ill patients with AKI for a total of 12416 RRT sessions performed. Among this population, 402/2756 (14.6%) were NRSOT recipients. We treated by RRT 10.8 % of all patients subjected to liver transplantation, 27.5% of heart transplanted patients and 26.2% of lung transplanted patients. Baseline characteristics were: age 59.2 yrs (SD 7.6), male gender 62.5%, serum creatinine 3.76 mg/dl (SD 1.34), number of organ failures 3.7 (SD 1.87) and ATN_ISS score 0.68 (SD 0.16). The

prevalent cause of AKI in NRSOT patients was sepsis (52.5%), associated with high mortality, multiple organ failures and a difficult management of the immunosuppressive therapy. Overall mortality in NRSOT patients was 42.6% and in particular 38.5% for liver, 48% for heart and 41.5% for lung transplant recipients, respectively. Mean serum creatinine at the end of the study period (ICU or hospital discharge) was 2, 43 mg/dl (2.06 mg/dl in liver, 2.42 mg/dl in heart and 2.82 mg/dl in lung graft recipients, respectively).

In conclusion, we observed a continuous increase of AKI incidence in the NRSOT population. The main cause of AKI was severe sepsis which was associated with an increase of mortality and with an impairment of renal function that may be responsible for the progression toward CKD in survivors. Early goal-directed therapies to inhibit AKI may potentially improve outcome and limit progression toward CKD in NRSOT recipients.

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The Effect of the Choice of Contrast Media on Renal Failure Events in Inpatient Cardiovascular Procedures

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PURPOSE OF STUDY: The physiochemical properties of iodinated contrast media (CM) may increase the likelihood of renal failure, which may lead to a significant increase in morbidity, mortality, and cost associated with the procedure. The objective of this study was to assess the relationship between iso-osmolar CM and low-osmolar CM (LOCMs), and renal failure events in patients undergoing inpatient cardiovascular procedures.
METHODS: The Premier Hospital database was used to identify patients between January 2008 and September 2013. Eligible patients had a primary cardiovascular procedure (interventional or diagnostic) defined by International Classification of Diseases, 9th Revision (ICD-9) and/or Current Procedural Terminology (CPT®) codes, inpatient admission, and LOCM or iso-osmolar CM agent. CM agents were identified by Standard Charge Master codes and text mining algorithms. One iso-osmolar CM, iodixanol, was identified. Six LOCMs were identified: iohexol, ioversol, iopamidol, ioxaglate, ioxilan, and iopromide. Renal failure during the visit was determined by ICD-9 diagnosis codes. Multivariable regression analysis was conducted using Ordinary Least Square (OLS) and hospital fixed-effects specification to assess the relationship between renal failure and CM use.
RESULTS: A total of 662,299 cardiovascular procedure visits met the inclusion criteria. Patients receiving iso-osmolar CM comprised 29% of the visits. In 74% of the hospitals identified, both iso-osmolar CM and LOCM was used. Iso-osmolar CM was used in older patients (66.7 vs. 62.8; $p < 0.0001$) compared to LOCM. Patients receiving iso-osmolar CM were generally sicker as measured by Charlson Comorbidity Index Score compared to patients receiving LOCM (3.9 vs. 3.3; $p < 0.0001$). Univariate OLS analysis indicated that patients receiving iso-osmolar CM had 1.9% ($p < 0.01$) more renal failure events during the visit compared to patients receiving a LOCM. Controlling for unobserved heterogeneity across hospitals using a hospital fixed-effect specification, we found 2.3% ($p < 0.01$) fewer renal failure events with iso-osmolar CM. This absolute difference represents an approximately 55% relative difference from the 4.2% rate for the overall population.
CONCLUSION: In this retrospective study, the use of iso-osmolar CM was associated with fewer renal failure events compared to LOCMs in patients who underwent inpatient cardiovascular procedures. This may translate to reduced hospital costs.

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Change of Estimated Glomerular Filtration Rate to Assess the Extent of Renal Recovery after Cardiac Surgery Associated Acute Kidney Injury

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Objective:
The extent of renal recovery after acute kidney injury (AKI) is often assessed by change of serum creatinine post- and pre-operation. Our study tried to find out if the change of estimated glomerular filtration rate (eGFR) can do the assessment more accurate and the relationship between different extent of eGFR decrease and long-term outcome of the AKI patients.
Methods:
We collected data of patients who underwent cardiac surgery from April 2009 to December 2012. Complete renal recovery was defined as SCr concentrations at discharge ≤44 mmol/L above baseline values. The eGFR was determined according to the simplified MDRD formula. The 2 years primary endpoint was all-cause of mortality and secondary endpoint was progressive CKD(CKD stages 4–5 including ESRD).
Results:
Among the total of 3245 patients enrolled, the AKI incidence was 39.9% (n=1295). According to SCr criteria, there are 72.9% (n=944) patients had “completely renal recovery”. Using the simplified MDRD formula to calculate the eGFR before and after AKI patients who was assessed as “complete renal recovery” by SCr criteria, the eGFR after AKI was significantly lower than before AKI (88.9± 33.6 vs 94.5±29.7 ml/min/1.83m2,p<0.001). According to simplified MDRD formula, there are 33.7% (n=436) patients with eGRF≥90ml/min/1.73m2 and 66.3% (n=859) patients with eGRF＜90ml/min/1.73m2 at discharge.
After 2 year period followed up, we first analyze the outcomes of AKI patients with “complete renal recovery” assessed by SCr criteria. Cox proportional hazards regression model showed that AKI with completely renal recovery is still the risk factor for accumulated overall survival (RR 1.79, 95%CI 1.28 to 2.52) and progressive CKD (RR 1.92, 95%CI 1.37 to 2.69).
Then we analyze the outcomes of AKI patients whose extent of renal recovery assessed by eGFR criteria. Cox proportional hazards regression model showed that AKI patients with eGRF < 90ml/min/1.73m2 at discharge is the risk factor for accumulated overall survival (RR 3.7, 95%CI 2.66 ~ 5.16;) and progressive CKD (RR 5.28, 95%CI 3.86 ~ 7.21). But AKI patients with eGRF ≥90ml/min/1.73m2 at discharge is not the risk factor for accumulated overall survival and progressive CKD.
Conclusions:
The change of SCr criteria may over-estimate the extent of renal recovery of CSA-AKI patients.CSA-AKI patients with eGRF(simplified MDRD formula) ≥90ml/min/1.73m2 at discharge can be the clinical criteria for completely renal recovery.

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Effect of Body Mass Index on Acute Kidney Injury after Cardiac Surgery

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Objective :Among maintenance hemodialysis patients, the higher body mass index(BMI) was, the higher survival rate was. This study was to explore the relationship between BMI and incidence, mortality of AKI and AKI requiring RRT (AKI-RRT) after cardiac surgery.
Methods :Clinical data of patients undergoing cardiac surgery, which included demographic data of preoperative、intraoperative、postoperative, were prospectively collected in Zhongshan hospital affiliated Fudan University from January 2009 to December 2013. According to BMI classification for Chinese: low weight group (BMI>18.5kg/m2), normal weight group (18.5 ≤BMI<24kg/m2), overweight group (BMI<28kg/m2), obese group (BMI≥28 kg/m2).
Results: A total of 8013 patients enrolled, including 4477 males and 3536 females with the mean age of 53.1±14.0years. The overall AKI incidence was 34.0%(n=2723). The hospital mortality of AKI was 5.7%(n=156). The incidence of AKI-RRT was 4.9%(n=133). The morality of AKI-RRT was 58.6%(n=78).The incidences of AKI in low weight group, normal weight group , overweight group, obese group were 27.8%,31.4%,35.7%,45.0% (P<0.001). The hospital mortality of AKI in four groups were 9.0%,6.5%,4.6%,5.0%,there was no significantly statistical difference (P =0.062). The hospital mortality of AKI-RRT in four groups were 62.5%、61.3%、51%、75%,also no significantly statistical difference (P =0.426).
Conclusion: BMI is an independent risk factor for AKI after cardiac surgery, the AKI incidence increased, as BMI gained. The hospital prognosis of AKI and AKI-RRT were optimum, when BMI was 24-28 kg/m2.

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Early Diagnosis of Severe Sepsis and Acute Kidney Injury, Judgment of Rapid Transport to Critical Care Center: Better Prognostic Factor

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Purpose of the study
The prognosis of patients with severe sepsis or septic shock is improving. In our center, although promoting the standardization and individualization of sepsis treatment, some patients die. We examined whether acute kidney injury affects the prognosis of septic patients.
Methods
We included the patients with severe sepsis and septic shock who admitted from the emergency department to the ICU from Jan. 2014 to Jun. 2015. We defined severe sepsis as patients with SOFA score 2 points worse than sepsis onset before. Gender, age, APACHE2, SOFA, KDIGO classification of AKI, time from sepsis onset to

our center visits, and time from sepsis onset to the first antibiotic administration, were examined.
Results
The number of patients was 60: non-survivor 18(30%), and survivor 42(70%).
As APACHE2, SOFA and KDIGO classification of AKI was bad, life prognosis was bad. The table showed the relationship between KDIGO classification and the prognosis. As the definitive treatment or the first antibiotic administration was earlier, KDIGO classification of AKI and life prognosis was better.
Conclusion
The early diagnosis of severe sepsis and acute kidney injury and the judgment of rapid transport to critical care center were better prognostic factor.

KDIGO classification	Non-survive	Survive	Mortality (%)
Non-AKI	2	22	8.3
1	7	13	35.0
2	4	4	50.0
3	3	2	60.0
Hemodialysis Patients	2	1	66.7
Total	18	42	30.0

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Changes of Epidemiology and Influencing Factors of Acute Kidney Injury After Cardiac Surgery- A Five year Study from 2009 to 2013

Zhouping Zou[1], Jiarui Xu[1], Yi Fang[1], Jianzhou Zou[1], Xiaoqiang Ding[1], Jie Teng[1]

[1]*Department of Nephrology,Zhongshan Hospital*

Objective :We collected the epidemiological data of patients with AKI from 2009 to 2013 in order to explore the influencing factors of changes of epidemiology after cardiac sugery.
Methods: Clinical data, which included demographic data of preoperative, intraoperative, postoperative, were prospectively collected in our hospital from January 2009 to December 2013. The main endpoint was poor prognosis including overall mortality and abandon of treatment. The second point was renal outcome.
Results :A total of 11693 patients enrolled, including 6637 males and 5056 females. The overall AKI incidence was 34.5%. The AKI incidence increased during the five years from 34.2% to 36.5% (P<0.05).There was no significantly statistical differences in AKI-RRT incidences during the five years (p=0.360); The hospital mortality of AKI decreased from 6.3% in 2009 to 3.8% in 2013.The incidence of poor prognosis in AKI were 8.3%,7.5%,6.8%,5.1%,8.0% (P=0.196).The mortality of AKI-RRT decreased from 47.1% in 2009 to 29.5% in 2013 (P= 0.230). The incidence of poor prognosis in RRT decreased from 66.7% to 57.4% (P=0.825). Multivariate logistic regression analysis showed that male, old age, body mass index(every additional 5 kg/m2) ，hypertension, chronic heart failure, pre-operative serum creatinine>115μmol/L,CPB（every additional 30min ）were the risk factors of AKI after cardiac surgery.
Conclusion: The incidence of AKI after cardiac surgery increased from 2009 to 2013 and the rate of poor prognosis did not change.

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Positive Fluid Balance as a Predictor of ICU Free Days in Patients with Kidney Disease Requiring Dialysis

sharad patel[1], Hernan Rincon-choles[1], Tarik Hanane[1], Duncan Hite[1], Sevag Demirjian[1]

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Positive fluid balance as a predictor of ICU Free Days in patients with kidney disease requiring dialysis
Sharad Patel, Hernan Rincon-Choles, Tarik Hanane, Duncan Hite, Sevag Demirjian
Department of Critical Care Medicine, Department of Nephrology and Hypertension, Cleveland Clinic

Background:
Optimal fluid management in critically ill patients has recently come under scrutiny due to volume driven morbidity such pulmonary edema, intra-abdominal hypertension, renal venous pressures, and bowel edema. The latter is further compounded by renal impairment, prevalent in these patients. Our aim in this study was to assess volume burden on ICU-free days in patients with renal failure.
Methods:
We retrospectively studied adult critically ill patients with renal failure requiring renal replacement therapy (RRT) between the years 2011 and 2014. We examined the effect of 7-day ICU cumulative fluid balance on ICU-free 28-days using linear regression.
Results:
The cohort included 1328 subjects with renal failure requiring RRT: 841 with AKI, and 487 with ESRD. The median age was 63 (54,71), 69% were white, and 56% male. Median cumulative fluid balance at one week was 3,315 ml (range -1,078 to 7,730 ml). Univariate analysis of the effect of fluid balance on the outcome showed a curvilinear shape ($p<.001$, nonlinearity $p<.001$).

Conclusion
In patients with renal failure requiring RRT, positive fluid balances is associated with reduced ICU-free days. The association is non-linear in nature, and dose-dependent with increasing fluid balance. Further research should incorporate adjustment of severity of illness which may confound the observed association.

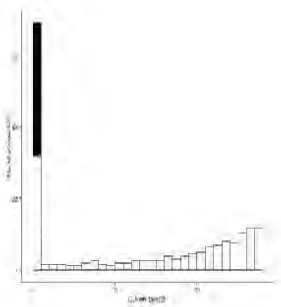

Figure 1

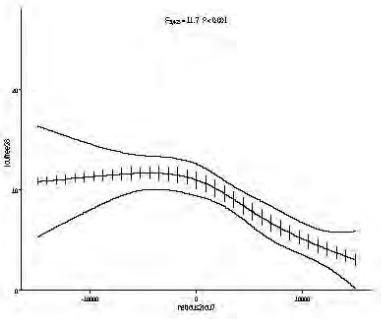

Figure 2

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Clinical Significance Of Renal Biopsy In AKI

SANTOSH HEDAU[1], RAJASEKARA CHAKRAVARTHI[1], VIJAYA TAURANI[1]

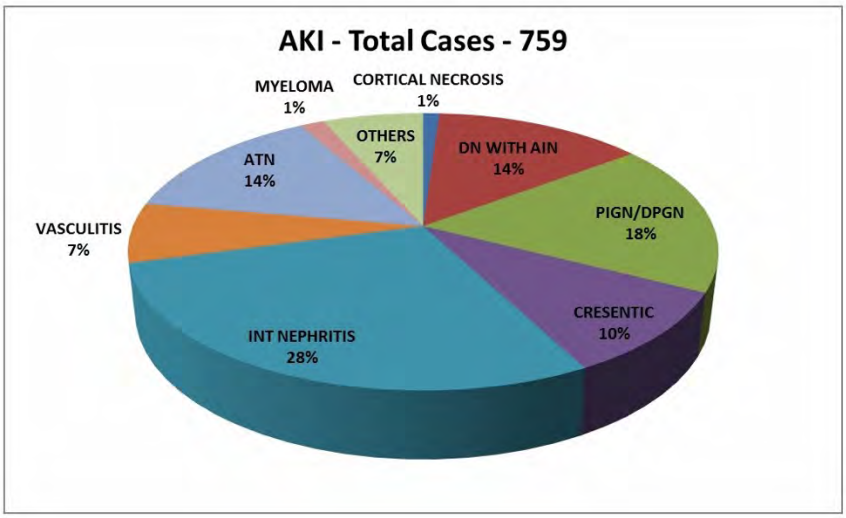
[1]*CARE HOSPITAL*

PURPOSE OF STUDY
Renal biopsy in AKI helps us to diagnose, effectively treat and prognosticate patients based on histopathology. The renal biopsy confirms clinical diagnosis on many occasions and helps in precise treatment.

METHOD USED
We did retrospective analysis of renal biopsy data at our institute from January 2003 to September 2015. Total 3293 renal biopsy were done during this period. the indication of biopsy was AKI in 759 patients out of 3293 biopsies. This cohort of AKI was separated and analysed based on histopathology findings.

SUMMARY OF RESULTS
The commonest histopathological lesion was acute interstitial nephritis (AIN) in 28.5% patients (n=216). Proliferative glomerulonephritis (PIGN and DPGN) was found in 17.8% (n=135). Acute tubular necrosis (ATN) was found in 14.1% (n=107) as third most common lesion.
The other findings included cresenteric glomerulonephritis in 9.7% (n=74), vasculitis in 6.9% (n=53). Cortical necrosis and myeloma was found in 1.05% and 1.5% respectively.
Patients with diabetic nephropathy were analysed separately. AIN with background diabetic nephropathy was seen in 13.7% (n=104).
Hence the commonest lesion was AIN in 42.2% patients.

CONCLUSION
It is important to biopsy patients with AKI to know histopathology. The commonest lesion found was AIN which is potentially treatable and can avoid rapid loss of renal function if treated in time. This is in contrary to present understanding where ATN is presumed to be the commonest lesion.
It looks justified in doing renal biopsy for diabetic patients with AKI. The treatment of potentially treatable lesions which are often missed helps in preventing decline of renal parameters to ESRD.



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Acute Kidney Injury Recovery and the Risk of Chronic Kidney Disease in Sepsis Survivors

Javier A Neyra[1], Xilong Li[1], Beverley Adams-Huet[1], Orson W Moe[1], Robert D Toto[1]

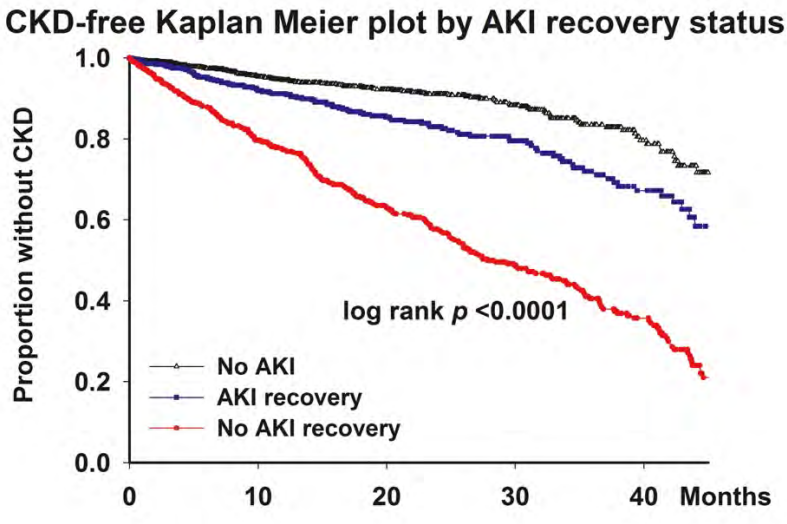
[1]*University of Texas Southwestern Medical Center*

Background: AKI is a frequent complication of sepsis and is associated with an increased risk for subsequent CKD. The purpose of this study was to investigate whether the absence of 90-day AKI recovery increases the risk of CKD in sepsis survivors.

Methods: We conducted a retrospective cohort study of patients admitted to the ICU with a diagnosis of severe sepsis or septic shock from May 2007 to December 2011. We excluded patients with eGFR <15 or receiving chronic dialysis prior to enrollment. Baseline serum creatinine (SCr) was defined as the most recent SCr within the 3-month period before ICU admission. The highest SCr during ICU admission was used to diagnose AKI (KDIGO criteria). The independent variable, AKI recovery, was determined by the ratio of 90-day post-discharge SCr / baseline SCr in RRT-free survivors: <1.1 indicated AKI recovery and ≥1.1 no AKI recovery. The primary outcome measure was incident or progressive CKD based on relative or absolute eGFR changes during the follow-up period. A Cox proportional hazard regression analysis adjusting for age, baseline eGFR, diabetes, AKI severity, SOFA score, and the need for acute RRT was performed.

Results: Of 6268 ICU patients included in the study, 3703 (59%) suffered from AKI and 729 (12%) required acute RRT. A total of 4949 (79%) patients survived the hospitalization. Of these, we identified 2401 sepsis survivors that were RRT-free at 90 days following hospital discharge and had available follow-up data. Incident or progressive CKD occurred in 399 (32%) of patients that suffered from AKI (47% in those without AKI recovery and 18% in those with AKI recovery) and in 124 (11%) of patients that did not suffer from AKI, median follow-up 2.5 years. 90-day AKI recovery status was an independent predictor of CKD (adjusted HR 4.04, 95% CI 3.18 – 5.13 for absent AKI recovery vs no AKI; 1.59, 1.20 – 2.11 for AKI recovery vs no AKI; and 2.54, 2.01 – 3.03 for absent vs AKI recovery). Other independent predictors of CKD post-AKI were older age, lower baseline eGFR, the need for acute RRT, and higher admission SOFA score.

Conclusions: The absence of AKI recovery within 90 days following hospital discharge is a strong and independent predictor of CKD in sepsis survivors. The timely evaluation of AKI recovery may serve to risk-stratify sepsis survivors and implement more vigilant surveillance for CKD in this susceptible population.



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Post-Operative Acute Kidney Injury After Major Non-Cardiac Surgery and its Association with Death in the Following Year

Michael E O'Connor[1], Russell W Hewson[1], Christopher J Kirwan[1], Rupert M Pearse[2], John R Prowle[2]

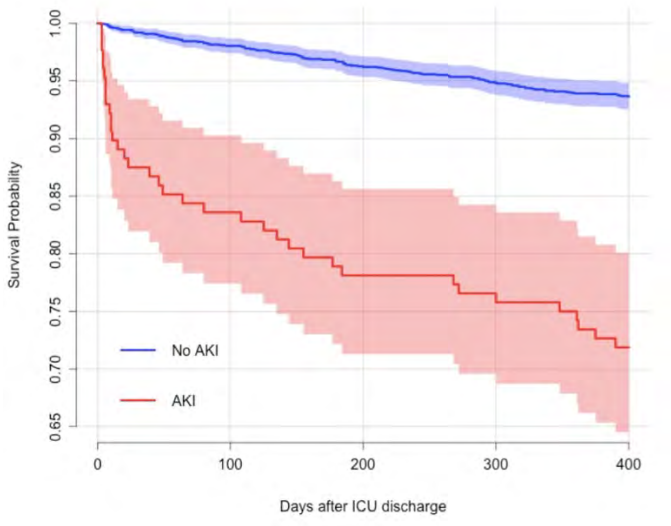
, [2]*William Harvey Research Institute, Queen Mary University of London*

Background: Acute kidney injury is a common complication after major surgery that has been associated with adverse outcomes.

Method: We performed a retrospective cohort study of major non-cardiac surgery in a teaching hospital over an eighteen-month period, examining the incidence of AKI and relationship with post-operative outcomes over one-year follow up. AKI was defined by KDIGO creatinine criteria. Major surgery was defined as inpatient procedures of >1h duration. End stage real disease and those without pre or post-operative creatinine measurement were excluded. To assess the independent effect of AKI on survival, a multi-variable Cox proportional-hazard survival model was developed examining survival from 7 to 365 days after surgery.

Results: 1897 patients were included in our final analysis, post-operative AKI occurred in 128 patients (6.8%), of these 101 had KDIGO stage 1 (5.4%), 19 KDIGO stage 2 (1%) and 8 KDIGO stage 3 (0.4%). Patients who developed AKI were significantly older, had a lower baseline eGFR, were in a higher ASA class and spent longer in hospital post-operatively compared to those patients who did not develop AKI. Hospital Mortality occurred in 17/128 (13.3%) of patients that developed AKI post-operatively compared to only 16/1741 (0.9%) of those that did not ($p<0.001$). However, by one year after surgery 34/94 (27%) of patients who developed post-operative AKI had died compared to only 106/1741 (6%) who had not had AKI (Fig1), $p<0.001$. In the multi-variable model accounting for multiple confounders AKI was associated with a hazard ratio for death of 3.0 (1.91-4.72) in the year after surgery. Importantly AKI defined by only a 26µmol/L creatinine rise and AKI with recovery remained associated with on-going increased risk of death to one year.

Conclusions: In a well-characterised population of patients undergoing major surgery we have demonstrated a strong association between even mild post-operative acute kidney injury and increased risk of death in the next year.



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Trajectory of Serum Creatinine after Major Surgery and Relationship with Acute Kidney Injury

Michael E O'Connor[1], Russell W Hewson[1], Christopher J Kirwan[1], Rupert M Pearse[2], John R Prowle[2]

[1]Adult Critical Care Unit, The Royal London Hospital, [2]William Harvey Research Institute, Queen Mary University of London

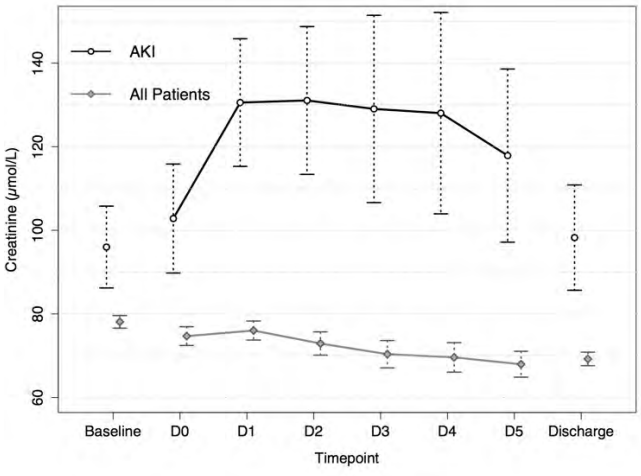
Background: We have demonstrated that even mild and transient perioperative acute kidney injury is associated with significantly worse survival in the year after major surgery (see accompanying abstract). However, confounding effects of major illness on serum creatinine levels may cause severity of AKI to be underestimated and recovery from AKI over-estimated (1).

Methods: From a population of 1897 patients undergoing major surgery (of which 128 had peri-operative AKI) we examined baseline and hospital discharge estimated GFR (CKDEpi creatinine formula) and the trajectory of serum creatinine in patients who were hospitalized for ≥5 days after surgery.

Results: In 1836 patients who survived to hospital discharge median duration of hospitalization was 7 days (IQR: 4-11) overall and 11 days (6-25) in patients who had peri-operative AKI. In all hospital survivors mean eGFR rose significantly from baseline to discharge: 88.4 to 94.7ml/min/1.73m2 ($p<0.001$). However in those with AKI discharge eGFR was similar to baseline 76.4 to 74.5 ($p=0.6$). 1225 patients stayed ≥5 days after surgery, in those with AKI mean creatinine rose rapidly and eventually settled to near baseline, however in all patients creatinine fell progressively in the five days after surgery and was ~10% below baseline at discharge (Figure). In a regression analysis a higher discharge eGFR significantly correlated with longer hospital length of stay ($p<0.001$), however no such relationship existed for baseline eGFR ($p=0.79$).

Conclusion: Underlying reduction in serum creatinine after major surgery may confound our ability to identify AKI and to assess its severity and recovery. Importantly, these effects may be more pronounced in patients with longer hospital admissions who are at higher risk of complications including AKI.

Figure Legend
Figure: Trajectory of serum creatinine in 1225 patients with post-operative length of stay of 5 or more days who survived to hospital discharge. Mean with SEM.
Ref 1) Prowle et al Clin J Am Soc Nephrol 9: 1015-1023



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Effect of Renin Angiotensin Blockade on Renal Function at Short and Mid Term in Patients Undergoing Coronary Angiography

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[1]*Instituto Nacional de Cardiología Ignacio Chavez*

INTRODUCTION: The use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) on short-term renal function after contrast medium is still controversial; moreover, its impact on mid-term renal function in populations with proven cardiovascular benefit has not been studied.
METHODS: A retrospective cohort of patients undergoing coronary angiography in a third-level academic reference center in Mexico City from January 1st to December 31st 2011. The clinical and biochemical characteristics were obtained from medical records, including a 3 year follow-up after coronary angiography. Specifically, the use of ACEI/ARB peri-procedure and during follow-up was assessed.
RESULTS: A total of 353 pts were analyzed, 283 (80.2%) were male, aged 58.9 ± 12.1 years, 164 (46.4%) were diabetic, 189 (53.5%) had hypertension, 331 (93.8%) had acute coronary syndrome, 42 (11.9%) had pre-existing chronic kidney disease (CKD). A total of 106 pts received ACEI/ARB (30%) prior to catheterization and 285 (80.7%) during follow-up. The overall incidence of contrast-induced nephropathy (CIN) was 13.3% (47/353), with a significant reduction in pts with ACEI/ARB (28 of 277 [10.1%] vs 19 of 76 [24.7 %], p<0.01). This short-term protective effect remained in pts with anemia, diabetes, CKD and/or previous use of ACEI/ARB, although no difference was observed in pts with NYHA functional class III-IV, and a higher incidence of CIN was shown in pts with mean arterial pressure (MAP) <85 mmHg in presence of ACEI/ARB. In multivariate analysis by Cox proportional risk for progression to CKD up to 3 years of follow-up, the use of ACEI/ARB showed a HR 1.41 (95% CI, 0.91-2.18, p=0.116). The change in glomerular filtration rate over time was -0.348 (-2.073 to -0.071) ml/min/month with ACEI/ARB vs -0.325 (-1.567 to 0.125) ml/min/month without ACEI/ARB (p=0.177).
CONCLUSIONS: The use of ACEI/ARB peri-catheterization showed a decrease in the incidence of CIN in our population, except for patients with MAP <85 mmHg. Up to 3 years of follow-up, ACEI/ARB showed no deleterious effect in progression to CKD. A randomized controlled trial is warranted.

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97 *(number out of sequence)*

Risk factors for acute kidney injury and mortality after orthotopic liver transplantation

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Blood Purification Center, Zhongshan Hospital of Fudan University,
Department of Liver surgey, Zhongshan Hospital of Fudan University
ICU, Shanghai public health clinical center

Purpose: The aim of this study is to identify the risk factors for acute kidney injury (AKI) classified according to AKI network criteria, and mortality after orthotopic liver transplantation (OLT).
METHODS: From January 2001 to October 2010, patients undergoing OLT were retrospectively included in the study. Risk factors for AKI and death were investigated.

RESULTS: A total 809 patients were included, with median age of 50 years. AKI was found in 265 (32.75%) patients in the first 7 days after OLT. Risk factors for AKI were: age (OR=1.02, 95% CI: 1.00, 1.04), low-Blood pressure during operation (OR=1.78, 95% CI: 1.63, 1.95) and pre-eGFR (OR 1.02, 95%CI: 1.02, 1.03). The mortality was 9.43%. AKI was an independent risk factor for 30-day mortality after OLT (OR=0.001, 95% CI: 1.24, 2.30). Low-Blood pressure during operation was a predictor for hemodialysis need (OR=1.42, 95%CI 1.26, 1.59). Of the 265 post-OLT AKI patients, 22 did not recover renal function within 1 year.
CONCLUSIONS: AKI after OLT is not an uncommon complication and associated with a poor clinical outcome. Age, low-Blood pressure during operation and pre-eGFR are risk factors for post-OLT AKI. AKI is a risk factor for perioperative death and can lead to prolonged renal function impairment after OLT. Low-Blood pressure during operation is a predictor for hemodialysis need.

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Incidence and Risk Factors of Acute Kidney Injury Following Transcatheter Aortic Valve Replacement

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[1]*Mayo Clinic, Rochester, MN, USA*

Background: This study aimed to determine the incidence and risk factors of Acute Kidney Injury (AKI) following Transcatheter Aortic Valve Replacement (TAVR).
Methods: We included all adult patients undergoing TAVR for aortic stenosis from January 1, 2008 through June 30, 2014 at a tertiary referral hospital. AKI was defined based on Kidney Disease Improving Global Outcomes (KDIGO) criteria. We performed a multivariate logistic regression to identify factors associated with post-procedural AKI occurrence.
Results: Three hundred eighty-six patients met the inclusion criteria, of which 106 (28%) developed AKI. In multivariate analysis, AKI development was independently associated with a transapical approach (OR, 2.81; 95% CI, 1.72-4.65 compared with transfemoral approach), and the need for an intra-aortic balloon pump (OR, 9.11; 95% CI, 1.77-68.29) [Table 1]. Higher baseline renal function (OR, 0.77 per 10ml/min/1.73m2 increment in glomerular filtration rate; 95% CI, 0.68-0.87) was significantly associated with a decreased risk of AKI. Patients who developed AKI had significantly higher in-hospital mortality than patients without AKI (6.6% vs 1.4%, respectively; P=.01).
Conclusion: In a cohort of patients undergoing TAVR for aortic stenosis, AKI commonly occurred and was significantly associated with increased mortality. Baseline renal function, procedure approach, and the need for circulatory support were important predictive factors for post-procedural AKI occurrence.

Variables	Odds Ratio (95% CI)	
GFR (per 10mL/min/1.73m2)	0.78 (0.68-0.87)	<0.001
Arterial approach		
Transfemoral	1 (ref)	-
Transapical	2.81 (1.72-4.65)	<0.001
Transaortic	1.54 (0.47-4.41)	0.45
Intra-aortic balloon pump	9.11 (1.77-68.29)	0.01

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Proteomics of AKI induced by Maleic Acid on renal tubule cells

Hugo Y Lin[1], Shih-Shin Liagn[2]

[1]Kaoshiung Medical University Hospital, [2]Department of Biotechnology, College of Life Science, Kaohsiung Medical University

Purpose of the study:
Maleic acid (MA) was used in the manufacturing process in order to augment the productivity of preparing the conventional comestible starch foodstuffs in Taiwan. At the same time, in the process of manufacturing to add the malic anhydride which is the hydrolyzed form of maleic acid. Thus, the maleic anhydride will interact with water and invert maleic acid, and simultaneously, maleic acid integrates into the foods. Nevertheless, the critical thing is that the human being could eat the food which may have envenomed. Up to present, there are plenty of food additives; the most common used to increase a great number of decent traditional foods is furan-2, 5-dione (Maleic anhydride) which is the acid hydride of maleic acid, and in other words, it is an archetypal product from hydrolyzing maleic anhydride. On top of that, when the food additives, maleic anhydride, degrade in the processing, maleic acid in the products will be released. Furthermore, depending on Fanconi's syndrome, maleic acid could similar stimulate a speedy, reversible, elaborate dysfunction in the renal tubule
Methods used:
The silicon dioxides (SiO2) particles will sediment to a silanized linker (3-aminopropyl triethoxyslane, APTES), and moreover, the maleic acid and APTESSiO2 fabricate to the maleate chemical probes.
Summary of the results:
The probe can be used to detect the target proteins of maleate in this study and demonstrate the protein-protein interactions which are associated maleic acid. We expect that synthetic maleic acid chemical probes incubated the cell lysates of normal human kidney (HK-2) cell lines, and establish the relationships between maleic acid and HK-2 cells for protein-protein interaction analysis.
Conclusion reached:
By means of STITCH database networks software in order to understand the relationship between maleic acid chemical probes and HK-2 cells whether they were proteinprotein association and specific binding or not. Judging by D/H ratios <1.8, we could remove the most possible non-specific proteins by using the method.

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Analysis of hypo and hyperphosphatemia in an ICU cohort

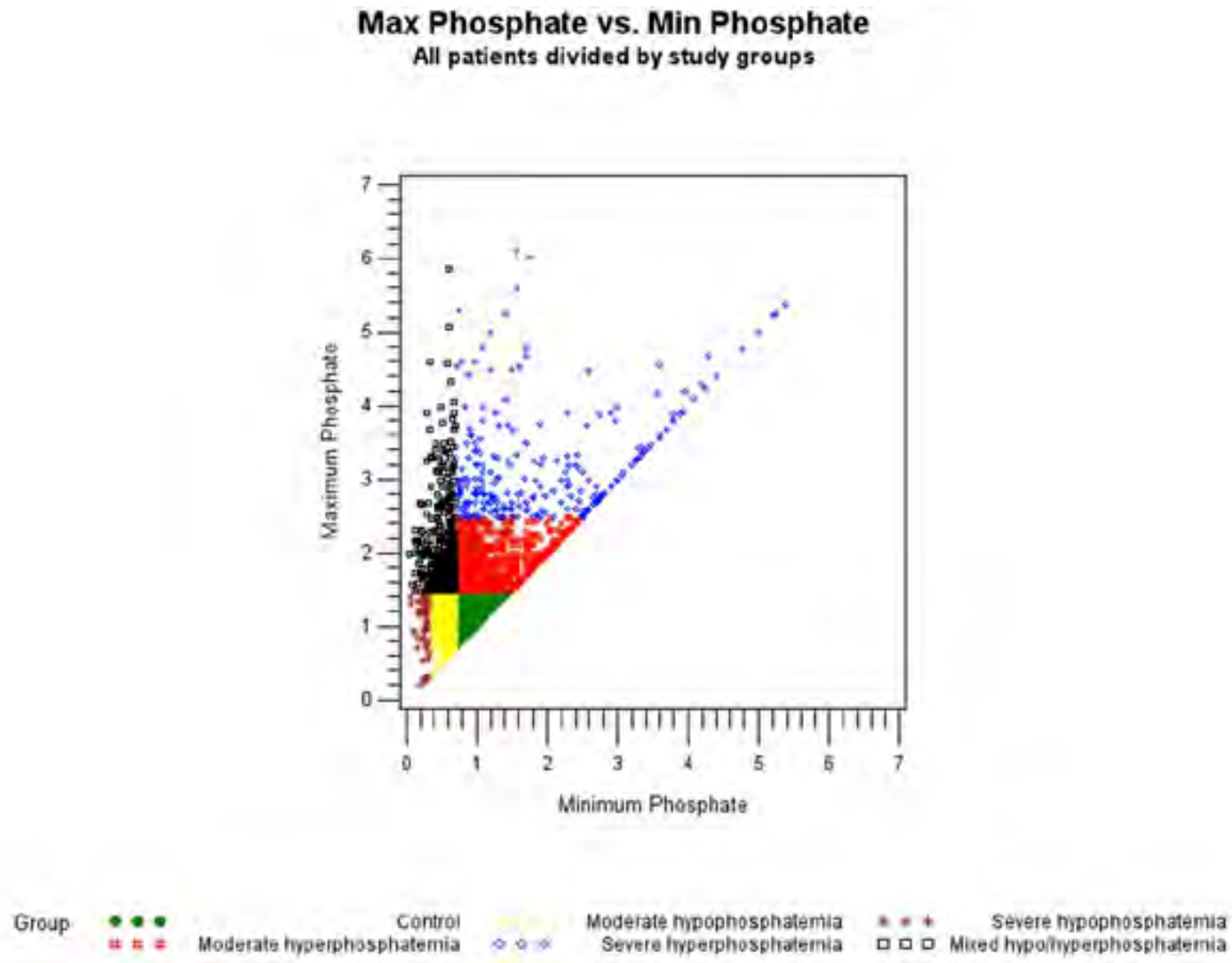
Marcus Broman[1], Amanda Wilsson[1], Bengt Klarin[1]

[1]*Skane University Hospital*

Purpose of the study
The aim was to evaluate the epidemiology of phosphate disturbances and their adjusted morbidity and mortality.
Methods used
5337 patients were screened, 681 were excluded, resulting in a final cohort of 4656 patients, divided in a control group (0.7<phosphate<phosphate<phosphate2.5 mM) and a mixed group (phosphate<0.7 AND >1.5 mM), as shown in Figure 1.
Summary of the results
The distribution of phosphate values was; 19467 measurements, mean 1.18 mM, SD ±0,52, min 0,04 and max 6,1 (Figure 1).
Kaplan-Meier survival curves were plotted over 180 days. Mean survival days were 177 days in moderate hypo, 141 in severe hypo and 114 in moderate hyper, 47 in severe hyper and 112 in the mixed group, compared to 179 days in the control group.
A COX proportional hazards pairwise equation was used to calculate hazard ratios (Table 1). Severe hyper was the only study group showing significantly increased hazard ratio 1.639 p<0.0001. Moderate hyper showed a tendency towards increased hazard ratio 1.168 p=0.0656. Study groups in the hypophosphatemic arm did not show significantly increased hazard ratios, neither did the mixed group. 13/38 covariates in the hyperphosphatemic arm compared to 9/39 in the hypophosphatemic arm showed increased hazard ratios.
The mixed group showed significantly longer ventilator treatment time compared to all other groups; 177,25 hours to 25,82 in the control group and to 77,27 in moderate hypo and to 109,60 in severe hypo and to 76,35 in moderate hyper and to 86,42 in severe hyper, p<0.001.
233/4656 (5,0 %) patients got CRRT and only 9 were in the control group meaning that 96,1 % of the CRRT patients showed a phosphate deviation.
Hyperphosphatemia could exert its action through chelating calcium and thus causing hypocalcemia.
Regression analysis showed that there were no correlation between phosphate and simultaneous ionized calcium values; pearson coefficients were 0,039 for minimum and -0,051 for maximum phosphate.
Reached conclusions
Hypophosphatemia in absence of organ failure seems not to increase mortality. Increasing level of hyperphosphatemia is connected to worse outcome and COX analysis indicated that organ system failure may be the main reason.</phosphate

Table and figure on following pages

	severe hypo	moderate hypo	control	moderate hyper	severe hyper	mixed hypo/hyper
number of patients in group	82	844	2002	961	254	513
studygroup compared to control	0,734 p=0,2192	0,912 p=0,322		1,168 p=0,0656	1,639 p<0,0001	0,812 p=0,0741
age additional year	1,035 p<0,0001	1,035 p<0,0001		1,032 p<0,0001	1,032 p<0,0001	1,036 p<0,0001
gender female	0,966 p=0,7441	1,025 p=0,7814		1,02 p=0,7954	1,072 p=0,4384	0,904 p=0,2536
SOFA score total	1,214 p<0,0001	1,201 p<0,0001		1,196 p<0,0001	1,196 p<0,0001	1,189 p<0,0001
SOFA score renal	1,215 p<0,0001	1,179 p<0,0001		1,156 p<0,0001	1,138 p=0,0015	1,201 p<0,0001
diagnosis circulatory	4,961 p=0,1118	2,915 p=0,1342		1,853 p=0,0712	2,126 p=0,017	1,841 p=0,1438
diagnosis coagulation	0 p=0,9887	0 p=0,9878		1,689 p=0,6189	1,291 p=0,8071	0 p=0,9823
diagnosis diabetes	0 p=0,9819	2,347 p=0,4877		0,889 p=0,8801	0,694 p=0,7269	0,884 p=0,881
diagnosis fluid balance	1,121 p=0,9357	0,416 p=0,4747		1,131 p=0,8260	1,205 p=0,0813	0,301 p=0,2666
diagnosis GI tract	5,328 p=0,0988	3,065 p=0,1201		2,084 p=0,0369	2,241 p=0,0161	1,738 p=0,1989
diagnosis infectious	3,567 p=0,2099	2,855 p=0,1441		1,363 p=0,3767	1,539 p=0,1912	1,231 p=0,6282
diagnosis intoxication	0,446 p=0,5692	0,581 p=0,5882		0,122 p=0,0469	0,169 p=0,0906	0,144 p=0,7624
diagnosis multiple trauma	3,075 p=0,2750	2,313 p=0,2518		1,125 p=0,7616	1,267 p=0,5336	1,091 p=0,8223
diagnosis neoplasm	2,99 p=0,2823	2,25 p=0,2619		1,303 p=0,4665	1,321 p=0,4246	1,142 p=0,7624
diagnosis neurological	3,227 p=0,2575	2,475 p=0,2191		1,257 p=0,5570	1,067 p=0,8705	1,143 p=0,7818
diagnosis neursurgical	7,575 p=0,046	5,928 p=0,013		3,03 p=0,0025	2,968 p=0,0022	3,355 p=0,0058
1,269 p=0,5105	1,3 p=0,4595	1,065 p=0,8879	diagnosis pulmonare	6,538 p=0,0628	4,603 p=0,03	
2,2 p=0,0218	2,52 p=0,0042		2,252 p=0.2662	diagnosis obstretric	0 p=0,9727	0 p=0,9678
	0 p=0,9587	0 p=0,9662	0 p=0,9513	diagnosis other	3,04 p=0,2782	2,643 p=0,0215



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Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN): Design of a Retrospective Cohort Study

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On behalf of the Neonatal Kidney Collaborative
Background: Acute kidney injury (AKI) affects ˜30% of NICU patients. The Neonatal Kidney Collaborative (NKC) is a multidisciplinary, international group of neonatologists and pediatric nephrologists interested in investigating important questions related to neonatal AKI.
Objective: To design and establish the infrastructure for a retrospective cohort study (AWAKEN) to: define the epidemiology of neonatal AKI, determine if current categorical definitions of AKI are associated with mortality, length of stay, and discharge serum creatinine, determine how neonatal fluid balance relates to biochemical data and short term outcomes.

Design/Methods: In 2014, the NKC was established with at least 1 pediatric nephrologist and 1 neonatologist from institutions in 4 countries (USA, Canada, Australia, India). A Steering Committee and 4 subcommittees were created. The database subcommittee oversaw the development of case report forms (CRFs) and the web-based database using MediData Rave™ housed at Cincinnati Children's Hospital that captured, managed, and reported data for AWAKEN. Individual centers were responsible for entering data on all NICU admissions from 1/1/2014-3/31/2014.
Results: The NKC grew from 16 to 24 sites. CRF development took 9 mo, the electronic database build took 10 wk, and pilot testing took 8 wk. All site PIs and research staff completed standardized training. The database includes ~325 unique variables representing >4 million discrete data points. Data entry began 3/15. Each subject required 1-2 h for data extraction and 30-60 min for data entry. Over 28,000 queries were generated and resolved to date. By 10/1/15, 20 sites completed data entry (3397 subjects screened, 1742 enrolled). Data entry from all sites will be completed by 12/15.
Conclusions: AWAKEN is the largest, most inclusive neonatal AKI study to date. In addition to validating the neonatal AKI definition and identifying risk factors for AKI, this study will uncover variations in practice patterns related to fluid provision, renal function monitoring, and involvement of pediatric nephrologists during inpatient hospitalization. The time and effort needed to establish the collaborative and develop the database was considerable, but it is anticipated that the AWAKEN study will position the NKC to achieve the long-term goal of improving the lives, health and well-being of newborns at risk for kidney disease.

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Computerized Prediction of AKI Outperforms Plasma NGAL: a Retrospective Analysis

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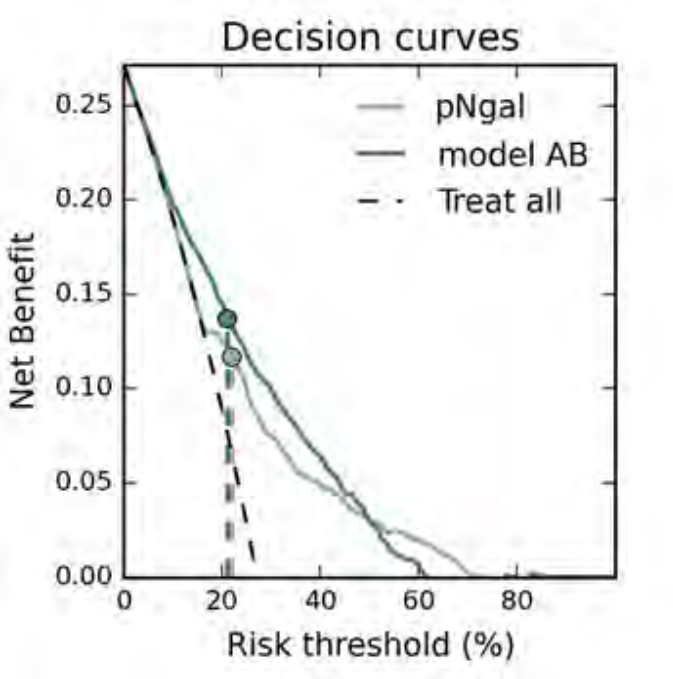
Purpose
Critically ill patients at risk for Acute Kidney Injury (AKI) may benefit from early detection of this condition. We aimed to develop and validate accurate prediction models for AKI during the first week of Intensive Care Unit (ICU) stay. Additionally, we aimed to compare the models' predictive performance against plasma NGAL (pNGAL), a well-studied biomarker for early detection of AKI.
Methods
Retrospective analysis of patient data from the multicenter randomized EPaNIC trial, comparing early versus late supplemental parenteral nutrition in critically ill patients. Data were split into a development (n=2194) and a validation (n=2434) cohort. pNGAL upon ICU admission was determined in 2274 patients from the validation cohort. We derived and validated 4 multivariate random forest models to predict AKI (defined according to the creatinine-based KDIGO criteria) within the first week of ICU stay. To mimic the availability of patients' data in the ICU, models were based on routinely collected patient information available at baseline (model B), ICU admission (model AB), at the end of the first day (model D1AB) and using the first 24 hours of monitoring and medication data (model D1-24hAB). Model performance was assessed using area under the ROC curve (AUC), decision curve analysis, and calibration.
Results
Table 1 reports the performance of the models in development and validation cohorts, and pNGAL performance in the validation cohort. Figure 1 specifically shows the decision curves of pNGAL and model AB in the

validation cohort. Overall, all models presented good discriminability, net benefit and calibration, which remained after external validation. Model AB achieved a higher discriminability and net benefit than pNGAL. Predictive performance increased when information from later time points was added.

Conclusion

Prediction models based on routinely collected patient information accurately identify patients at risk for developing AKI within the first week of ICU stay. Additionally, models developed with information available upon ICU admission outperformed pNGAL. Whether such 'in silico' model could outperform any biomarker for AKI remains to be investigated. To be of any clinical use, these biomarkers should always demonstrate an added value over routinely collected data. Alternatively, computer models could be used to select those higher-risk patients in whom biomarkers could be of additional value to predict AKI or stratify patients.

	Development cohort				Validation cohort				
Model	B	AB	D1AB	D1-24hAB	B	AB	D1AB	D1-24hAB	pNGAL
N	2123	2034	1774	1774	2367	2081	1954	1752	2081
AKI prevalence	0.28	0.24	0.14	0.14	0.29	0.27	0.15	0.15	0.27
AUC	0.77+-0.01	0.79+-0.01	0.85+-0.01	0.86+-0.01	0.76	0.77	0.80	0.82	0.74
Net benefit	0.13+-0.01	0.12+-0.01	0.08+-0.01	0.09+-0.01	0.14	0.14	0.09	0.09	0.12
Calibration slope	0.84+-0.05	0.92+-0.05	0.88+-0.08	0.97+-0.01	0.80	0.84	0.76	0.85	0.83
Calibration in the large	0.00+-0.01	0.00+-0.01	0.00+-0.01	0.00+-0.01	-0.01	-0.02	-0.01	-0.04	0.00



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A Case of Successful Treatment via Continuous Renal Replacement Therapy in Patient with Acute Kidney Injury due to Liver Abscess.

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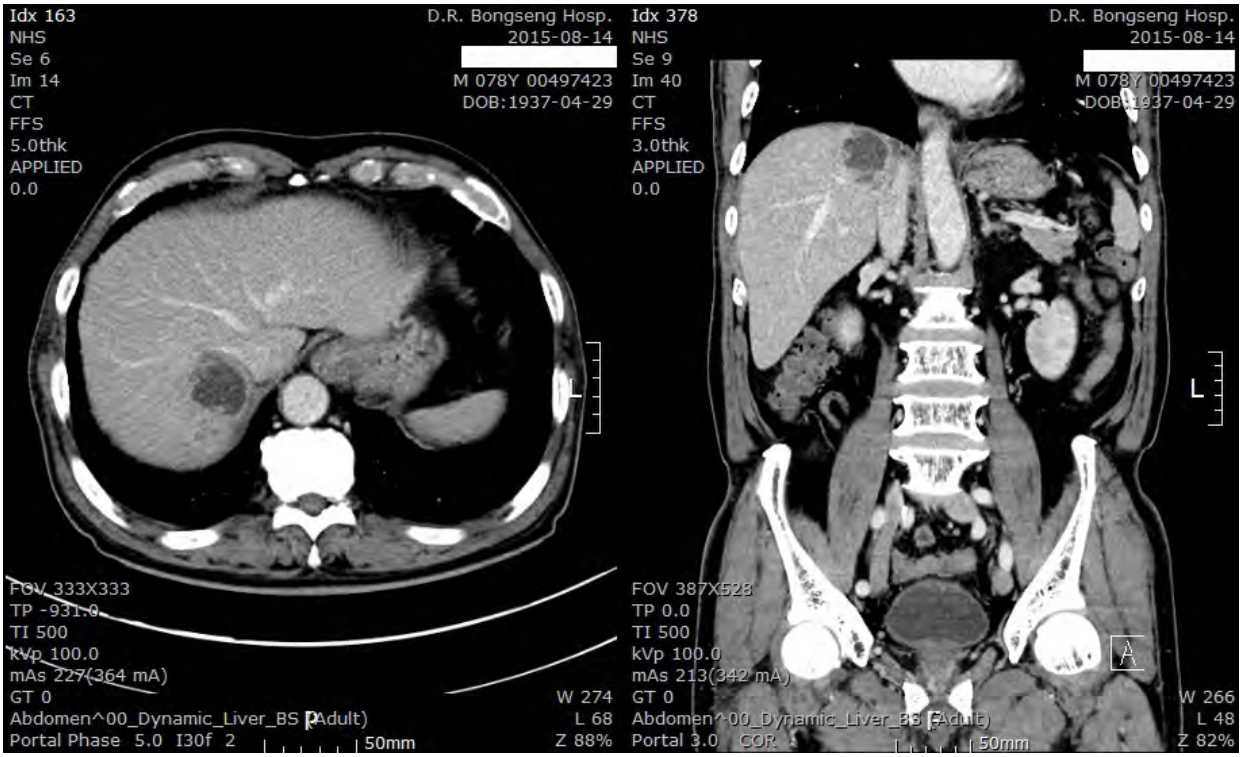
Pyogenic liver abscess is an uncommon complication of intra-abdominal or biliary tract infection and is usually associated with high mortality in Korea. We report a 78-year-old male survived from acute kidney injury due to septic shock caused by pyogenic liver abscess without aspiration. He was referred from gastroenterology of our hospital because of hypotension, anuria, thrombocytopenia, elevated liver enzyme and unknown origin fever. He had elevated serum BUN and creatinine levels, requiring hemodialysis treatment at the time of referral. But conventional hemodialysis was not available because of hypotension. So, we started continuous renal replacement therapy (CRRT) with inotropic agents at intensive care unit. We checked his abdominal CT scan before CRRT and multiloculated cystic/ necrotic lesion (5x5x3cm) in S7 was noted. The day after we started CRRT for him, we received his blood culture report. Klebsiella pneumoniae were identified in 3 sets of his blood samples. So we changed administrated antibiotics from ceftriaxone to meropenem and decide to prepare aspiration of abscess after observation. After 3 more days of continuous venovenous hemodiafiltration (CVVHDF), his blood pressure and urine output recovered to normal range and CRRT was stopped. We decided to deliver intravenous antibiotics for 6 weeks and maintain oral antimicrobial treatment for consolidate the effect of treatment without aspiration of abscess for technical difficulties. The patient has been treated follow-up care in outpatient department for 3 months.



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Use of Cell-Cycle Arrest Biomarkers for Prediction of AKI in Infants Following Cardiac Surgery

Katja M Gist[1], Jeffrey Alten[2], Danielle Soranno[3], Jane Duplantis[3], Julia Wrona[1], Christopher Altmann[4], Zhiqian Gao[5], Stuart L Goldstein[6] , Sarah Faubel[4]

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Purpose: Acute kidney injury (AKI) following pediatric cardiac surgery (CS) is common, occurring in 20-40% of children, and is associated with increased morbidity and mortality. Early diagnosis of AKI has been hampered because rises in serum creatinine (SCr) – the current method by which AKI is diagnosed – occurs late after AKI. Currently, an increase in urine TIMP2*IGFBP1 ≥ 0.3 ((ng/ml)2/1000) measured by the Nephrocheck (Astute Medical, La Jolla, CA) device is the only FDA approved AKI biomarker test, yet its approval is only for adults. The utility of TIMP2*IGFBP7 to predict AKI in infants is uncertain. The purpose of this study was to evaluate the utility of TIMP2*IGFBP7 for prediction of AKI in infants following CS.

Methods: Stored urine samples from a large multi-center study were analyzed for TIMP2*IGFBP7 using the clinically validated Nephrocheck device according to manufacturers directions. Samples were measured at baseline (before CS) and then 2, 6, 12, 24, 48 and 72 hours after the initiation of cardiopulmonary bypass. The primary outcome was severe AKI defined by at least a 100% increase in SCr (KDIGO Stage 2 or greater) within 72 hours of cardiac surgery.

Results: 94 infants (birth to 1 year) from 3 pediatric centers were included in the study, of which 26 (28%) developed severe AKI. Cross clamp time was 107 minutes (IQR: 62-128min) vs. those without AKI (62.5min, IQR: 34.5-97min)(p = 0.012) and urine output was 23.5ml/kg + 13.6ml/kg vs. 34.2 + 16.9ml/kg on the day of surgery (p=0.016) and 33.8 + 27 vs. 72.1 + 33.8ml/kg on post op day 1 (p = 0.016). Infants with severe AKI had a higher urinary TIMP2*IGFBP7 by 12 hours (1.1, IQR: 0.9-3.4 vs. 0.4, IQR: 0.1-1.1)(p = 0.0009)(Table 1). Urine TIMP2*IGFBP7 12 hours following CS demonstrated an AUC of 0.78, sensitivity of 0.81, specificity of 0.7 for a cutoff value of 0.78, which is more than double the cut-point used in adults. The relative risk of developing AKI when TIMP2*IGFBP7 was >0.78 was 4.48 times (95%CI: 1.81 – 11.08) compared to those with TIMP2*IGFBP7 < 0.78 (p = 0.0002). Using the adult cut-off of 0.3 yielded a sensitivity of 0.9 and specificity of 0.5. This was not predictive of AKI.

Conclusion: Similar to adults, urine TIMP2*IGFBP7 represents a sensitive, specific and predictive biomarker of AKI in children, although different urine cut-off levels than adults were necessary to identify AKI.

Table on following page

Variable	No AKI (n = 68)	AKI (n = 26)	p-value
Age (days)	155.8 +/- 85.1	150.1 +/- 88.7	0.78
Gender (male)	43 (63%)	20 (77%)	0.21
Cardiopulmonary bypass time (median, IQR)	150 (91.5, 186.5)	148.5 (123, 205)	0.41
Cross clamp time (median, IQR)	63.5 (35.5, 97)	107 (62, 128)	0.012
Urine output (ml/kg) Post-operative day 0	34.2 +/- 16.9	23.5 +/- 13.6	0.05
Urine output (ml/kg) Post-operative day 1	72.1 +/- 33.8	53.8 +/- 27	0.016
TIMP2*IGFBP7 (median, IQR) Baseline	0.5 (0.1, 1.6)	0.3 (0.2, 0.8)	0.99
TIMP2*IGFBP7 (median, IQR) 2 Hour	0.5 (0.2, 1.2)	1.1 (0.1, 2.3)	0.38
TIMP2*IGFBP7 (median, IQR) 6 Hour	0.7 (0.4, 1.5)	0.7 (0.5, 1.6)	0.99
TIMP2*IGFBP7 (median, IQR) 12 hour	0.4 (0.1, 1.1)	1.1 (0.9, 3.4)	0.0009
TIMP2*IGFBP7 (median, IQR) 24 Hour	0.3 (0.1, 1.2)	0.6 (0.1, 3.8)	0.38

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Plasma Pro-Enkephalin (penKid) and Renal Impairment in Severe Sepsis and Septic Shock: Data from the ALBIOS Trial

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Purpose of the study:
Acute kidney injury (AKI) is a frequent complication in sepsis, associated with increased lethality. In such setting accurate prediction of incident AKI by biomarkers has been frequently impaired by delayed response and/or influence of the systemic inflammation. Pro-Enkephalin (penKid), a stable surrogate marker for Enkephalins, has emerged as a novel promising plasma biomarker reflecting kidney dysfunction in acute diseases. Here we describe performance of penKid as predictor of incident AKI in a large cohort of patients with severe sepsis or septic shock from the Albumin Italian Outcome in Sepsis (ALBIOS) trial (Caironi P et al., N Engl J Med. 2014 Jul 3;371(1):84.).

Methods:
In a predefined biologic substudy of the ALBIOS trial, which randomized patients to albumin replacement in addition to crystalloids or crystalloids alone, EDTA plasma samples were obtained from 995 patients on days 1, 2 and 7 after randomization. Relations between plasma penKid concentrations, clinical characteristics and outcomes were analyzed.

Results:
Multivariable regression analysis identified serum creatinine as the strongest independent determinant of elevated penKid levels (F=254.4, p<0.0001). When kidney function was normal (renal SOFA score=0), penKid levels were essentially within the normal range, whereas penKid increased with the renal SOFA score (Spearman correlation: r=0.66). Elevated penKid predicted incident acute worsening of renal function (AKI) as well as the use of renal replacement therapy (RRT) (unadjusted p<0.0005 for both). In a multivariate Cox model after adjustment for serum creatinine, chronic kidney disease, and other variables penKid was an independent risk predictor for 90 day mortality (HR=1.6 [1.3-2.0] per 1 IQR). Serial measurement of penKid further improved mortality risk prediction.

Conclusions:
In this large study including almost 1,000 patients with severe sepsis or septic shock from 40 Italian ICUs, plasma penKid was associated with both prevalent and incident kidney dysfunction and independently predicted mortality. The absence of influence of systemic inflammation on penKid levels along with the fact that penKid is assayed in plasma (not urine) makes it a novel kidney biomarker especially attractive for use in critically ill patients.

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Milrinone Clearance in Critically Ill Infants with Acute Kidney Injury Following Cardiac Surgery

Katja M Gist[1], Tomoyuki Mizuno[2], Julia Wrona[1], Jeffrey Alten[3], Zhiqian Gao[4], Stuart L Goldstein[5], David Nelson[6] , David Cooper[6] , Alexander A Vinks[2]

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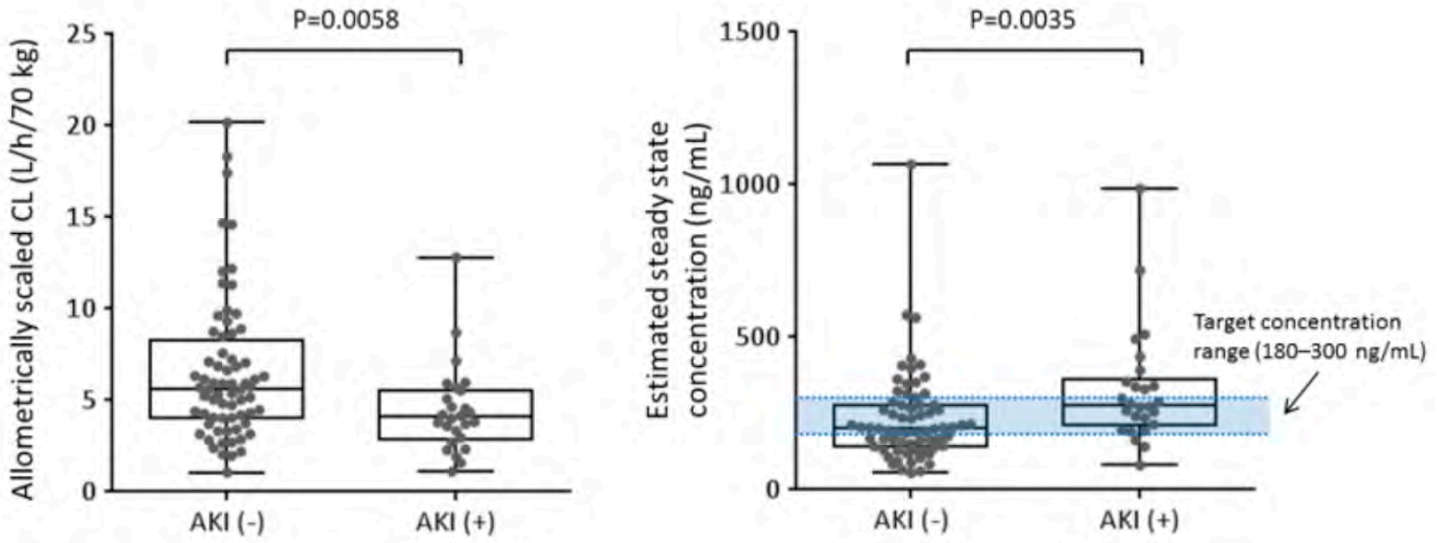
Purpose: Milrinone is used as an inotropic agent with vasodilating properties for treatment of ventricular dysfunction. Milrinone is eliminated as unchanged drug in the urine, and accumulates in acute kidney injury (AKI). The purpose of this study was to evaluate the effect of AKI on milrinone clearance in critically ill infants following cardiac surgery.
Methods: Prospective multicenter observational study in infants undergoing surgery with cardiopulmonary bypass. Serum creatinine (SCr) was measured to assess milrinone pharmacokinetics (PK). Blood was collected at serial time points after milrinone initiation, dose changes and termination, and analyzed for using a validated LC-MS/MS assay. Pharmacokinetic parameters were estimated using MW/Pharm (Ver. 3.82, Mediware, The Netherlands). A 2-compartment population PK model was used in the Bayesian analysis. Milrinone clearance was allometrically scaled to account for body size differences. The primary outcome was severe AKI defined by at least a 100% increase in SCr (KDIGO Stage 2 or greater) within 72 hours of cardiac surgery.
Results: 94 infants (67% male) were included. Twenty-six (28%) patients developed severe AKI. There was no difference in age, gender and weight between those with and without AKI. Milrinone clearance was significantly lower in pts with severe AKI (4.1L/h/70kg (IQR: 3-5.5) vs. (5.7L/h/70kg (IQR: 4-8))(p = 0.006). Clearance in those without AKI was also significantly lower than previously reported in PK studies in adult patients (18.9L/h/70kg). Urine output on the day of surgery and the first post-operative day was significantly

lower in those with AKI (p = 0.005 and p = 0.016 respectively). Lower milrinone clearance was associated with AKI (p = 0.02). Finally, AKI influences milrinone concentration and estimated highest steady state concentration. At a standard dose of 0.5mcg/kg/min, estimated steady state concentration was higher in AK pts (277ng/mL (range: 81-988) vs. 203ng/mL (range: 55-1067))(p = 0.0035)(Figure 1).
Conclusion: Milrinone clearance is significantly lower in critically ill infants than in previously reported studies in adults. We suggest overdosing of milrinone in the setting of AKI is possible, and caution should be taken in critically ill infants. The estimated steady state concentration at a standard dose was lower than the target range. We suggest monitoring of milrinone concentrations with PK model based guidance could be beneficial in patients at risk for AKI.



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Alkaline Phosphatase Protects Against Renal Inflammation Through Dephosphorylation of Lipopolysaccharide and Adenosine Triphosphate

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Background: Two phase-II trials demonstrated improved renal function in critically ill patients with sepsis-associated Acute Kidney Injury (AKI) treated with the enzyme alkaline phosphatase (AP). Here, we elucidated the dual active effect on renal protection by human recombinant AP (recAP) presumably related to dephosphorylation, thereby detoxifying, lipopolysaccharide (LPS).
Methods: Human proximal tubular epithelial cells (ciPTEC) were incubated with LPS (10µg/ml) or TNF-α (10ng/ml). RecAP (10U/ml) was added 2h prior to LPS and cytokine production was studied after 24h by ELISA (n=5 per group). After 20 minutes, supernatant was collected to determine LPS-induced cellular adenosine triphosphate (ATP) release by bioluminescence (10µg/ml or 100 µg/ml LPS). Male SD rats were treated with placebo (n=6), LPS (n=6) or LPS+recAP (n=5). At t=0, LPS (IV, 0.3mg/kg) was administered to induce AKI, followed by an recAP bolus (IV, 1000U/kg) at t=2h. GFR was assessed by transcutaneous measurement of FITC-sinistrin elimination in freely moving, awake rats. Urine was collected during 16h. At

t=24h animals were sacrificed followed by blood and organ sampling.
Results: In ciPTEC, recAP significantly reduced LPS induced cytokine response of TNF-α (40.4±7.9%), IL-6 (47.5±3.1%) and IL-8 (39.6±2.4%). Similar effects were observed in ciPTEC stimulated with TNF-α (IL-6: 21.0±4.2%; IL-8: 21.6±4.6% reduction). Inactive AP had no effect on LPS- or TNF-α-induced cytokine response, confirming the relevance of dephosphorylation. Extracellular ATP concentrations increased following LPS incubation, which was more pronounced with a higher LPS concentration but reversed by recAP preincubation. In vivo, LPS significantly prolonged FITC-sinistrin half-life (placebo: 19 [18-25] min, LPS: 55 [33-73] min), for which recAP treated animals were protected (33 [29-47] min). Also, recAP prevented LPS-induced increase in fractional urea and KIM-1 excretion and renal KIM-1 expression.
Conclusion: These results indicate that the ability of recAP to reduce renal inflammation may account for the beneficial effect observed in septic acute kidney injury patients, and that dephosphorylation of ATP and LPS are responsible for this protective effect.

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"Código IRA" Proposing a Rapid Response Team for the Detection and Management of Acute Kidney Injury in a University Hospital in Mexico

Lilia Rizo-Topete[1], Giovanna Arteaga-Müller[1], Mara Olivo[1], Jesús Cruz[1], Elisa Guerrero[1], Concepción Sánchez[1], Jose G. Martínez[1], Dionicio Galarza[1], Edelmiro Pérez[1], Marco Hernández[1]

[1]*Monterrey University Hospital*

Introduction: Acute Kidney Injury (AKI) is common in hospitalized and critically ill patients is, associated with high morbidity and mortality. The 5 to 7% develop it during internment, from 5 to 25% develop in ICU. Inpatients with severe AKI the Renal replacement therapy (RRT) serves as a cornerstone in the treatment, where mortality for AKI and multiple organ failure (MOF) is 50% and if RRT is required it would be 80%. Objective: If the fact of starting RRT increases morbidity and mortality, so why wait to start RRT if we can make a detection of a high risk patient during hospitalization. If we use the concept of Renal Angina we can identify minimal changes in serum creatinine, oliguria and volume overload in combination with the risk factors we could detect an early stage of AKI and prevent it. Methods: Based on the conceptual model of AKI and the proposal 0 by 25, in the 5 Rs between risk and recognizing a flowchart for detection inpatients at risk for AKI is proposed with an early management flowchart. To set the proposal in our hospital we made an statistical study with the following results: The Nephrology service has an average of 30 inpatients per day, the last 6 months were evaluated 438 patients, 193 were interconsulted by AKI, 118 were male (61.1%), Middle Age 52.1 years. The most common comorbidities were DM (39.9%) and hypertension (37.8%). Interconsultations were made for ICU and internal medicine (IM). The main cause of AKI was infectious. 90 (46.6%) patients need RRT and 30 of these stay in Chronic RRT (33.3%) . Of all interconsulted patients died 31.6% but this increase in ICU to 59.6% Proposal: Our Hospital (third level) offers all medical services from ICU, Surgery, Neurosurgery, Orthopedics, Urology, Gynecology, Plastic Surgery and Internal Medicine (IM) this last with all its subspecialties like nephrology , because of this IM is the proposed base of the flowchart.
Forming the team: IM service coordination and Nephrology. Primary care physician: Family, emergency room staff (surgeon, internist). Educate satellite services to identify: Emergency room (doctors and nurses), Surgical Service (General, Traumatology, Urology, Gynecology), Radiology, Oncology, Pulmonary and Critical Care Medicine. The proposal has been accepted by the Department of IM and will start the makeup of the group in January 2016, education block in February 2016 and the pilot group start activitiesin March 2016.

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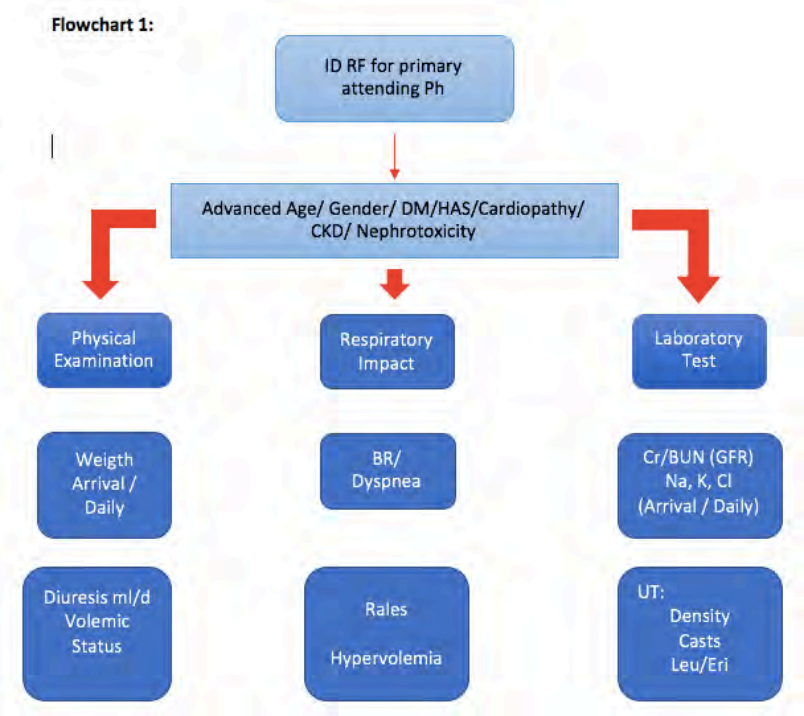

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Ineffective Diuresis as a Biomarker During Early Postoperative Period Predicts Cardiac Surgery Associated Acute Kidney Injury

Salvador Lopez-Giacoman[1], Carlos Garza-Garcia[2], Jose L Salas[2], Faeq Husain-Syed [1], Sara Samoni[1], Silvia De Rosa[1], Gerardo Gamba[2], Magdalena Madero[2], Claudio Ronco[1]

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Background: Cardiac surgery associated acute kidney injury (CSA-AKI) significantly increases morbidity and mortality. Difficulties in prediction and early identification of AKI have hindered the ability to develop preventive and therapeutic measures for this.. The present study aims at verifying that an “ineffective diuresis”, defined as less than 1.6ml/kg/h (IUO) during the early postoperative period (first 6h post-cardiopulmonary bypass (CPB)), may be a useful parameter to identify high risk patients (pts) for development of CSA-AKI.
Methods: We performed a dual center prospective cohort study (2012-2015) in pts requiring CPB, admitted to San Bortolo Hospital Vicenza/Italy and National Institute of Cardiology, México City/México. AKI was defined according to AKIN criteria. Pts were classified in two groups on the basis of urinary output (UO): 1) less than 1.6mL/kg/h (IUO group) and 2) equal or more than 1.6 mL/kg/h (control group). Primary outcome was AKI incidence, secondary outcomes were AKI severity, length of stay in intensive care unit, and 30-day mortality.
Results: A number of 458 pts who underwent CPB were enrolled. The mean UO was 2.3±0.7 mL/kg/h. During the first 96h post-CPB, 158 pts (34.5%) developed AKI, among these 61 pts (13.3%) had severe AKI. In the IUO group, 98 pts developed AKI (45.4%), while in the control group, AKI occurred in 60 pts (24.8%) ($p<0.001$). Moreover, 44 pts (20.4%) and 17 pts (7%) respectively in the IUO group and control group had severe AKI ($p<0.001$). Ineffective diuresis was associated with increased odds of AKI and severe AKI [adjusted odds ratio OR 4.2 (2.5-7.2, CI 95% p:0.001) and 3.8 (2.1-7.7, CI 95% p:0.001) respectively]. The value of

1.6mL/kg/h for UO may be considered as cut-off value to predict CSA-AKI with an AUC of 0.72. Table 1 summarizes characteristics of two groups.
Conclusion: An “ineffective diuresis” (<1.6mL/kg/h) during the early postoperative period should be included in the early evaluation of cardiac surgery pts to identify those at clinical high risk of CSA-AKI, could even improve the performance of new molecular biomarkers NGAL, TIMP2/IGFBP7, KIM-1 and others.

Table 1. Population characteristics.

	Entire Cohort (n= 458)		
Variable	**UO ≥ 1.6mL/kg/h n=242**	**UO < 1.6mL/kg/h n=216**	**p**
	PRE-OPERATIVE		
Age (years)	54 (18.2%)	54.2 (17.3%)	0.89
Male	158 (65%)	119 (55%)	0.26
Systolic BP (mmHg)	114 (±20.5)	115 (±17)	0.9
MAP (mmHg)	83 (±13)	83 (±11.2)	0.78
Albuminemia (g/dL)	3.9 (±0.48)	3.9 (±0.56)	0.22
Serum creatinine (mg/dL)	0.88 (±0.2)	0.98 (±0.32)	**0.001**
	OPERATIVE		
Valve surgery	178 (73.6%)	167 (77.3%)	0.35
CABG	54 (22.3%)	49 (22.7%)	0.92
CABG and valve surgery	16 (6.6%)	18 (8.3%)	0.48
CPB (min)	119 (±45)	**129 (±52)**	**0.031**
Aortic Clamp Time (min)	80 (±34.8)	**89 (±57)**	**0.032**
Intraoperative Fluid Balance (mL)	2655 (852-3957)	**1140 (380-2412)**	**0.001**
UO (mL/Kg/h)	3.1 (±1.4)	**0.79 (±0.43)**	**0.001**
Delta hemoglobinemia (g/dL)	-5.3 (-6.6 to -4.1)	**-5.3 (-6.6 to -4.2)**	0.8
	OUTCOMES		
AKI	60 (24.8%)	**98 (45.4%)**	**0.001**
Severe AKI	17 (7%)	**44 (20.4%)**	**0.001**
ICU length of stay (days)	3 (2-4)	**4 (3-5)**	**0.01**
Death	7 (2.9%)	11 (5.1%)	0.22

Nondimentional variables are expressed in absolute numbers (percentages), dimensional variables with normal distribution are expressed in mean ± (SD) and dimensional variables with non-normal distribution in median (RIQ: 25-75). UO: urinary output, BP: blood pressure, MAP: mean arterial pressure, CABG: coronary arterial bypass graft, CPB: cardiopulmonary bypass, AKI: acute kidney injury, ICU: intensive care unit. Severe AKI : AKI stage 2 and 3 from AKIN criteria

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Endothelial Progenitor Cell-Derived Extracellular Vesicles Protect From Sepsis-Associated Acute Kidney Injury

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Sepsis-associated AKI is due to a detrimental effect of pro-apoptotic circulating plasma factors able to induce endothelial (EC) and tubular epithelial (TEC) cell injury. Endothelial Progenitor Cells (EPC) are bone marrow-derived precursors able to accelerate tissue regeneration through the release of paracrine mediators such as extracellular vesicles (EV), small particles carrying RNA.The aim of this study was to evaluate the protective role of EPC-derived EV on EC and TEC injury induced by plasma of septic patientts.

We enrolled in the study 20 critically ill patients with septic shock and AKI Peripheral blood EPC were evaluated by FACS (CD34+/CD133+/flk-1+ cells) and isolated on fibronectin-coated plates. EV were isolated from EPC supernatants and characterized for RNA content. In vitro, kidney-derived EC and TEC were cultured with septic plasma and EPC EV from healthy subjects.

Patients with sepsis-associated AKI presented an increased number of circulating EPC. However, isolated EPC showed a decrease of proliferation and of EV release. EV isolated from EPC of healthy donors were internalized in both EC and TEC and protected from septic plasma-induced injury. On EC, septic plasma induced leukocyte adhesion, decreased angiogenesis through eNOS reduction and induced apoptosis through activation of the complement cascade. EPC EV reduced all these effects through the transfer of pro-angiogenic microRNA (miR-126, miR-296) and mRNA coding for inhibitors of apoptosis (Bcl-XL) and of complement activation such as CD55 (DAF), CD59 and Factor H. On TEC, septic plasma induced death receptor (Fas, TNF-R) apoptosis and mitochondrial dysfunction through decrease of PGC-1alpha. In addition, septic plasma induced loss of cell polarity as assessed by TEER and a decreased expression of the tight junction protein ZO-1, the endocytic receptor megalin and other TEC-specific solute carriers. All these effects on TEC were reduced by EPC EV stimulation. The EV-associated protection on both EC and TEC was significantly abrogated by their pre-treatment with RNase, the enzyme able to destroy mRNA and microRNA within EV.

In conclusion, EPC isolated from peripheral blood of patients with sepsis-associated AKI showed functional alterations, a decreased proliferation rate and EV release. EPC-derived EV may be exploited as innovative therapeutic approach in sepsis-associated AKI for their ability to inhibit apoptosis and functional alterations of EC and TEC.

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Immunomodulation of Regional Citrate Anticoagulation in Acute Kidney Injury Requiring Renal Replacement Therapy: A Randomized Controlled Trial

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Background: Currently, Regional Citrate Anticoagulation (RCA) has become the standard anticoagulation for acute kidney injury (AKI) patients requiring continuous renal replacement therapy (CRRT) support. Beyond the anticoagulant effect, data from in vitro showed RCA might have anti-inflammatory effect. We aim to study the immunomodulation effect of RCA in patients with AKI undergoing CRRT.
Methods: This prospective randomized controlled trial was conducted at medical and surgical Intensive Care Unit, King Chulalongkorn Memorial hospital. The participants were randomized to either regional citrate group (n = 15) or control group (n = 15). Blood samples were collected at baseline, six hours and 24 hours after starting CRRT. We measured CD11b, human leukocyte antigen-DR (HLA-DR) expression by using flow cytometry technique. We also tested the RCA effect on coagulation cascade by measurement the level of C3a, C5a and plasminogen activator inhibitor-1 (PAI-1) in plasma by using enzyme-linked immunosorbent assay technique.
Results: Thirty AKI patients with CRRT were recruited and randomized into control and citrate group. The demographic data between two groups are not different in each group. The percentage change of CD11b (0-24 hours) in RCA group had significantly higher than the control group, -41.5 vs. 7.1 %, p = 0.02), concordantly with the percentage change of HLA-DR, -5.17 vs. 35.63 %, p = 0.02). The percentage change of PAI-1 in RCA had also decreasing higher than the control group (-18.92 vs. 21.41, p = 0.03). However, there was no significant different level of C3a and C5a between two group over 24 hours during CRRT. The mortality rate at day-28 after enrollment between RCA and control group was no significant difference.
Conclusion: RCA had the benefit beyond the anticoagulation effect by decreasing the inflammatory process during CRRT. The larger randomized controlled trial is still warrant.

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Low Normal Values of Circulating Immune Cells with Increased Proportion of Vδ2 T-Cells are Associated with Acute Kidney Injury after Endovascular Thoraco-Abdominal Aortic Repair

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Purpose
To assess the postoperative course of tubular cell cycle arrest biomarkers expression after mild ischemic-reperfusion injury and intravenous contrast during endovascular multi-branched aortic repair and to identify cellular immunological phenotype associated with tubular cellular stress and acute kidney injury (AKI).
Methods
Prospective single-center pilot study including 18 patients. Incidence of tubular cellular stress as measured by expression of cell cycle arrest biomarkers, incidence of AKI, clinical and laboratory parameters were evaluated. Robust immunological profile of 62 immune cell subsets based on flow cytometry was assessed before and 24

hours after surgery.

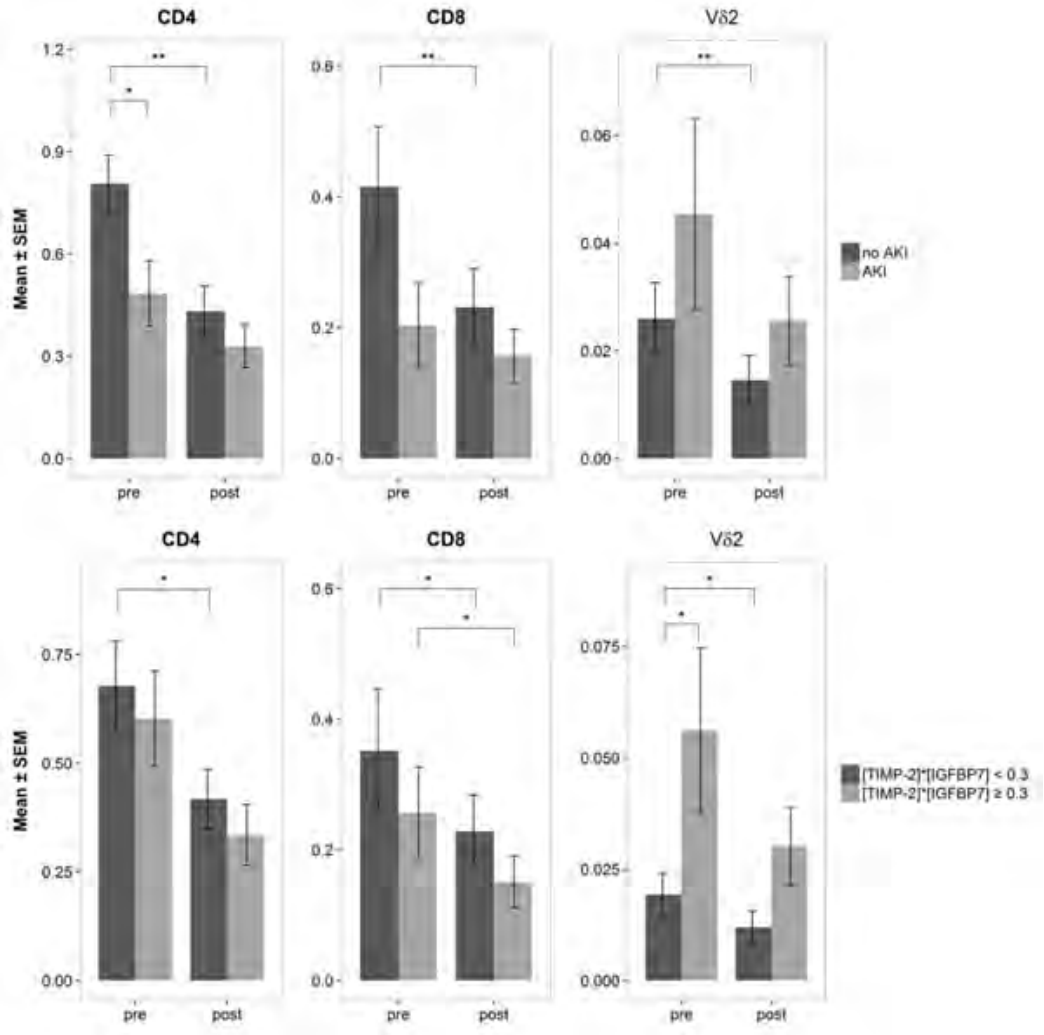
Results

Duration of surgery (p=0.03) and postoperative level of [TIMP-2][IGFBP7] (p=0.05) were associated with AKI. Strong cellular immune response with decrease of absolute numbers of circulating T, B and natural killer (NK) cells within first 24 hours was detected in all patients (from 1.29 /nL (SD 0.60) to 0.81 /nL (SD 0.37), p<0.01). By contrast, only limited cellular reaction was detected in patients, who developed AKI (from 0.96 /nL (SD 0.49) to 0.73 /nL (SD 0.38), p=0.36). This was due to significantly lower cell number prior to surgery as compared to patients without AKI (1.61 /nL vs 0.96 /nL, p=0.02). Trend to increased proportion of Vδ2 T-cells was identified in patients at AKI- risk, while other T-cells decreased, showing moderate correlation between cell cycle arrest biomarkers and number of Vδ2 T-cells (r=0.46, p=0.07) [Fig 1].

Conclusion

Strong systemic immune response with migration of cells from peripheral blood compartment in to organs occurs after surgery. Low pre-operative level of circulating T, B and NK cells and increased proportion of Vδ2 T-cells within first 24 hours represents the immunological risk factors for early AKI after aortic surgery.

Fig 1. Comparison of T-cells subgroups showing increased absolute count of Vδ2 T-cells in patients with cellular stress and patients with AKI, while CD4 and CD 8 cells are decreased. * p<0.05, ** p<0.01



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Biomarkers of Acute Kidney Injury and Outcome in Critically Ill Patients

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Purpose of the study:

Acute kidney injury (AKI) has been associated with an increased risk of poor outcome in critically ill patients. Pro-Enkephalin (penKid), a stable surrogate marker for enkephalins, has emerged as a promising novel plasma biomarker predicting renal function and mortality. The objective of this study was to explore the diagnostic and prognostic value of a panel of biomarkers of renal injury and renal function in critically ill patients.

Methods:

The French and euRopean Outcome reGistry in Intensive Care Units (FROG-ICU) study was a multicenter observational study, including 2087 critically ill consecutive patients. Plasma and urine samples were collected on admission. Primary endpoint was AKI, defined by KDIGO definition using the creatinine criteria on admission as the baseline. Secondary endpoints included severe AKI (defined by KDIGO stage 2 or 3), transient AKI and major adverse kidney events (MAKE, including – death, RRT and non-renal recovery). The association between outcomes and biomarkers was assessed by univariate analysis. Predictive values were assessed using area under the ROC curves.

Results:

893 (43%) patients developed AKI including 716 patients with severe AKI. 338 (37%) patients had transient AKI. 832 (40%) patients developed a MAKE including 480 requiring RRT. On admission all biomarker levels were higher in patients with AKI compared to non-AKI: 110.6 (63.3 to 193.3) vs 43.2 (30.6 to 66.8) pmol/L for penKid, 1.8 (1.2 to 2.7) vs 0.8 (0.6 to 1) mg/dl for Screat, 494 (247.8 to 909.2) vs 126 (74 to 225.8) for pNGAL, 631.5 (158.9 to 1500) vs 62.5 (27 to 204.9) for uNGAL, 2 (1.4 to 3) vs 1 (0.8 to 1.4) for pCyst and 0.8 (0.2 to 3.4) vs 0.2 (0.1 to 1) for uCyst (all $p<0.001$). Area under the ROC curve (AUC-ROC) for AKI was: 0.805 [0.786 - 0.824] for penKid, 0.822 [0.803 - 0.84] for pNGAL, 0.821 [0.801 - 0.838] for pCyst. AUC-ROC for transient AKI was: 0.63 [0.593 - 0.666] for Screat, 0.675 [0.639 - 0.713] for penKid, 0.649 [0.611 - 0.687] for pNGAL and 0.688 [0.654 - 0.724] for pCyst. AUC-ROC for MAKE was: 0.686 [0.662 - 0.709] for Screat, 0.736 [0.713 - 0.758] for PenKid, 0.737 [0.713 - 0.759] for pNGAL and 0.743 [0.72 - 0.765] for pCyst. A strong correlation was observed between penKid and eGFR on admission (Spearman $r=-0.68$, $p<0.001$)

Conclusion:

Plasma penKid, pNGAL and Cystatin C appear to be valuable biomarkers of AKI in critically ill patients. penKid is not influenced by systemic inflammation.

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Urinary TIMP2xIGFBP7 Detects Patients with Positive Urine Microscopy Findings

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Background and objectives
Urine microscopy is an established technique to assess kidney disease, including acute kidney injury (AKI), and can add valuable information about the mechanism of damage. However, it requires the time and expertise of an experienced nephrologist and, therefore, is typically used for a limited number of patients in practice. A rapid biomarker test that identifies patients to have positive urine microscopy findings would likely enable more efficient use of this technique. We hypothesized that urinary TIMP2xIGFBP7, a new FDA-approved test to assess AKI risk, would indicate likelihood of a positive urine microscopy finding in emergency department (ED) patients.

Design, settings, participants & measurements
400 patients were enrolled in the ED; thereof 362 patients had available both TIMP2xIGFBP7 and Urine-Score (U-Score) data at enrollment. TIMP2xIGFBP7 results are reported in units of (ng/mL)2/1000. U-Score was assessed through urine microscopy as described previously. AKI was assessed within 24 hours of enrollment using serum creatinine and urine output.

Results
Fifteen (4%) of 362 patients had a U-Score >0. When patients were stratified into three groups using the validated TIMP2xIGFBP7 cutoffs of 0.3 and 2.0, the proportion of patients with a positive U-Score increased across the three strata from 1% to 6% to 24% ($p<0.001$). At the 0.3 cutoff, TIMP2xIGFBP7 had a sensitivity of 87%, specificity of 62%, negative predictive value (NPV) of 99% and positive predictive value (PPV) of 9% for prediction of a positive U-Score. At the 2.0 cutoff, specificity increased to 95% and PPV increased to 24%.

Conclusions
In ED patients, urinary TIMP2xIGFBP7 had a high NPV (99%) for ruling out a positive U-Score using the 0.3 cutoff and had a PPV of 24% (6-fold greater than the pre-test probability) using the 2.0 cutoff. As such, urinary TIMP2xIGFBP7 may enable more effective use of urine microscopy in these patients and thereby save time and personnel resources.

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Vitamin D Deficiency is Common in Severe Acute Kidney Injury

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INTRODUCTION
In patients with chronic kidney disease (CKD), Vitamin D deficiency is very common and the supplementation with active Vitamin D preparations is recommended. To date, it is unknown whether patients with severe acute kidney injury (AKI) also suffer from Vitamin D deficiency and whether there is a role for supplementation.

OBJECTIVES
To determine Vitamin D3 levels in patients with AKI stage 3 on the day of diagnosis of AKI stage 3 and 6 days later.

METHODS
We prospectively identified adult patients on the Intensive Care Unit (ICU) with AKI III. Following informed consent, we measured plasma Vitamin D3 levels at diagnosis of AKI III and 6 days later. Vitamin D3 levels were measured by immunoassay. Vitamin D3 deficiency was defined as Vitamin D3 <30nmol/L. We differentiated between patients with and without continuous renal replacement therapy (CRRT) and excluded patients on parenteral nutrition.

RESULTS
We analysed 54 patients of whom 12 patients received CRRT for 6 days, 31 patients had CRRT for 1-5 days and 12 patients did not have CRRT. Vitamin D3 deficiency was very common in all groups (Table 1). There was no clear evidence that CRRT was contributing.

CONCLUSIONS
Vitamin D3 deficiency is common in patients with AKI III. More research is necessary to investigate its impact on patient outcome and the role of Vitamin D supplementation.

	CRRT for 6 days	CRRT for 1-5 days	AKI III without CRRT
Mean Vitamin D3 on day of diagnosis of AKI III [nmol/L]	27.5	24.8	19.3
Presence of Vitamin D3 deficiency on day of AKI III	60%	74%	84.6%
Mean Vitamin D3 on day 6 of AKI III [nmol/L]	28.3	23.6	22

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Serum Cystatin C Predicts Renal Recovery Earlier Than Serum Creatinine Among Hospitalized Patients With Acute Kidney Injury

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Background/Aim
Limited evidence suggests serum cystatin C (cys C) peaks earlier than serum creatinine (sCr) during the course of acute kidney injury (AKI). Earlier identification of AKI recovery could allow better resource utilization and earlier hospital discharge. Thus, we conducted an observational pilot study to determine the relative time course of sCr and cys C in hospitalized patients with AKI in our tertiary medical center.

Methods
Hospitalized patients with AKI at our institution between May and November of 2015 who had serial sCr and cys C levels measured during their hospitalizations were identified. AKI was defined based on the Acute Kidney Injury Network criteria. Demographic data, baseline creatinine, causes of AKI, and other significant comorbidities were collected by review of the medical record.

Results
Overall, 29 patients were identified. Mean age was 57.1 ± 14.3 years, 48.3 % were women, 93% were white, and median BMI was 29 kg/m2. Baseline median creatinine was 0.9 (IQR 0.8-1.2), 17% had a kidney transplant and 42% had received steroids. Co-morbidities included hypertension (55%), malignancy (52%), diabetes (31%), thyroid disorder (24%) and heart failure (10%). Two (7 %) patients had AKI stage I, 6 (21 %) AKI stage II, and 21 (72 %) AKI stage III, with 10 (34%) requiring dialysis. The cause of AKI was ATN in the majority of patients (69%). Overall, cys C peaked before sCr in 69 % of patients (10% 3 days, 24% 2 days, 34% 1 day prior), and on the same day in 28% of them. In only 1 patient (3%) cys C peaked after SCr (2 days). The cause of AKI in this patient was obstruction. Exploratory analyses did not suggest any effect of the various co-morbidities on the timing of peak cys C as compared to sCr. Overall cys C peaked a mean of 1.1 days prior to sCr (95% CI 0.64-1.50; $p<0.001$) and performed equal or better than sCr in 97% of patients in this study for monitoring recovery from AKI

Conclusion
This pilot study suggests cys C peaks earlier than sCr in the majority of hospitalized AKI patients. A larger study is warranted to confirm the magnitude of this effect, and the potential confounders (if any). These findings have significant clinical implications for managing AKI with the potential for shortening hospital stay and reducing cost.

Timing of Cys C peak compared to creatinine peak	N (%)
-3 days	3 (10%)
-2 days	7 (24%)
-1 day	10 (34%)
Same day	8 (28%)
+2 days	1 (3%)
Total	29 (100%)

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AMPK is activated in mice after CLP and that it protects from AKI

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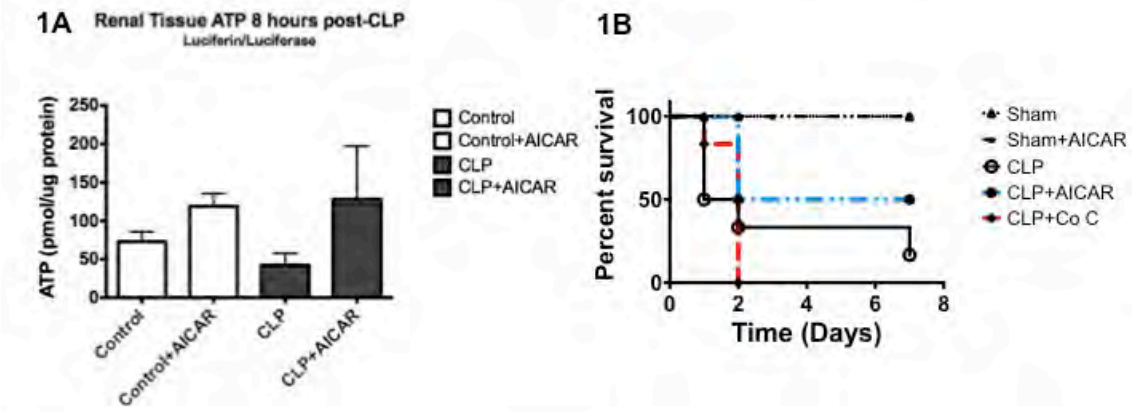
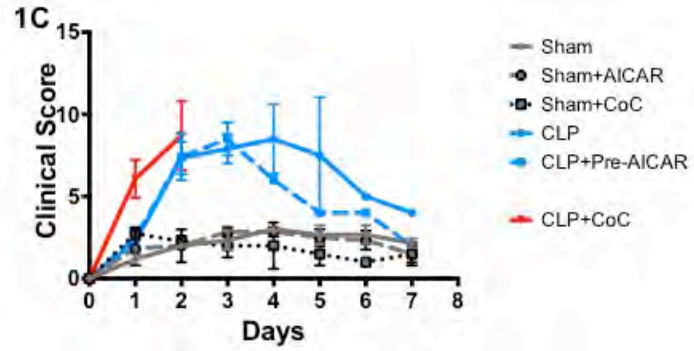
Purpose: The role of energy regulatory pathways in the protection from sepsis-induced acute kidney injury (AKI) is uncertain. We have previously shown that AMP-activated protein kinase (AMPK), a master regulator of energy balance, is activated early after cecal ligation and puncture (CLP), and its exogenous activation with AICAR limits sepsis-induced AKI and inflammation. Here we tested the hypotheses that activation of AMPK with AICAR H1: limits both ATP depletion and inflammation, and H2: improves clinical status and survival. Methods: H1: 15 C57BL/6 wild type, 10-12 week old, 30-35g mice were subjected to CLP (n=12) or sham surgery (n=3), and sacrificed after 8 h to measure renal tissue ATP. H2: 27 mice were subjected to CLP (n=18) or sham surgery (n=9) were randomly assigned to pretreatment with AICAR (100 mg/kg intraperitoneal (IP), 24h before), Compound C (AMPK inhibitor, 30mg/kg IP) or vehicle (control). Functional status was assessed using a 6-item clinical severity score (score range 0-3) daily for 7 days. Results: AMPK activation limited the decline in renal ATP (Fig 1A), and was associated with a trend towards improved mortality (Fig 1B), whereas compound C was associated with worse clinical score (Fig 1C) and survival (Fig 1B). Conclusion: AMPK activation limits ATP depletion in the kidney, decreases inflammation, and was associated with decreased clinical severity score and with a trend towards improved survival. These data suggest that immune modulation and energy conservation may play a role in the protective effects of AMPK activation during sepsis.





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Clinical and Subclinical Acute Kidney Injury in An Experimental Model of Sepsis

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Propose: Sepsis is commonly followed by clinically apparent acute kidney injury (AKI) but injury to the kidney may occur even when serum creatinine is normal. This subclinical AKI may increase risk for recurrence of AKI, chronic kidney injury (CKD) and even death. This study was intended to document patterns of subclinical AKI and to explore the mechanisms underlying sepsis associated AKI.
Methods: Male BALB/c mice were divided into various sepsis severities (mild, moderate and severe) using a cecal ligation and puncture (CLP) model according to different punctures (1, 2, and 3) or sham surgery. In different animals, blood and kidneys were harvested at 6hrs, 24hs and 14ds.
Results: Mild CLP did not result in any differences, while severe CLP resulted in high mortality (75%). Increased tissue staining for neutrophil gelatinase-associated lipocalin (NGAL) and diffuse kidney inflammation was seen at 6hrs in moderate and severe groups while expression of kidney injury molecular-1(KIM-1) in kidney tissue and serum creatinine increased only in the severe group. NADP/NADPH ratio increased at 24hrs in the severe group. Interleukin-6(IL-6) in blood was elevated at 6h and 24hrs while TNF-alpha elevated at 24hrs in all groups. The expression of bone morphogenetic protein receptor type 1a (BMPR1a) increased in started from 6h to 24 hours and continued to 14 days without concomitant changing of Bone Morphogenetic Protein 7(BMP7) in moderate and severe groups. Although serum creatinine concentration in CLP groups was similar to sham group, NGAL in kidney tissue was high with evidence of fibrosis including increased level of collagen I at 14 days post injury.
Conclusions: Moderate CLP induced sepsis was a reliable model to study subclinical AKI. In addition to oxidase stress and inflammatory reactions, epithelial cell injury, fibrosis was also seen even as early as 14 days post injury. The imbalance of BMP7/BMPR1a signaling emerged to be a potential therapeutic target for preventing CKD in sepsis.

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Urinary TIMP2xIGFBP7 for Risk Prediction of Cardiorenal Syndrome

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Background and objectives
Acute decompensated heart failure (ADHF) is a common reason for hospitalization and the risk of acute kidney injury (AKI) is high. The interaction of cardiac and renal dysfunction is well known as cardiorenal syndrome, and early detection of patients at risk for this condition is important. We tested urinary TIMP2xIGFBP7, a new FDA-cleared test to assess AKI risk, in a cohort of ADHF patients in the emergency department (ED).

Design, settings, participants & measurements
400 patients were enrolled in the ED. Serum creatinine values and urine output were recorded for AKI staging by KDIGO criteria. Urinary TIMP2xIGFBP7 was analyzed in samples collected during the first day (at 0, 6 and

24h) after enrollment. We examined the predictive ability of TIMP2xIGFBP7 for development of KDIGO stage 2 or 3 within 12 hours of sample collection in the 40 patients with ADHF, urinary TIMP2xIGFBP7, serum creatinine, and urine output data. Operating characteristics were determined for the previously validated TIMP2xIGFBP7 cutoffs of 0.3 and 2.0. TIMP2xIGFBP7 results are reported in units of (ng/mL)2/1000.

Results
Seven (17.5%) of the 40 ADHF patients met the AKI stage 2-3 endpoint. TIMP2xIGFBP7 discriminated for risk of AKI stage 2-3 with an AUC (95% confidence interval) of 0.84 (0.72-0.95). At the 0.3 cutoff for TIMP2xIGFBP7, the sensitivity was 86% and the specificity was 71% for prediction of AKI stage 2-3. At the 2.0 cutoff, the sensitivity was 43% and the specificity was 95%.

Conclusions
In ADHF patients presenting to the ED, urinary TIMP2xIGFBP7 enables good risk prediction of cardiorenal syndrome.

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Intraoperative CRRT Could be Useful During Liver Transplantation in Critically Ill patients with Renal Dysfunction

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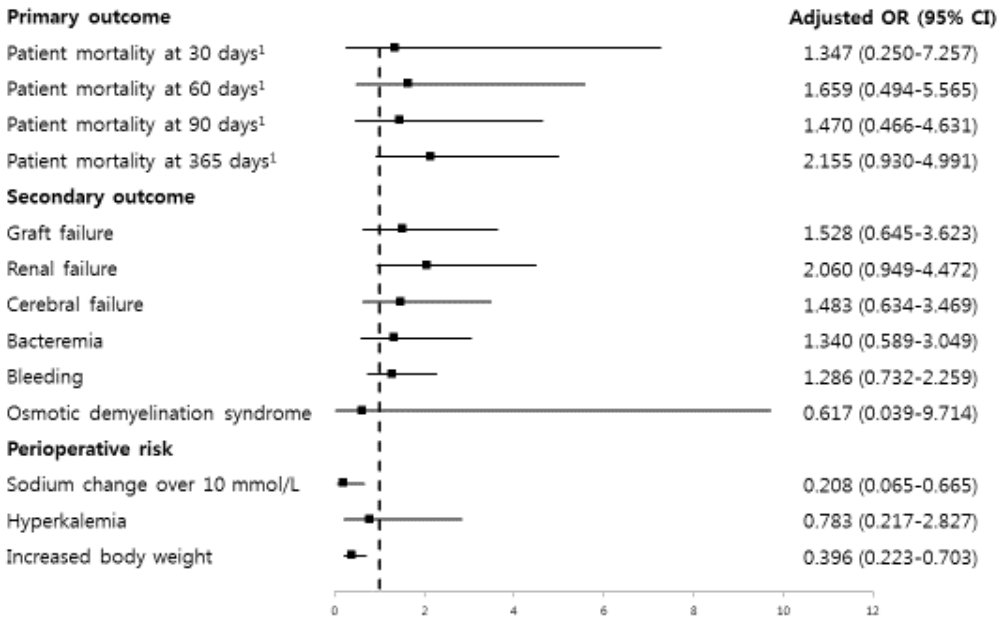
Purpose
Renal dysfunction frequently complicates liver transplantation (LT). Volume overload aggravate the morbidity and mortality in major surgical procedure. Continuous renal replacement therapy (CRRT) is well known for its hemodynamic stability and tolerance. However, comparative outcomes of CRRT during LT are unproven.

Methods
We investigated retrospectively clinical outcomes of intraoperative CRRT compared with those of non-dialytic conservative treatment in 240 LT patients with preoperative renal dysfunction (estimated GFR (eGFR) < 60 ml/min/1.73m2) from 1st January 2011 to 31st December 2014.

Results
Compared with non-dialytic conservative group (n=98, age 53.1+/-8.0 yrs, M:F=64:34), intraoperative CRRT group (n=142, age 51.3+/-10.2 yrs, M:F=108:34) revealed more severe critical illness including MELD score (34.9+/-8.8 vs. 23.4+/-10.2, p<0.005), ascites (83.1% vs. 64.3%, p=0.001), hepatic encephalopathy (73.2% vs. 38.8%, p<0.005), preoperative renal dysfunction (eGFR 31.4+/-15.4 vs. 49.3+/-11.4, p<0.005), ventilatory care (52.1% vs. 10.2%, p<0.005), and ICU admission (52.1% vs. 10.2%, p<0.005). Despite of above problems, there was no significant difference between two groups in 1-year survival, graft failure, recovery of renal dysfunction, frequency of hyperkalemia and postoperative complications by multivariate analysis. In an adjusted variables model, intraoperative CRRT group significantly escaped volume overload such as pulmonary edema (OR 0.396, 95% CI 0.223-0.703, p=0.002) and the unnecessary change of serum sodium concentration > 10 mmol/L (OR 0.208, 95% CI 0.065-0.665, p=0.008).

Conclusion
Considering more severe critical illness of intraoperative CRRT group and low frequency of volume overload, intraoperative CRRT could be useful during LT in critically ill patients with renal dysfunction. In the future, randomized controlled studies to prove the definite advantage of intraoperative CRRT during LT are needed.



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Early CRRT Could be Defined as the Initiation of CRRT within 24 hours after vasopressor infusion

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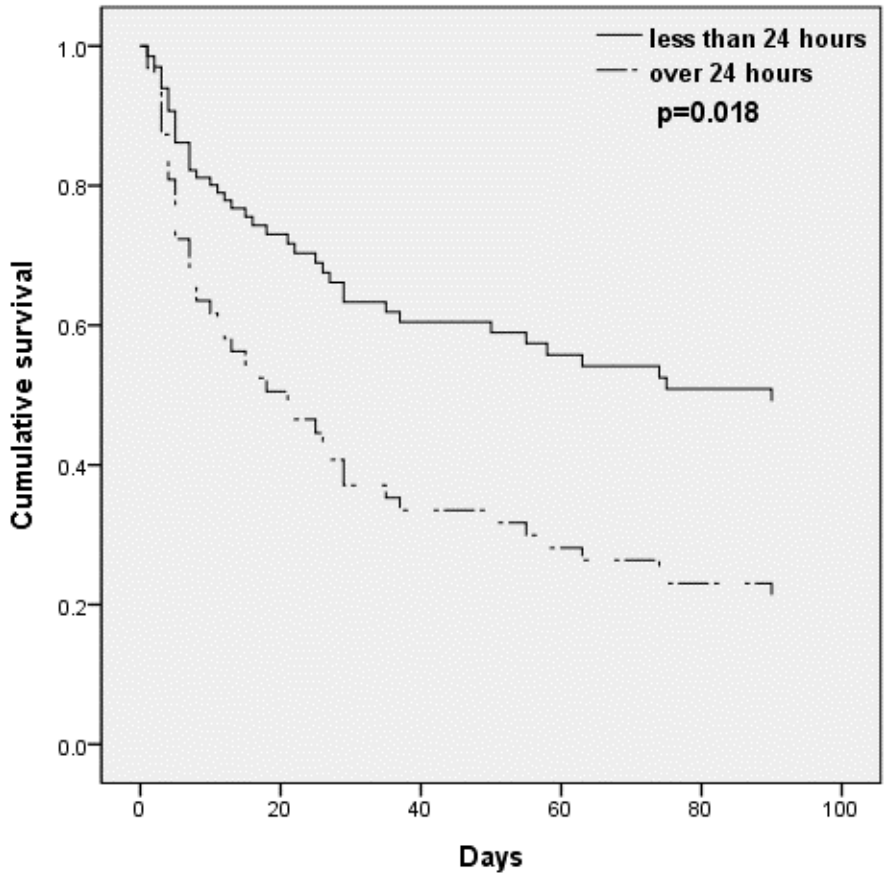
Purpose
Although institution of early continuous renal replacement therapy (eCRRT) reduces morbidity and improves the conditions of the patients with septic acute kidney injury (AKI) by removing inflammatory cytokines, the optimal timing for the initiation of eCRRT is uncertain and requires practically feasible definition and acceptable evidences.

Methods
We investigated the clinical impacts of three parameters about time interval such as (1) from the start of vasopressor to the initiation of CRRT (Tvaso-CRRT), (2) from the time of ICU admission to CRRT (TICU-CRRT), and (3) the time from endotracheal intubation to CRRT (Tendo-CRRT), on morbidity and mortality of 75 patients (age 66.9 +/- 13.3 yrs, M:F=39:36, SOFA score 14.4+/-2.2, NGAL 1002+/-390 ng/mL, procalcitonin 76+/-129 ng/mL, RIFLE criteria R:17, I:26, F:32) who need CRRT for septic AKI.

Results
The proportion of the patients with Tvaso-CRRT (median 21, range 10-38 hours) less than 24 hours was significantly higher in survival group than non-survival group (26/30(86.7%) vs. 19/45(42.2%), p<0.005). Tvaso-CRRT less than 24 hours and SOFA score were independent factors associated with 28-day mortality (HR 0.430, 95% CI 0.209-0.885, p=0.022; HR 1.434, 95% CI 1.149-1.790, p=0.001) and 90-day mortality (HR 0.460, 95% CI 0.242-0.875, p=0.018; HR 1.340, 95% CI 1.089-1.649, p=0.006). TICU-CRRT (19, 6-52 hours) and Tendo-CRRT (13, 3-39 hours) were significantly correlated with the length of stay in ICU (p=0.005) and the duration of mechanical ventilation (p=0.005).

Conclusion
Considering the possible therapeutic measurement by physician on the basis of the results in this study, the definition of early CRRT could be Tvaso-CRRT less than 24 hours. TICU-CRRT and Tendo-CRRT were only associated with morbidity, but not mortality. In the future, randomized controlled trials are needed to prove the usefulness of our definition of early CRRT.



55

Clinical Factors to Discriminate the AKI Patients Requiring CRRT over 6 days

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Purpose
To avoid unnecessary "early CRRT" increasing cost without measurable clinical benefit, the factors to predict the duration of CRRT should be settled. We investigated factors influencing the duration of CRRT including clinical parameters and the biomarker of AKI such as NGAL and serum creatinine.

Methods
We extracted 124 patients who required CRRT for AKI in ICUs and were followed for 28 days from January 1st to December 31st, 2014. We excluded patients with chronic kidney disease, prior liver or kidney transplantation, and death during 28-day follow-up. We divided patients (n=124, median duration of CRRT: 6 days) into the shorter group (=< 6 days, n=65) and longer group (>6 days, n=59) and retrospectively analyzed. We also tested the performance of the predictors.

Results
The presence of acute respiratory distress syndrome (p=0.002), mean arterial pressure (p=0.086), urine output (ml/kg/hour, p=0.006), the duration of mechanical ventilation (p<0.005), the duration of ECMO (p=0.001), platelet count (p=0.013), serum creatinine (p=0.086) and serum total CO2 (p=0.064) were considered significantly correlated with the duration of CRRT in univariate linear regression analysis. Among them, urine output (p=0.012) and duration of ventilation (p<0.005) were independently significant in multivariate analysis. As the predicting factors of the duration of CRRT over 6 days, urine output (OR 0.381, 95% CI 0.207-0.704, P=0.002), application of mechanical ventilation (2.321, 1.083-4.974, p=0.03), and the presence of ECMO support (5.187, 1.757-15.315, p=0.003) were independent factors in multivariate logistic regression analysis. Serum creatinine and NGAL were not significant. A clinical model using above three parameters demonstrated the discriminatory ability with AUC of 0.764 (95% CI, 0.704-0.818) to predict the duration of CRRT over 6 days.

Conclusion
Simultaneously considering of urine output, mechanical ventilation and ECMO could select the AKI patients requiring CRRT over 6 days and avoid unnecessary "early CRRT". These criteria should be confirmed by other randomized studies.

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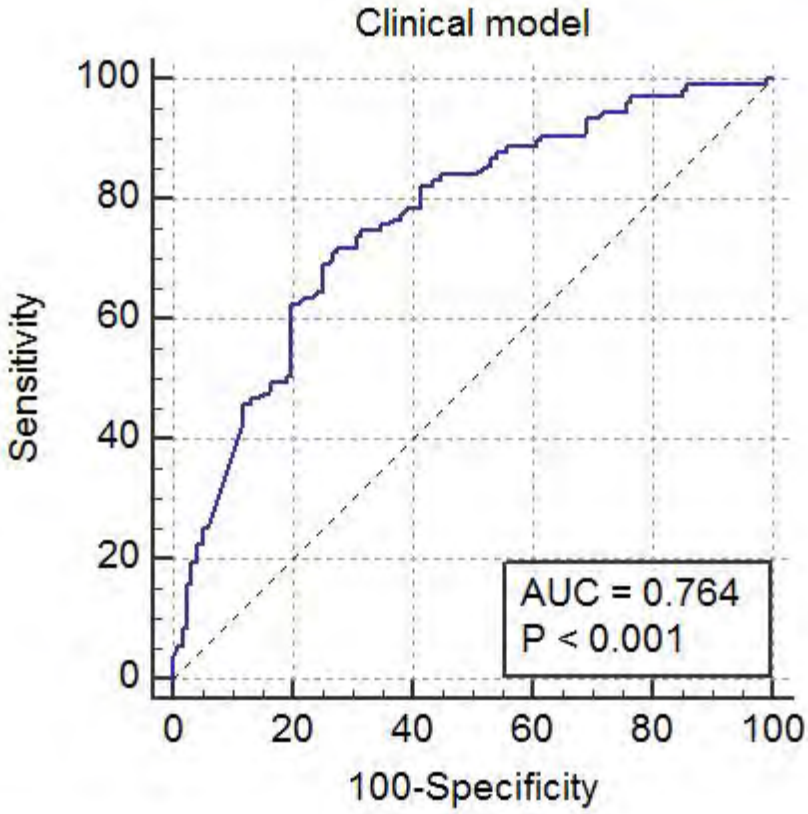

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IGFBP7 and TIMP2 Expression and Secretion in Human Kidney Tubule Epithelial Cells

David R Emlet[1], Nuria Pastor-Soler[2], Allison Marciszyn[1], Xiaoyan Wen[1], Hernando Gomez[1], Jacob K Volpe[1], William H Humphries IV[3], Xiukai Chen[1], Seth Morrisroe[1], John A Kellum[1]

[1]University of Pittsburgh, [2]University of Southern California, [3]B&B Microscopes

Purpose: Acute kidney injury (AKI) continues to be a significant issue in the critically ill patient, and discovery of novel biomarkers for the disease have not yet significantly contributed to improvements in patient care. Our group has recently identified IGFBP7 and TIMP2 as early superior biomarkers for prediction of development of AKI in critically ill patients, but their potential role in the disease remains unknown. Methods: Human kidney samples were procured from the local Organ Procurement Organization CORE with institutional approval. Cortex tissue was isolated and dissociated with Collagenase and sieving. Viable cells were cultured to confluence, and epithelial cells of proximal (PTEC) and distal (DTEC) tubule origin were immunoaffinity isolated with antibodies directed against CD13 and CD227 respectively using the Dyanbead pan-mouse IgG system. Cells and conditioned media were characterized and studied by immunoblot and immunofluorescence. Immunofluorescence of fixed cortical tissue sections was used to assess protein expression in vivo. Summary: In immunoaffinity isolated cells in culture, both proteins are expressed and secreted, where IGFBP7 is primarily secreted by cells of proximal origin, and TIMP2 is primarily secreted by cells of distal origin. Furthermore, TIMP2 is primarily secreted from the apical/luminal surface of polarized cells. In human cortical kidney tissue,

IGFBP7 and TIMP2 were compared to panels of markers for proximal and distal tubule cells, where IGFBP7 staining is seen strongly in the luminal brush border region of a subset of proximal tubule cells, and TIMP2 is mostly seen intracellularly in distal tubule cells. Lastly, while tubular co-localization of both markers can be identified with the markers of injury Kidney Injury Molecule-1 (KIM-1) and Neutrophil Gelatinase-Associated Lipocalin (NGAL), only partial co-localization can be identified, suggesting a separate mechanistic and temporal profile of these markers from injury markers. Conclusion: Together, these data show that IGFBP7 and TIMP2 are expressed and secreted in primary human kidney tubule cells, exhibit differential expression and secretion patterns within cells and across tubule types, and suggest that the expression and secretion of IGFBP7 and TIMP2 only partially correlates with markers of injury. This work sets into place the ability to investigate any potential role of these markers in the etiology of AKI.

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Mitochondrial Pathology And Glycolytic Shift During Proximal Tubule Atrophy After Ischemic AKI

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A subset of proximal tubule cells regenerating after ischemia-reperfusion injury (IRI) fail to redifferentiate after early dedifferentiation, undergo premature growth arrest, and become “atrophic”. These atrophic cells display pathological signaling that triggers production of profibrotic peptides and proliferation of fibroblasts. We now report that tubule atrophy after IRI is associated with striking alterations of metabolism, glycolytic enzyme expression and mitochondrial structure. Proximal tubule regeneration after IRI was accompanied by enhanced hexokinase activity, accumulation of pyruvate and lactate, and increased expression of glycolytic enzymes. Late during regeneration, protein expression of hexokinase 2 (HK2), phosphofructokinase platelet (PFKP), 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3), and pyruvate kinase M2 (PKM2) increased markedly in atrophic tubules, unlike declines seen during normal recovery. Tubules undergoing atrophy showed simplified mitochondria, reduced mitochondrial number, and autophagolysosomes containing damaged mitochondria. Atrophic tubules exhibited depletion of Mpv17L, an inner membrane protein that protects mitochondria from oxidant damage. Also, atrophic tubules showed increased S293 phosphorylation of pyruvate dehydrogenase E1 alpha, consistent with inhibition of this rate limiting enzyme for pyruvate entry into Krebs cycle. These alterations were accompanied by expression of hypoxia markers and prevented by TGF-beta antagonism. Hypoxia can trigger TGF-beta and both hypoxia and TGF-beta may induce glycolysis and mitochondrial oxidant species. Therefore, we examined metabolic regulation by hypoxia and HIF1 alpha in cultured proximal tubule cells. Exposure to 0.5% O2 for 48 hours increased the expression of PFKP, PFKFB3, and PKM2 proteins. HIF1 alpha knockdown abrogated these hypoxic effects. Hypoxia also induced S293 phosphorylation of pyruvate dehydrogenase E1 alpha in a HIF1 alpha independent manner. Taken together, our findings suggest that tubulointerstitial hypoxia gives rise to a “metabolic switch” from oxidative metabolism to glycolytic metabolism in proximal tubules regenerating after IRI. Failure to reverse the metabolic switch appears to be an integral part of the process that prevents tubule redifferentiation and causes tubule atrophy after IRI. How these metabolic alterations relate to other aspects of the failed differentiation program that leads to tubule atrophy needs investigation.

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Renal Angiogenesis and Inflammatory Mediator Patterns Differ in Murine Models of Sepsis and VILI

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PURPOSE:
Acute respiratory distress syndrome (ARDS) that leads to acute kidney injury (AKI) carries a mortality of 58% compared to 28% in ARDS alone. There are roughly 190,000 new cases of ARDS in the United States each year, and AKI is twice as likely in these patients. Many of the potential etiologies of AKI in ARDS may stem from consequences of mechanical ventilation on the kidney, as ARDS patients often require mechanical ventilation as a life saving intervention. Injurious mechanical ventilation in ARDS may lead to the release of inflammatory mediators from the lung via ventilator induced lung injury (VILI), and these mediators may have detrimental effects in the kidney. This process is termed, biotrauma. The purpose of this study was to gain mechanistic insight into the mediators involved in lung to kidney biotrauma by comparing protein expression changes in the kidneys of mice exposed to VILI with, and without sepsis. We hypothesized that biotrauma related to VILI would have a unique renal inflammatory pattern compared to sepsis induced by cecal ligation puncture (CLP) and CLP with VILI.
METHODS:
C57BL/6 wild type mice underwent either CLP (23g, 1 hole, 100%) or sham operation 24 hours prior to mechanical ventilation (or spontaneous breathing control) with 20cc/kg tidal volumes for 4 hours using a Flexivent rodent ventilator. Tissue lysates from harvested whole kidneys were prepared from each group, and protein expression analyzed using a proteome array (mouse XL cytokine array, R&D Systems). The team performing the array analysis was kept blinded to the etiology of each sample.
RESULTS:
Markers of septic tubular injury, such as NGAL and TNF-alpha, were significantly increased in both CLP groups compared to control and VILI without sepsis (Figure 1). VILI with and without CLP led to increased levels of vascular endothelial growth factor (VEGF). Proteins involved in the Angiopoetin/Tie2 axis, such as angiopoetin-2, were not remarkably increased in CLP or VILI samples alone, but there was significantly increased expression in the CLP with VILI group.
CONCLUSION:
Angiopoetin-2 is a known mediator of endothelial leak, and persistently elevated levels have been associated with kidney injury in sepsis and ARDS. VILI may be a mechanism of increased renal angiopoetin-2 in mechanically ventilated patients with sepsis. Further research is necessary to determine the potential role of VILI induced angiopoetin-2 as a cause of AKI in sepsis induced ARDS.

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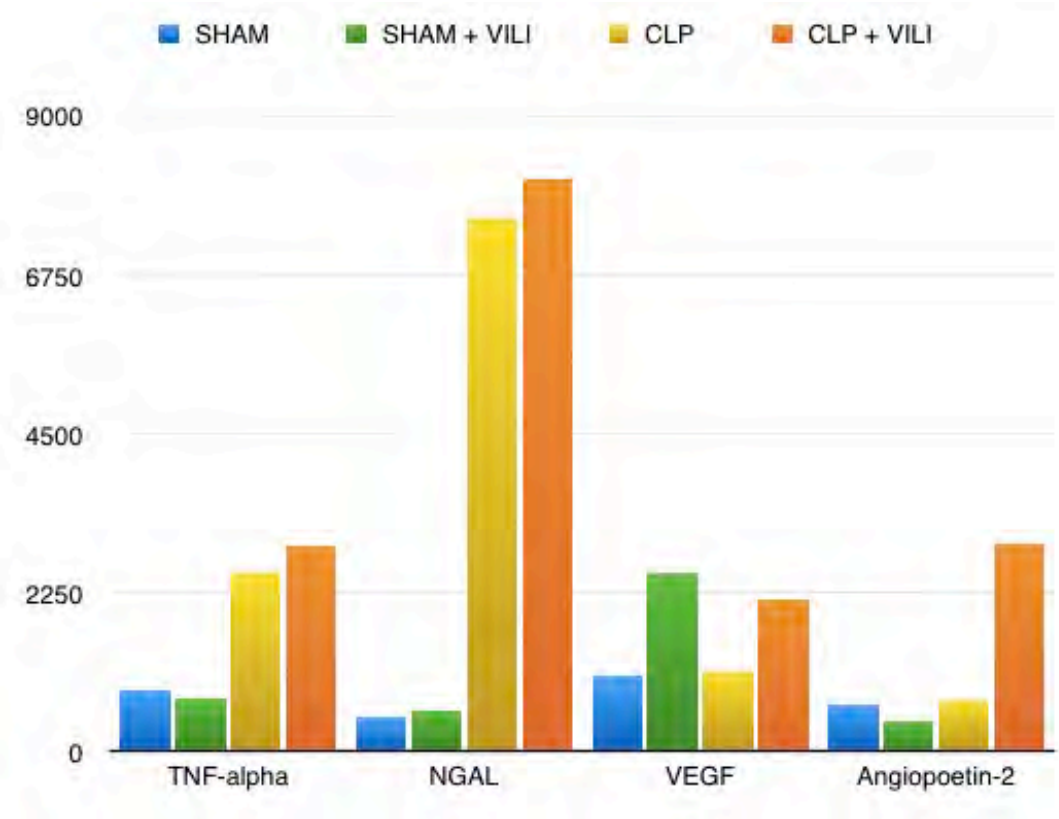

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The Prognostic Value of the Furosemide Stress Test in Predicting Delayed Graft Function Following Kidney Transplantation.

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Background: The Furosemide Stress Tess (FST) is a novel dynamic assessment of tubular function that has been shown in preliminary studies to predict patients who will progress to advanced stage Acute Kidney Injury, resulting in the need for renal replacement therapy in a substantial proportion of patients.

Aim: To investigate if the urinary response to a single intraoperative dose of furosemide predicts delayed graft function (DGF) in patients undergoing kidney transplant (KT).

Methods:
This was a single center retrospective cohort analysis of patients undergoing KT from 01/2010 to 06/2015. As standard of care at Johns Hopkins Hospital, all patients undergoing KT receive a single dose of intraoperative furosemide after the anastomosis of the renal vessels and their urine output (UO) is measured hourly via a Foley catheter. Inclusion criteria for the study were: 1) KT, 2) age ≥ 18 years, 3) patients who received a 100mg of furosemide intraoperatively. Clinical variables were obtained from the institutional transplant database. DGF

was defined as the need for renal replacement therapy (RRT) within 1 week of KT. UO was evaluated at 2 and 6hrs post renal vessel anastomosis. Multiple logistical regression (MLR) analysis was used to predict DGF based on different values for UO at 2 and 6hrs. Area under the receiver operator curves (ROC) that predicted DGF for different values of UO at 2 and 6hrs were calculated. Both the MLR and the ROC were adjusted for age, race and gender.

Results: A total of 803 patients met the inclusion criteria. Preliminary analysis of a random subsample of 200 patients was performed. The mean age was 52.9 ± 13.7 years, 41% were male, 51% were African American, 38% were white and 11% were other race. The UO associated with the greatest odds ratio (OR) and AUC at 2 and 6hrs were, 150mls and 600mls, respectively. The adjusted OR for DGF in patients who had a UO of ≥150mls compared to patients who had a UO of < 150mls at 2 hours was 9.57 (95% CI:3.94-23.24, p<0.001). The adjusted OR for DGF in patients who had a UO of ≥600mls compared to patients who had a UO of <600mls at 6 hours was 12.13 (95%CI:4.80-30.64, p<0.001). The AUC for DGF based on a UO of <150mls at 2 hours was 0.78 (95%CI: 0.70-0.87). The AUC for DGF based on a UO of <600mls at 6 hours was 0.80 (95%CI: 0.72-0.88).

Conclusion: The FST is a predictor of DGF post KT and has the potential to identify patients requiring RRT early after KT.

RRT TECHNIQUE CHARACTERISTICS

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Cost Analysis Of Standardizing CRRT Processes

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Purpose of the study:
Acute Kidney Injury in the ICU has been increasing in incidence over the last decade. It has been estimated that approximately 5% of patients admitted to an ICU require renal replacement. Because of hemodynamic instability and need for volume removal, continuous therapies (CRRT) have become the procedure of choice. Because of decreasing reimbursement it is essential that healthcare systems maximize cost efficiency. We therefore analyzed the cost savings of changing from a single dialysate solution that was tailored to the patients' needs to using multiple different solutions.

Methods:
Baylor University Medical Center operates 118 ICU beds and performs approximately 220 CRRT treatments a month. Because of storage issues we purchased only 0 meq K+ dialysate (NxStage- RFP-402) and added electrolytes as needed. In September 2015 we began purchasing premixed 2 and 4 meq K+ solutions and except in exceptional cases supplemented Mg, PO4 and HCO3 peripherally. We analyzed labor and material costs during a one month period and then estimated the costs for 12 months. Total costs were calculated and included wasted bags, compounding costs and labor costs divided between pharmacist and pharmacy technician. .

Results:
Annualized over a 1 year period approximately 48,500 five-liter bags were dispensed. Preparation time for six 5-liter bags declined from 25.5 minutes in the old system to 12 minutes in the new. 67 bags were discarded because they were compounded but never used. In addition to the cost of wastage, 12 minutes were required to process each wasted bag. Over a 12 month period it estimated that we will save $469,879 in labor and material costs.

Conclusion:
By changing our practice we will be able to produce a significant cost savings without jeopardizing quality. In fact by eliminating compounding we have removed a possible source of error. Because of this we have changed our purchasing practice, revised our CRRT order set, educated our prescribers on decreasing unnecessary additives and enhanced patient safety.

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The comparison of double lumen temporary hemodialysis catheter and tunneled cuffed hemodialysis catheter on vascular access of continuous renal replacement therapy

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Objective:
A vascular access is needed for performing continuous renal replacement therapy (CRRT). The type of vascular access in the most case is temporary and permanent catheter in intensive care unit. But double lumen temporary hemodialysis catheter is occurred more catheter malfunction and filter clotting more than permanent catheter. Therefore, we retrospectively evaluated which vascular access may affect filter life during CRRT.
Method:
We evaluated 44 patients with acute kidney injury requiring CRRT from March 2014 through October 2015. 22 patients used double lumen temporary hemodialysis catheter and 22 patients used tunneled cuffed hemodialysis catheter. All catheters were inserted in the internal jugular position. We obtained age, gender, duration of CRRT, number of use of CRRT filter, dose of anticoagulation.
Result:
The mean durations of CRRT were 3.77 ± 2.67 days, mean ages were 68.68 ± 11.51 years, number of use of CRRT filter was 1.02 ± 0.37 / day, nafamostat mesilate which is anticoagulant was 12.13 ± 5.44 mg / hour in double lumen temporary hemodialysis catheter groups. The mean durations of CRRT were 5.31 ± 6.09 days, mean ages were 68.13 ± 6.76 years, number of use of CRRT filter was 1.18 ± 0.37 / day, nafamostat mesilate was 20.25 ± 14.85 mg / hour in tunneled cuffed hemodialysis catheter.
Conclusion:
Tunnel cuffed hemodialysis catheter is less occurred CRRT filters clotting and less needed anticoagulation.

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Using a Bridging Technique for Continuous Renal Replacement Therapy Circuit Change Reduces Time off Therapy and Exposure to Blood Products

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Introduction: Continuous Renal Replacement Therapy (CRRT) is the preferred method of dialysis for critically ill pediatric patients with acute renal failure. Manufacturers recommend changing the CRRT circuit every 72 hours to ensure the integrity of the tubing and support adequate flow rates. This necessitates a circuit change for patients requiring therapy longer than three days. However, some circuits show signs of failure prior to the end of 72 hours. Circuit changes traditionally resulted in the patient being without therapy for over an hour. In addition, the circuit set up for neonates and infants requires a blood prime due to the large extra-corporeal circuit volume.

Methods: Our institution implemented a new circuit changing procedure (bridging) in 2013 to rapidly exchange CRRT circuits and reduce blood exposure as described by Yorign et al. Bridging is the preferred method for patients who are hemodynamically unstable, require a blood prime, or are showing signs of clotting. Bridging includes setting up a separate circuit with new filter and tubing. All routine aspects to set up the pump are performed. During this time, the patient is still on their "old" circuit, receiving CRRT therapy as ordered. Once the "new" circuit is ready, the old circuit is stopped and the patient's dialysis catheter is flushed and packed. The old circuit is then connected to the new circuit and rinsed so that the blood from the old circuit is flushed into the new circuit. Then the patient is re-accessed and connected to the new circuit and therapy is restarted. This method requires the use of two CRRT pumps and two staff members trained on the procedure.

Results: Since 2013, 220 circuits have been changed. Of those, 59 were done so by bridging. The most common reason for bridging was to avoid a blood prime, of the 220 circuits 99 of them would have required a blood prime, and we bridged 43 of those. The time required for a circuit change by bridging (6.3 ± 3 min) was significantly ($p<0.05$) less than for traditional circuit changes (58 ± 14 min). The process of bridging was also well tolerated except on only one occasion. In contrast, significant hemodynamic events (hypotension, bradycardia) were seen in 19% of patients when the circuit was changed by conventional method.

Conclusion: Bridging exchange of the CRRT circuit is a safe and efficient method that significantly reduces exposure to blood products, therapy downtime, and hemodynamic instability.

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Underutilization of Citrate Anticoagulation for Continuous Renal Replacement Therapy: A Survey Study

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Purpose: Citrate use as an anticoagulant for the continuous renal replacement therapy (CRRT) circuit has been shown to improve safety and efficacy of CRRT and lead to overall decreased cost compared to heparin. While widely acknowledged to be an excellent extracorporeal regional anticoagulant, the routine use of citrate for CRRT has been limited. The purpose of this study is to investigate practice patterns and barriers to utilization of citrate for anticoagulation for CRRT among key stakeholders in an intensive care unit (ICU) in a single center.

Methods: Three survey questionnaires were created on REDCap and sent to a sample cohort of physicians and advanced practitioners, critical care nurses, and ICU pharmacists via email from September-November 2015. Three follow-up emails were sent after the initial invitation. For statistical analysis, Microsoft Excel 2010 (Microsoft Corporation, Redmond, VA) was used.

Results: Nearly half (44.6%) of all those invited to participate responded: 59.2 % (16/27) of physicians and advance practice providers, 40.9% (63/154) of nurses, and 100% (3/3) of pharmacists. There was significant difference regarding preference for heparin/no anticoagulation approaches compared to use of citrate. Forty-four percent of nurses preferred heparin versus only 13% who indicated preference for citrate ($p<0.05$). Physicians and advanced practice providers [31.2% for citrate compared to 68.8% for heparin/no anticoagulation ($p<0.05$)] and pharmacists [0% for citrate versus 100% for heparin or no anticoagulation ($p<0.001$)] also revealed a similar bias. The most commonly cited reasons for the preference of heparin included

ease of use and familiarity with heparin (25 respondents) and difficulty monitoring and managing abnormal laboratory values with citrate (8 respondents).

Conclusions: Our surveys indicate that a significant number of physician and advanced practice providers, nurses, and pharmacists in the ICU are uncomfortable using citrate for regional anticoagulation during CRRT. Given the known risks associated with systemic heparin, increased association with dialysis filter clots, and low risks associated with citrate use, further educational efforts and quality improvement initiatives are needed to address citrate under-utilization for CRRT in ICU settings.

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CRRT Without Anticoagulation. Feasibility and Prescription Factors.

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[1]Instituto Nacional de Cardiologia, [2]Centro de Diagnostico Angeles

INTRODUCTION: Filter coagulation is the most frequent complication during CRRT, leading to a lower delivered dose, blood loss and increased costs. On the other hand, avoiding heparin in order to reduce bleeding complications is justified, but when no citrate is available then CRRT without anticoagulation might be considered in our short experience.
METHODS: An observational cohort study analyzing filter life-span was carried out during CRRT in patients admitted into mixed ICUs in private hospitals in Mexico City from March to October 2015. Patient treatments were included if they fulfilled the following criteria: acute kidney injury, severe sepsis or septic shock, no systemic anticoagulation, no use of citrate anticoagulation, no new surface treated membranes. Usually, there is a trend towards avoiding the use of heparin; in case of losing a filter in less than 24 hours, and no citrate is available, then heparin is started in the next filter. There was no routine use of flushes or recirculation strategies to avoid clotting. We describe filter life-span up to clotting or clogging in filters without anticoagulation, compared to heparin, and we analyzed some prescription specifications that allowed running this treatment without anticoagulation.
RESULTS: A total of 85 filters from 31 patients were analyzed, 28 filters (32.9%) with heparin and 57 (67.1%) without anticoagulation. In general, most common prescription was pre-dilutional CVVHDF, blood flow was 180 (150-200), pre-dilutional replacement flow as 67% (61-72) of total dose, pos-dilutional replacement flow as 9% (0-9), and dialysate flow as 23% (12-28) of total dose. Median filter survival with heparin was 72 hours vs 38 hours without anticoagulation (Log rank 1.65, p=0.099). In filters treated without anticoagulation, a filtration fraction <0.175 had a significant benefit on filter life-span (Log rank 2.23, p=0.025). Due to a low number of pure CVVH treatments, only a non-significant trend towards increase filter life-span with use of higher dialysate flow was observed.
CONCLUSIONS: CRRT without anticoagulation is feasible under certain prescription factors, if heparin should be avoided and citrate is not available.

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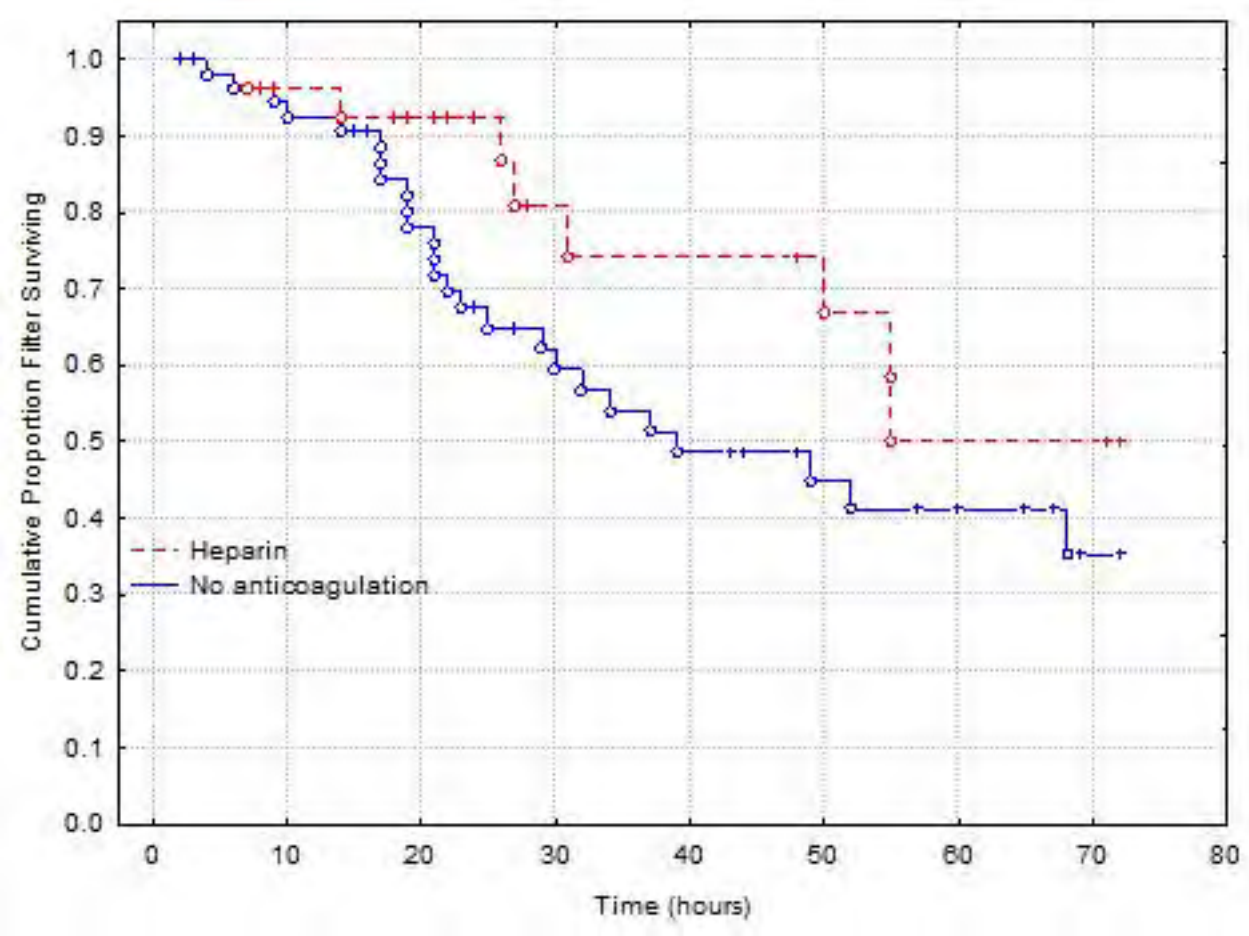
Cumulative Proportion Filter Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Heparin
No anticoagulation
0
10
20
30
40
50
60
70
80
Time (hours)

RRT APPLICATIONS AND TARGETED INTERVENTION

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Influence of Daily Fluid Balance prior to Continuous Renal Replacement Therapy on Outcomes in Critically Ill Patients

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[1]*Chung-Ang University Hospital, Seoul, Korea*

Background: Positive fluid balance is a risk factor for mortality in critically ill patients, especially those requiring renal replacement therapy. However, it remains unclear whether daily fluid balance is associated with various organ impairments, which can influence worse outcomes. The present study investigated the impacts of daily fluid balance prior to continuous renal replacement therapy (CRRT) on organ dysfunction, as well as mortality in critically ill patients. Methods: We recruited 100 patients who experienced CRRT, and identified the daily fluid balance between ICU admission and CRRT initiation. The time to CRRT initiation and 28-day mortality were evaluated. Furthermore, organ failure based on the sequential organ failure assessment (SOFA) score was also assessed according to daily fluid balance. Results: Included patients were followed for a median of 10 [3, 26] days, and CRRT was initiated within 2 [0, 4] days. The time to the start of CRRT was shortened in proportion to daily fluid balance ($P = 0.001$). This result was persistent after the adjustment for age, gender, and the renal SOFA score at ICU admission (HR 1.14, 95% CI 1.04 to 1.25, $P = 0.007$). The prevalence of respiratory, cardiovascular, and nervous failure was increased in patients with excessive positive fluid balance ($P = 0.075$, 0.004 and 0.004, respectively). Moreover, positive daily fluid balance was a risk factor for respiratory, cardiovascular, nervous, and coagulation failure, independent of age, gender, and each organ SOFA score at ICU admission (HR 1.36, 1.26, 1.24 and 1.38, all $P < 0.05$). We found that positive fluid balance increased the rate of 28-day mortality, independent of age, gender, and the baseline SOFA score (HR 1.14, 95% CI 1.01 to 1.25, $P = 0.007$). Conclusion: This study found that positive daily fluid balance prior to CRRT may not only accelerate the requirement for CRRT but could also increase the risk of multiple organ failure as well as mortality in critically ill patients. Therefore, judicious fluid therapy should be performed in critically ill patients, especially those requiring CRRT. Further studies to elucidate the protective effects of restrictive fluid therapy on multiple organ systems and mortality are needed.

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Use of Segmental Bioimpedance Analysis in Critically Ill Patients requiring Continuous Renal Replacement Therapy

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[1]*Chung-Ang University Hospital, Seoul, Korea*

Background: Fluid overload prior to continuous renal replacement therapy (CRRT) is an important prognostic factor. Accordingly, precise evaluation for fluid status is necessary to treat critically ill patients. In this study, we investigated whether fluid assessment using bioimpedance analysis (BIA) can predict outcomes in critically ill patients requiring CRRT.

Methods: A prospective observational study was performed between Mar 2014 and Dec 2014. Patients who admitted in the intensive care unit and required CRRT were recruited. Segmental BIA was conducted before CRRT in included patients to obtain the total and segmental ratio of extracellular water to total body water (ECW/TBW).

Results: A total of 35 patients treated with CRRT were included in the study. There were 23 (65.7%) men and 12 (34.3%) women, and the median age was 71 [47, 80] years. Of included patients, 20 (57.1%) were survived after treatment. Among the total and segmental ECW/TBW, that of right arm was correlated with levels of hematocrit, total protein, albumin and C-reactive protein, and total SOFA score (P = 0.083, 0.086, 0.030, 0.018 and 0.055), however, was not associated with levels of erythrocyte sedimentation rate, procalcitonin, 25-vitamin D and lactate. Survivors showed low levels of pH and total protein, and high levels of lactate and right arm ECW/TBW, compared with non-survivors (P = 0.021, 0.039, 0.002 and 0.033). Receiver operating characteristics (ROC) curve was constructed for ECW/TBW for predicting mortality. The ECW/TBW of right arm had an area under the curve (AUC) of 0.71 (95% CI 0.54 to 0.89, P = 0.033), on the other hand, the total and the other segmental ECW/TBW did not have significant AUCs for mortality.

Conclusion: Fluid status can be assessed using segmental BIA in critically ill patients requiring CRRT, moreover, it may predict poor outcomes, especially with the result from right arm. To confirm the usefulness of segmental BIA for predicting outcomes in critically ill patients, further large studies are needed.

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Unusual and no renal indications for continuos renal replacement therapy (CRRT)

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Latest publications have demonstrated that The CRRT is successful in orgánic failure from different etiologies to the renal one,such as venous congestive heart failure,poisonings,hepatic,pulmonary failure and sepsis between others.The aim of this article is to show our experience,with a group of 13 patients that were admitted to our Unit with diagnóstic and indications unusuals for having CRRT .table1

Method and Materials

We received 13 patients (6 m and 7 w),2 of them with hepatorenal failure,2 with Congestive HeartFailure,5 with sepsis and the last 6 with other patologíes.All patients were submitted to the modality (CVVDHF)with liquid remplacement Prisma Sate BGK 4/2.5 in predilution with replacement of 30 ml/kg,giving and average result of 30 liters.The therapy was carried out with a Prisma Flex Plus Gambro machine,with ST150 filter with membrane AN 69 HF.Heparine was use as Necessary.All the patients complete at least a mínimum period of 24 hours and 30 percent 48 hours,according todo the severity of cases seizure by SOFA (Sequential Organ Failure Assesment).

Results

From 13 patients,10 of them(76.9%) survive and were discharged from hospital,3 patients(23.1%)(2 w and 1 M) were dead. In groups 1,3 and 4 were dead 1 in each group.Those patients that were dead had a SOFA clasification moré than 3.Independently of the cause of dead,all patients achieve and important level decrease in azoemia,although in this group of patients the main objective was to lower sustances dificultt to detect (Piggy) In patients with cardiac failure we achieved ultra filtrations above 15 liters without hemodynamic instability or imbalance.Despite is a small group of patients,All of them carry pathologies were Clinics and no creatinin leves are the final predictors.

Conclusions

1. The continuous replacement therapy is efectivo in other pathologies different from The renal one. Specially in those patients with fluid overload. Independently of creatinin levels
2. La CVVDHF is the most common method used,because is easilly reproducible in other hospitals to increase our knowledge in this kínd of patients
3. The survival as group was bigger than the reports in literature for patients with similar SOFA
4. The ICU and hospital stay was lesser than the average with similar score
5. Mortality is associated to delayed treatment
6. We concluded that this kínd of therapy should be investigated deeply and compare control groups in hospitals with other modality of replacement therapy

Table on following page

NAME	SEX	AGE	DX	# SESIONS	LITERS REMOVED	DATE	MODALITY	RESPONDERS	UREA IN/END	CREATIN/END	HB	OTHER
JCF	M	84	ANASARCA	1	10	16/02/15	CVVHDF	YES	75/52	1.8/1.6	15.8/16	NO
LLP	F	64	PANCREATITIS/HEPATORENAL FAILURE	1	0	31/05/15	CVVHDF	YES	201/114	5.3/2.7	16/16	BT 39/33
AAA	M	78	SEPSIS/PACEMAKER	1	6	08/05/15	CVVHDF	NO	105/79	3.8/3.2	14/14	NO
SDM	M	76	EVC/ANASARCA	1	8	11/05/15	CVVHDF	YES	97.8/90	4.4/2.9	8.1/8.3	NO
JLA	M	80	SEPSIS	3	0	09/06/15	CVVHDF	YES	296/137	2.35/1	6.5/8.7	NO
ETA	M	44	HEPATORENAL FAILURE	1	0	19/06/15	CVVHDF	YES	160/80	2/1.6	10.1/10	BT 36/32
ALA	F	54	POISONING/ANASARCA	2	26	03/07/15	CVVHDF	NO	213/187	3.6/3	10/10	21 ID
GJB	F	34	SEPSIS	1	0	30/06/15	CVVHDF	YES	33/31	.95/.53	12/10.2	NO
RER	F	74	SEPTIC SHOCK/ANASARCA	1	8	23/06/15	CVVHDF	NO	CVVHDF			
TABLE 1	18 ID									ID = INTRAHOSPITALARY DAYS	10/10	.75/.6
CVVHDF	YES	57/40	1/.8	12/12	NO	GHL	F	34	SEPSIS/LES	1	0	18/09/14
116/96	YES	NO	96	ANASARCA/CHF	1	20	08/08/14	CVVHDF	YES	60/50	1.2/1.2	13/12
NO	BVC	M	82	GUILLEAN BARRE	1	F	DCC	5 ID	12/17/14	103/70	2.9/1.9	13/13
12 ID	GCX	31	F	LES/ANASARCA	1	4.3	15/04/15	CVVHDF	103/70	1.7/.5	9/9	0

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Extracorporeal Ultrafiltration Therapy for Acute Decompensated Heart Failure

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Background: There has been a renewed interest in the use of ultrafiltration (UF) for management of patients with acute decompensated heart failure (ADHF). While a number of studies reported on the efficacy of this therapy and lack of any significant adverse impact, the more recent trials have challenged its safety. The aim of this study is to provide a reappraisal of the current evidence on the use of UF in ADHF.
Methods: Articles cited in PubMed database from 2000 to 2015 using key words "ultrafiltration" and "heart failure" were searched. Those randomized and non-randomized trials using recent portable devices dedicated for UF were selected. Case reports, and case series were excluded. Relevant data such as renal function, cardiac status, and weight change were extracted and compared.
Results: A total 940 patients from 15 trials (7 randomized and 8 non-randomized) that used dedicated UF devices were included. Eleven studies reported either no change or non-significant decrease in serum creatinine, while 4 found worsening renal function after UF therapy; these studies had included patients with more severe renal dysfunction at baseline. Concerning weight, a reduction of 2 to 9 Kg was reported that was similar to conventional therapies in 9 studies but was significantly lower with UF in 6 trials. Length of stay was evaluated in 5 studies, 2 of which showed a significant reduction. Three studies showed fewer re-hospitalizations in the UF group at 30 days, 90 days, and 1 year follow ups. None of the studies evaluated long-term outcomes of patients undergoing UF therapy.
Conclusion: Based on the currently available data, UF is efficient for management of volume overload in ADHF. However, these studies do not support any beneficial impact for this therapy on renal function, and suggest that it might be associated with suboptimal renal outcomes if used for patients with more severe renal dysfunction at baseline. Currently there is no data on the effect of UF on long-term outcomes of patients with ADHF. Whether this would translate into a lack of effect for UF on these outcomes needs to be elucidated by future studies.

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The Assessment of Volume Status by Bioelectrical Impedance Analysis and Lung Ultrasound in Septic AKI Patients Undergoing CRRT

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Purpose: Septic acute kidney injury (AKI) is one of the most common causes in critically ill patients requiring continuous renal replacement therapy (CRRT). The fluid status of the patient is known as significant risk factor in those patients. Thus, it is necessary to find an objective assessment of volume status. The aim of present study is to elucidate the impact of fluid status assessment by bioelectrical impedance analysis (BIA) and lung ultrasound (US) in septic AKI patients with CRRT.
Methods: A single center prospective observational study was conducted between April 2014 and February 2015. We included 39 septic AKI patients undergoing CRRT in ICU. BIA and lung US were performed at the

time of CRRT initiation. We classified patients into two groups followed by survivor and non-survivor. We measured over-hydration (OH) values in BIA and number of B-lines in lung US. Primary endpoint was 28-day mortality. Logistic regression analysis was used to evaluate the risk factors affecting 28-day mortality.
Results: The mean age was 64.6 ± 14.1 years and 24 (61.5%) was male. The median follow up was 29 days. During the study period, 19 deaths (48.7%) occurred. Survivor group showed significantly lower weight gain, which was defined as a body weight difference from that of last visit, at CRRT initiation (2.0 ± 3.5 vs. 5.8 ± 5.5, P = 0.017) and APACHE2 score (21.7 ± 5.3 vs. 27.1 ± 1.5, P = 0.006) compared with non-survivor group. However, there was no significant difference in results of BIA and lung US between both groups. OH per body mass index (BMI) measured by BIA had significant correlation with mean arterial pressure (r = -0.340, P = 0.034) and NT-pro BNP (r= -0.450, P = 0.024), and B-line measured by lung US had significant correlation with APACHE2 score (r = 0.330, P = 0.040). Logistic regression analysis showed a trend that increasing OH per BMI (odds ratio (OR) 6.18, 95% confidence interval (CI) 0.15-248.7, P = 0.334) and number of B-lines (OR 1.14, 95% CI 0.80-1.63, P = 0.458) were associated with increasing risk of 28-day mortality, but there was lack of statistical power.
Conclusion: In this study, we found that OH status assessed by BIA and lung US correlated with traditional risk factors on poor clinical outcomes in septic AKI patients with CRRT. In addition, this study showed the association between OH per BMI measured by BIA and number of B-lines measured by lung US and 28-day mortality rate in critically ill patients undergoing CRRT.

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Development of Ciprofloxacin Dosing Recommendations for Critically Ill Patients Receiving SHIFT Renal Replacement Therapy

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Background: Ciprofloxacin is an antibiotic commonly used in the intensive care unit where acute kidney injury (AKI) is prevalent. SHIFT is a daily 8-10 hour prolonged intermittent renal replacement therapy that is growing in popularity. However, a lack of antibiotic dosing information in critically ill patients receiving SHIFT limits its use. The purpose of this study was to use Monte Carlo Simulations (MCS) to develop ciprofloxacin dosing recommendations for SHIFT.

Methods: Using previously-published pharmacokinetic & demographic data from critically ill patients, a population PK model was developed for SHIFT RRT. A series of 5000-subject MCS were performed for four shift regimens with varying duration (8 & 10 hr), effluent rate (4 & 5 L/hr), modality (HF/HD), and time of SHIFT initiation relative to ciprofloxacin administration. Ciprofloxacin regimens were evaluated on the probability of attaining a total drug concentration resulting in a ratio of area under the curve to minimum inhibitory concentration (MIC) ≥ 125 during the first 72 hours of therapy. Optimal regimens yielded a probability of target attainment (PTA) ≥90% for sensitive Pseudomonas aeruginosa (MIC=1mg/L) using the smallest total daily dose.

Results: Intravenous ciprofloxacin administered as a 1200mg loading dose and a maintenance dose of 800 mg every 12 hours was the smallest daily dose to yield a PTA ≥90% in all SHIFT settings for MIC values ≤1. (See Figure). No FDA-approved ciprofloxacin dosing recommendations for any population reached the PTA ≥90%.

Conclusions: In critically ill patients receiving daily 8 or 10 hour SHIFT, the lowest possible ciprofloxacin dose to meet 90% PTA was 1200mg LD and 800 mg every 12 hours, but this high dose is likely to be cardio- or neurotoxic. The use of ciprofloxacin in critically ill patients receiving SHIFT cannot be recommended as monotherapy for Gram negative infections.

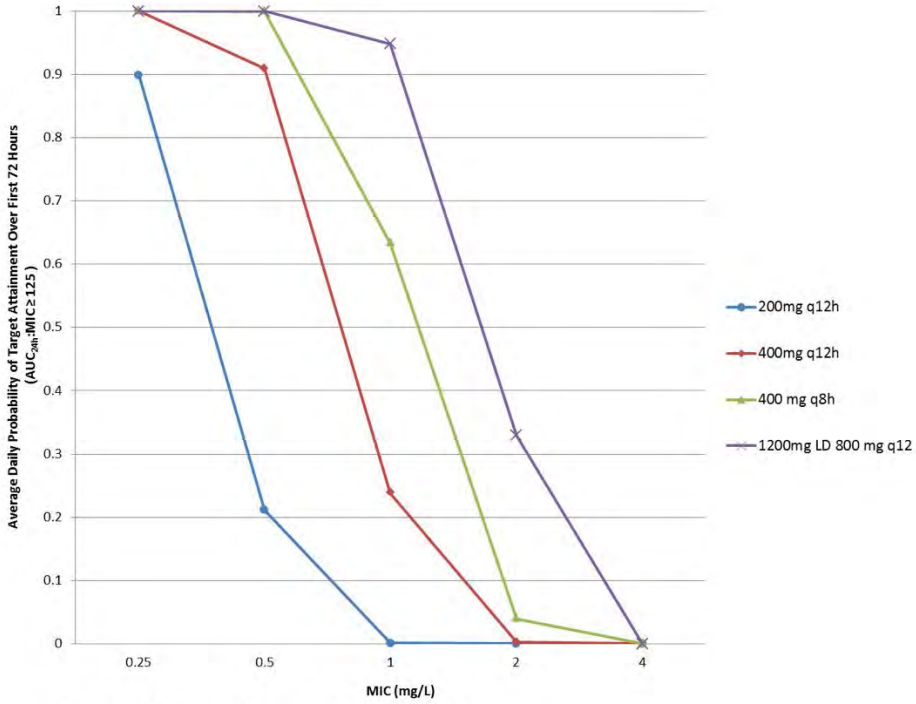

Figure PTA for ciprofloxacin in 8 -hour SHIFT RRT

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Monte Carlo Simulations (MCS) to Determine Optimal Levofloxacin Dosing for Gram Negative Infections in Patients Receiving SHIFT RRT

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[1]College of Pharmacy, University of Michigan, Ann Arbor, MI, USA: Faculty of Pharmacy, Siam University, Bangkok, Thailand, [2]College of Pharmacy, University of Michigan, Ann Arbor, MI, USA

Background: SHIFT is a daily 8-10 hour renal replacement therapy (RRT) for treating acute kidney injury in critically ill patients. Antibiotic pharmacokinetic data in SHIFT are lacking. At higher quinolone doses, cardio- and neurotoxicity can occur; doses are recommended to be reduced in renal disease. This study evaluated the likelihood of attaining levofloxacin exposures that correlate with antibiotic efficacy known as probability of target attainment (PTA).
Methods: Published levofloxacin pharmacokinetic data in critically ill patients were used to develop models for virtual patients receiving daily SHIFT with intermittent hemofiltration (HF) or hemodialysis (HD). Eight models were developed to account for the SHIFT variations including duration (8 and 10 hr), effluent rate (4 and 5 L/hr), modality (HF/HD), and time of SHIFT relative to drug dose. MCS generated drug concentration

profiles for each regimen in a different group of 5,000 virtual patients. The pharmacodynamic (PD) target was > 125 for area under the concentration-time curve to the minimum inhibitory concentration (MIC) of 2 mg/L (MIC for sensitive Pseudomonas aeruginosa) for the initial 72 hours of therapy. The optimal regimen required > 90% of PTA for this drug with the lowest daily doses to decrease toxicity risk.
Results: The attainment of > 90% of PTA required levofloxacin doses of >3,000 mg/day (Figure) in all 8 SHIFT models. Desired PTA could not be achieved by using the FDA-approved doses. A regimen with an extremely high loading dose and post-SHIFT dosing were the only regimens found to yield a PTA of 90%.
Conclusion: A levofloxacin dose of 2,000 mg loading dose with 1,000 mg q 24 hours post-SHIFT achieved the PTA for all SHIFT settings, but this regimen is likely to be toxic. No conventional levofloxacin doses could achieve 90% PTA. Using levofloxacin in patients with SHIFT RRT cannot be recommended as monotherapy for Gram negative infections.

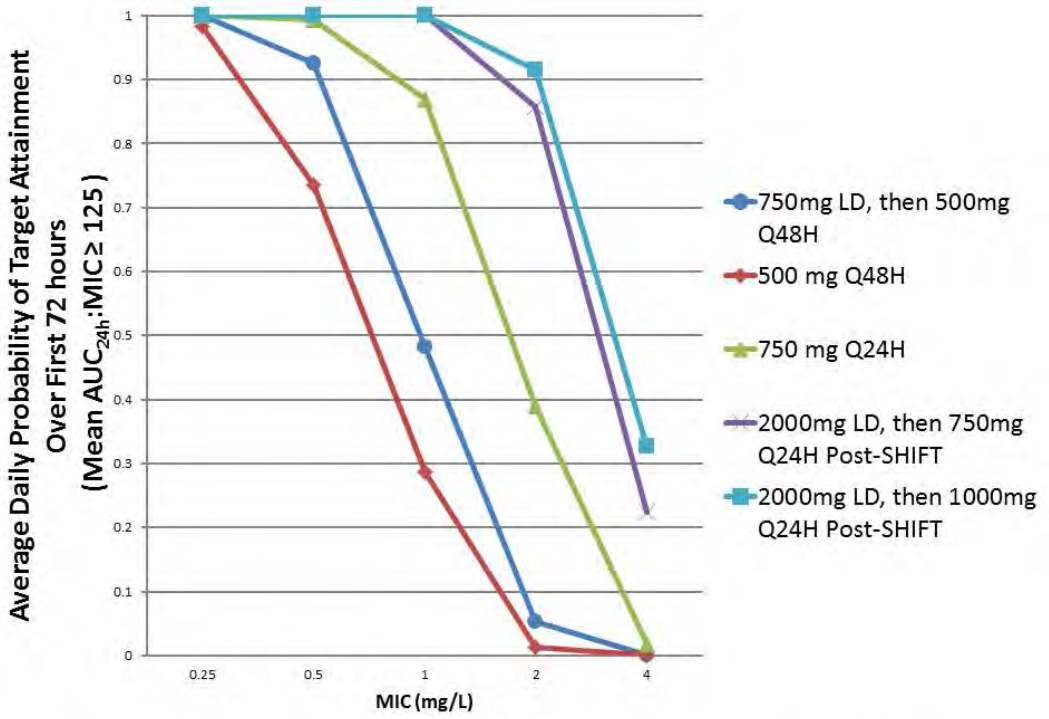

Figure PTA for levofloxacin in 8-hour SHIFT therapy with hemodialysis modality

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Monte Carlo Simulations (MCS) to Determine Optimal Levofloxacin Regimens for Streptococcus pneumoniae Infections in Patients Receiving SHIFT Renal Replacement Therapy.

Weerachai Chaijamorn[1], Susan J Lewis[2], Alex R Shaw[2], Katherine N Gharibian[2], Bruce A Mueller[2]

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Background: SHIFT is a daily 8-10 hour renal replacement therapy (RRT) for treating acute kidney injury in critically ill patients. A levofloxacin dose of 500 mg q 48 hours has been recommended for patients receiving continuous RRT, however levofloxacin pharmacokinetic (PK) data in SHIFT does not exist. Precise levofloxacin dosing is important because cardio- and neurotoxicity of higher doses have been reported and dosage reduction in renal disease patients is recommended. The purpose of this study was to use MCS to determine appropriate levofloxacin doses for S. pneumoniae infections in SHIFT.
Method: Pharmacokinetic models were developed using published demographic/PK data in critically ill patients with known variability and limits. Four daily-SHIFT settings (hemofiltration or hemodialysis with effluent rates of 5L/hour x 8 hours or 4L/hour x 10 hours) occurring at 2 different times relative to levofloxacin dose were modeled. A set of 5,000 virtual patients was created and tested for each dosing regimen. The pharmacodynamic (PD) target was > 50 for area under the concentration-time curve to the minimum inhibitory concentration (MIC) of 2 mg/L (MIC for sensitive S. pneumoniae) for the initial 72 hours of therapy. The optimal regimen required > 90% of PTA for this drug with the lowest daily doses to decrease toxicity risk.
Results: Levofloxacin administered as a loading dose of 750 mg with 500 mg q 24 hours post-SHIFT yielded a PTA > 90% in all 8 SHIFT settings.
Conclusion: Levofloxacin 750 mg loading dose with 500 mg every 24 hours post-SHIFT is recommended in acute kidney injury patients receiving SHIFT RRT who have S. pneumoniae infections. Levofloxacin doses for Gram negative infections that have higher PD targets will require much higher doses. PK validation studies for these findings are required.

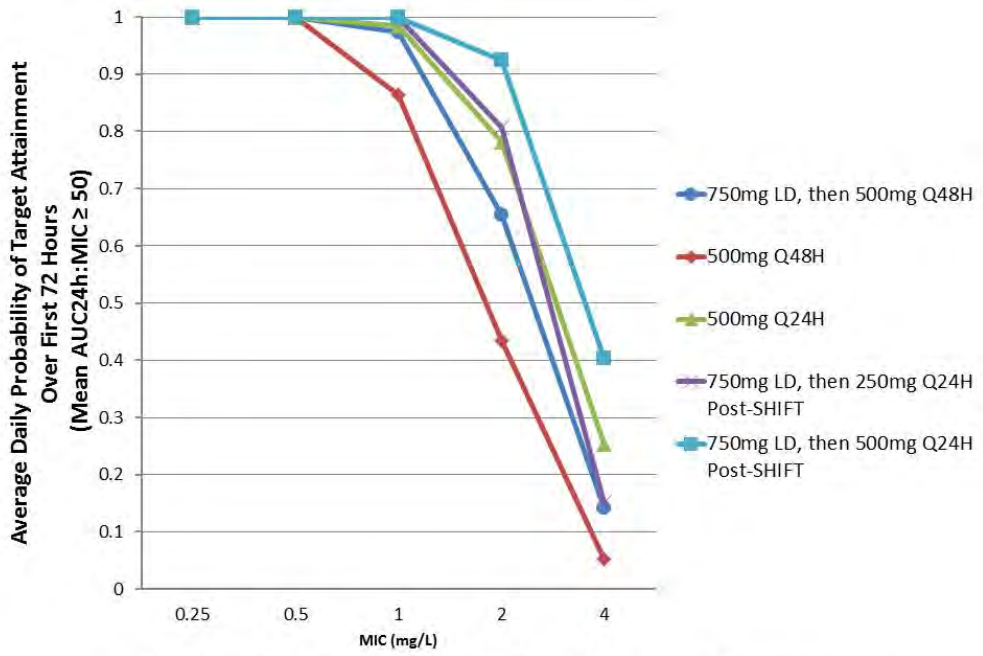

Figure PTA for levofloxacin in 10-hour SHIFT @ 4L/hr dialysate rate

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Slow Continuous Ultrafiltration Efficiently Improves Congestion in Acute Heart Failure without Adverse Impact on Renal Function: a Meta-analysis

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[1]*University of Florida*

Background: Diuretic-based conventional regimens of acute decompensated heart failure (ADHF) are commonly associated with suboptimal results. There has been a renewed interest in the use of slow continuous ultrafiltration (SCUF) for management of fluid overload in these patients. While a number of studies reported on the efficacy of this therapy in improvement of congestion, recently there has been concern about its safety. The aim of this meta-analysis is to provide a reappraisal of the current evidence on the impact of SCUF on fluid removal, weight loss, and renal function in the setting of ADHF.

Methods: Articles cited in PubMed, EMBASE, and Cochrane database from 1980 to 2015 using key words: "ultrafiltration" and "heart failure" were searched and those randomized controlled trials (RCTs) that addressed the role of SCUF in ADHF as compared with conventional therapy were identified. A total of 289 studies were selected after extensive database search. A meta-analysis was performed. Mantel-Haenszel random-effects model was used to calculate mean differences (MDs) with 95% confidence intervals (CIs). Comprehensive meta-analysis software version 3 was used for the analysis.

Results: After excluding duplicate, non-randomized, and studies not relevant to the primary question, a total of 7 RCT with 768 participants were found eligible for analysis. Fluid removal and weight loss were considered as efficacy endpoint and change in renal function as the safety endpoint. Fluid removal was significantly higher with SCUF compared to standard therapy, MD of 1.81 L (95% CI 1.01-2.62, $p<0.01$). It also led to higher net weight loss, MD of 1.38 Kg (95% CI 0.53-2.23,$p<0.01$). However, the MD for change in in serum creatinine was 0.06 mg/dl and was not statistically significant (95% CI; -0.11-0.22, $p=0.48$).

Conclusion: Currently available data suggest that compared to diuretic-based therapy, SCUF improves congestion in ADHF more efficiently as evidenced by greater fluid removal and weight loss without portending a notable adverse impact on their renal function.

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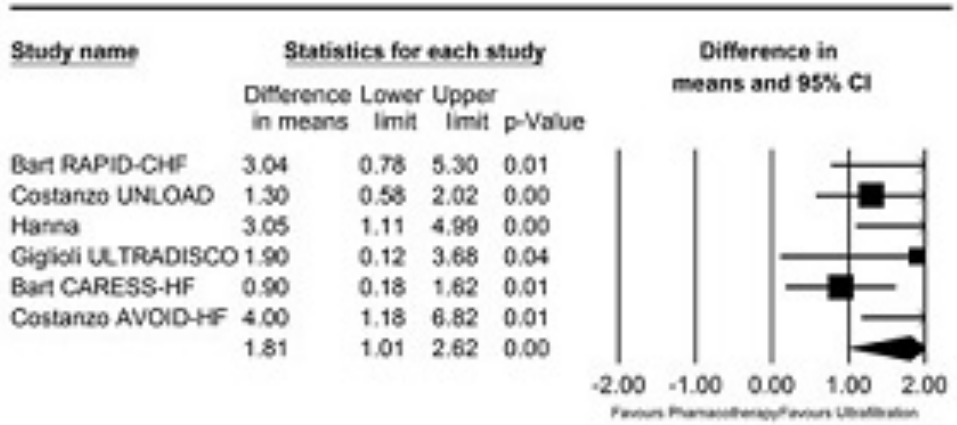
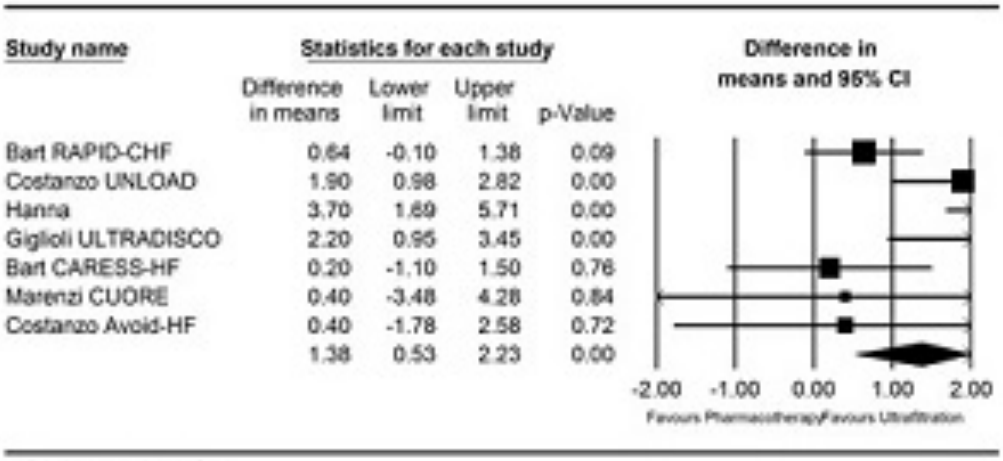
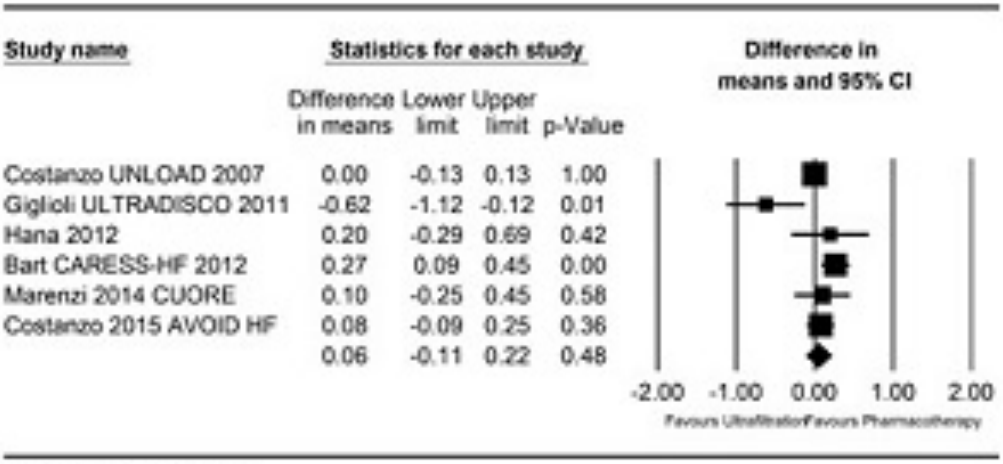


Fluid removal Meta Analysis



Weight Loss Meta Analysis



Creatinine change Meta Analysis

NEW TECHNOLOGY

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Outside-In Hemofiltration For Prolonged Operation Without Clogging - Hydrodynamics, Filter Designs and Challenges

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Hemofiltration (HF) is used extensively for continuous renal replacement therapy (CRRT), but long-term treatment is limited by thrombosis leading to fiber clogging. Maximum filter life in CRRT is typically less than 20 hours. For the first time in the field, we have achieved continuous and consistent hemofiltration for more than 100 hours using outside-in hemofiltration with the blood flow into the inter-fiber space (IFS) with minimal increase in filter pressure. Although thrombi do deposit in the IFS, they have minimal affect on the blood flow and filtrate flux due to the three-dimensional system of interconnected hydrodynamic flow channels in the IFS. Microscopic examination of sections of the fiber bundle showed that deposited thrombi have dimensions about the size of the gaps between the hollow fibers and remain isolated from each other. Mathematical models have been developed to describe the effect of thrombi deposition on the fluid flow which accounts for the enhanced filter performance arising from the interconnected flow. The hydrodynamic advantage of outside-in HF technology is expected to minimize the need for complex anticoagulation systems like regional citrate anticoagulation (RCA). For successful uninterrupted blood processing with the new outside-in HF technology, new filter configurations and designs are required. These results clearly demonstrate the significant potential advantages of using outside-in hemofiltration for long-term CRRT and for other extracorporeal therapies including hemodialysis and hemodiafiltration. The advantages, disadvantages and challenges of this new technology will be elaborated. Details of applications in both acute and chronic therapies will be presented.

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Extracorporeal Carbon Dioxide (CO2) Removal with Continuous Renal Replacement Therapy - A Novel Therapy

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[1]*Medanta The Medicity*

Introduction: Acute respiratory distress syndrome (ARDS) with renal failure is a common phenomenon in ICU. These patients may present with acidosis – respiratory due to low lung compliance, metabolic due to acute kidney injury (AKI). Extra-corporeal CO2 removal techniques are increasingly used to stabilise the metabolic consequences of respiratory acidosis(1).
The extracorporeal CO2 removal technique that we used in our patients consisted of a neonatal oxygenator placed in series to a hemofilter on a CRRT machine.

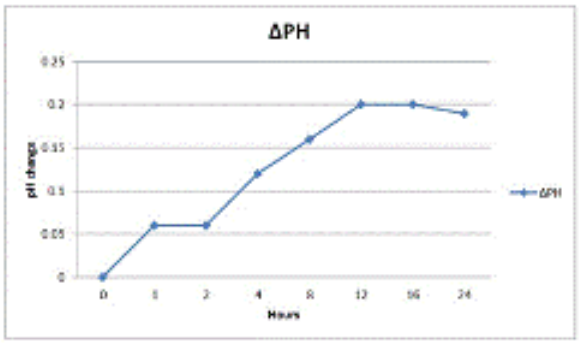
Purpose of the study: This was a retrospective data collection of three ventilated critically ill patients with AKI who underwent CO2 removal alongwith renal replacement therapy by a modified technique.

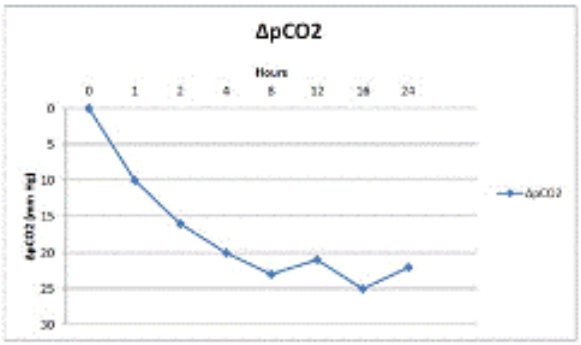
Method: We used a CVVHDF device (Prismaflex system, Gambro) with a standard setup and CRRT dose. The blood flow was maintained between 100-150 ml/min. For CO2 removal, a microporous polypropylene neonatal oxygenator (Capiox Baby RX05, Terumo) with a maximum permissible blood flow of 1.5L/min was applied in series with CRRT hemofilter (M100, Gambro). Oxygen at a flow rate of 4l/min was passed through the oxygenator as the sweep gas for CO2 diffusion. The gas exchanger had an approximate surface area of 0.5m2. The retrospective data was collected on three ventilated critically ill patients with ARDS and AKI treated with above modalities. Arterial Carbon dioxide (PCO2), arterial oxygen (PO2), arterial sodium bicarbonate (HCO3) levels and arterial pH were recorded as per arterial blood gases (ABG). Other parameters like Plateau pressure (Pplat) and mean arterial pressure (MAP) was also recorded.

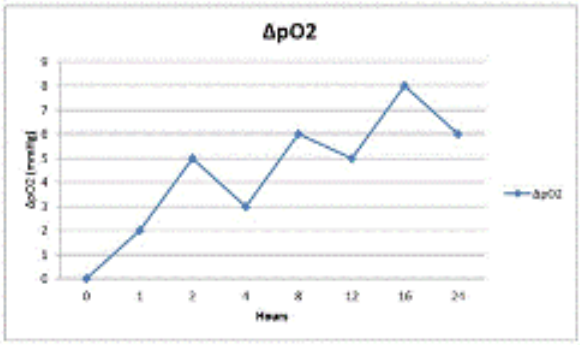
Results: This combination therapy reduced average PCO2 by 28.9% in about 4 hours. The pH concomitantly increased by 0.12 (0.05 to 0.23). There was no appreciable change in PO2 levels (around 2%). The HCO3 levels changed as per the dose of CRRT. All patients tolerated the procedure without change in hemodynamics. The Pplat decreased by an average of 10% due to ultrafiltrate removal. Two patients could be weaned off to conventional ventilator strategies without hypercapnia. The third patient dies due to refractory shock.

Conclusion: Extracorporeal CO2 removal alongwith CRRT may be a useful modality in patients with combined respiratory and metabolic acidosis with a positive impact on hemodynamic stability (2).

S.No	pH t=0	pH t=4 hrs	ΔpH	pCO2 t=0	pCO2 t=4 hrs	Δ pCO2 mmHg	pO2 t=0	pO2 t=4 hrs	Δ pO2 mmHg
Patient 1	7.13	7.27	0.14	68.0	46.8	21.2	58.8	57.5	-1.3
Patient 2	6.97	7.20	0.23	75.9	47.9	28	50.6	53.8	3.2
Patient 3	7.15	7.13	-0.02	62.5	50.1	12.4	66.1	64.5	-1.6







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Experiences of blood purification using cytokine- adsorbing hemofilter (AN69ST) in pediatric population in Japan

Masaaki Nunomura[1], Keiichi Motoyama[2], Hirota Saito[2], Fujiko Fukushima[2], Isho Izumi[2], Toshihiro Muraji[3]

[1]Department of Clinical Engineering, Ibaraki Children's Hospital, [2]Department of General Pediatrics, [3]Department of pediatric Surgery

Background
In Japan, blood purification with AN69ST (Sepxiris®: Baxter) has been included in the insurance-covered therapeutic modalities for sepsis since July 2014. The AN69ST membrane is an AN69 membrane that is surface-treated with highly biocompatible polyethyleneimine. Therefore, AN69ST is now the first choice for severe sepsis and septic shock because of its remarkable ability of adsorbing cytokines. We report our experiences in using the AN69ST in infants and children from July 2014 to May 2015.
Cases
Four patients required blood purification using AN69ST in our hospital during this period. Their average body weight was 21.9 kg and average age, 6 years 11 months. Their primary diseases were Crohn's disease, acute pancreatitis, post-operative infection, and acute kidney disease.
Equipment
We used a console of TR-55X (Toray Medical, JP) with a blood circuit (U520-SZK-M, JUNKEN medical, JP) and hemofilter (Sepxiris60, Baxter, USA).
Results
No initial drop in blood pressure was encountered at the beginning of the blood purification. In the second case, whereby nafamostat mesylate (NM) was used alone, the circuit (V chamber) was coagulated 7 h after the start, and heparin was added for anticoagulation following circuit exchange. In the third and fourth cases, coagulation of the circuit was prevented for 24 h with an NM and heparin combination. The average blood purification time

was 162 h 20 min. The average NM dose was 0.48 mg/kg/h; average heparin dose, 2.9 IU/kg/h; average activated clotting time (ACT), 185 s on the A side and 209 s on the V-side; and increase ratio, 12.6%. The active prothrombin time (APTT) was pre-blood purification 45.7s and 57.8 s during blood purification; the increase ratio was 12.6%. In the case of hemofilters other than AN69ST used previously, the increase ratios were 45.7% and 210.2% for ACT and APTT, respectively, with an average NM dose of 0.48 mg/kg/h.
Discussion
The second patient required a circuit exchange because of circuit coagulation only 7 h after the start. Other institutions have reported that the V chamber was coagulated with anti-coagulation therapy using NM alone. Our experiences have shown trends of shortened ACT and APTT with the use of AN69ST, compared to the use of other hemofilters. Further investigation is warranted to determine whether or not AN69ST adsorbs NM.
Conclusion
NM alone does not provide adequate anti-coagulation when an AN69ST membrane is used.
Heparin is recommended in combination with NM.

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oXiris – a novel continuous renal replacement therapy and cytokine & endotoxin adsorption in septic patients – an Indian clinical experience

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[1]*Medanta The Medicity*

Introduction: Most of the recent studies on sepsis have revealed the presence of high concentrations of cytokines and endotoxins in blood. This triggers the cascade of multiorgan dysfunction. Blood purification by removal of these cytokines have shown to improve the clinical outcome in septic patients[1].
oXiris hemofilter (oXiris, Gambro Hospal, Sweden) is an AN69-based membrane, surface treated with a polyethyleneimine (PEI) and grafted with heparin[2] and has been implicated to have an efficient cytokine adsorbing capacity[3].

Purpose of the study: A retrospective data collection of 10 critically ill septic shock patients who underwent oXiris membrane based CRRT and its effect on hemodynamics and mortality.

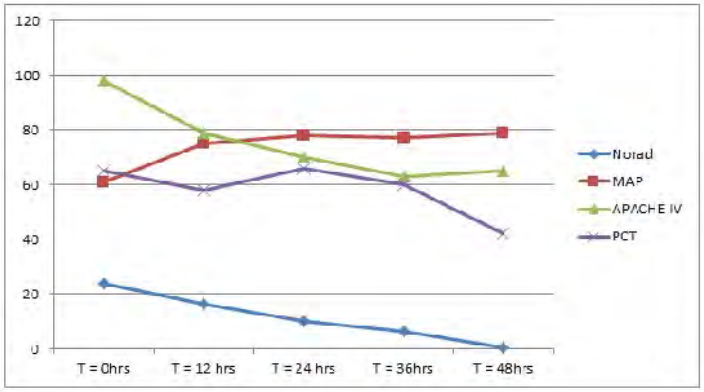
Method: We collected data on patients who underwent continuous venovenous hemodiafilteration (CVVHDF) by oXiris hemofilter. The blood flow was maintained between 100-120 ml/min with a CRRT effluent dose of 30-35 ml/kg. APACHE IV score, vasopressor requirement at T=0 (at start of therapy), at T=24 & T=48 (24 & 48 hrs after therapy) was recorded. Other variables like core temperature by rectal probe, mean arterial pressure (MAP), sepsis markers like procalcitonin (PCT) and percentage reduction in APACHE IV & SOFA score were recorded. Endotoxin assay was not measured in all patients and so was not recorded in the assessment. We also looked at the effect on mortality.

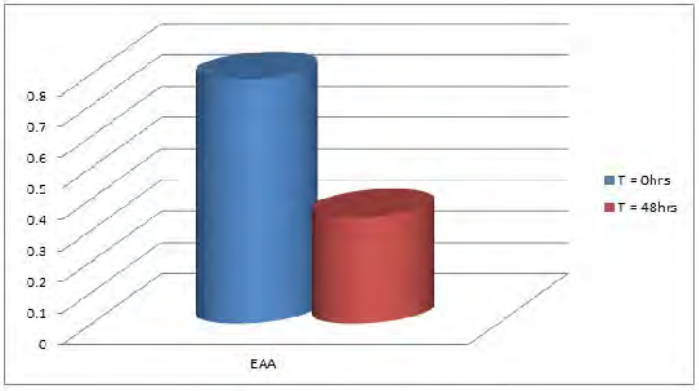
Results: The average vasopressor dosage reduction was 32% (14-64%) within first 12 hours of initiation of oXiris therapy and the effect persisted during the duration of therapy. This resulted in increase of MAP by an average of 22% over the same period. Patients experienced reduction in core temperature during the entire duration of therapy. Procalcitonin did not show any major change (average reduction of 5%). APACHE IV and SOFA scores showed an average reduction during the next 48 hours (20% and 18% respectively). The average

life of oXiris membrane was 52 hours without the need of heparin anticoagulation. The endotoxin assay although not a part of the assessment did show a significant reduction (average 56%) in 5 patients in whom it was done before the start of therapy. Four patients died within next 5 days.

Conclusion: oXiris membrane based CRRT does help in reduction in vasopressor dependency and improvement in hemodynamics and organ failure scores in critically ill patients. Mortality benefit could not be commented as we did not compare with a control cohort.

Variables	T = 0hrs	T = 12hrs	T = 24hrs	T = 36hrs	T = 48hrs
Noradrenaline dose (ml/hr)	24	16.3	10.2	6.4	0.6
MAP (mmHg)	61	75	78	77	79
PCT (ng/ml)	65	58	66	60	42
APACHE IV	98	79	70	63	65
SOFA	19	15	13	12	10





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In vitro and preliminary in vivo evalutation of new CRRT machine: KIBOUTM

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Introduction:
KibouTM (Asahi Kasei Medical Co., Tokyo, Japan) is a new multifunctional automatic machine for Continuous Renal Replacement Therapy (CRRT) (figure). Kibou can perform different CRRT therapies with the possibility to use only a single platform; in particular, modalities for both adults and pediatrics, counter-current and co-current configurations, the use of heparin or citrate-calcium anticoagulation therapies and plasma exchange can be delivered (figure).
Methods:

Based on the traditional experience of International Renal Research Institute of Vicenza (IRRIV), in vitro and α test evaluation of Kibou and related disposables has been conducted. In particular, during in vitro phase all the possible modalities and treatments have been performed, even for 24 hours. The 12 in vivo treatments were performed: 3 SCUF, 3 CVVH, 3 CVVHD, 3 CVVHDF, all for adult patients. The treatment parameters have been set based on the clinical needing of the patients. Machine's usability and accuracy has been evaluated by the staff (clinicians, nurses and engineers) through scores table. The measurement of the accuracy of fluid balance system (gravimetric) has even been performed comparing the displayed values in the monitor of the machine and in the bed scales. CurefloTM ACF-130W filter has been used for the in vivo evaluation.
Results:
Based on score given by the staff, the machine hardware results compact and well organized (figure), with 3 well separated compartments (dialysate/replacement, blood and effluent) that facilitate the preparation phase. Auto-priming function allows short priming time. The interface is user friendly in all the modalities (SCUF, CVVH, CVVHD, CVVHDF, TPE, for adults and pediatrics). During the α test in vivo, the measured fluid balance error was always lower than 0.3%, in all the modalities. On the contrary CVVHDF pre-infusion and pre + post infusion are not performable. For pediatric treatment the continuity of the flow of peristaltic blood pump need to be maintained and improved.
Conclusion:
Kibou is a promising CRRT machine that can perform multiple continuous therapies with just one platform. In particular, we evaluated a highly accurate gravimetric fluid balance control system and a user friendly interface. Kibou is one of the first machines of the new frontier of CRRT devices: the fifth generation of CRRT machines.

CRRT TREATMENT	REPLACEMENT			DIALYSATE		ADULT		PEDIATRIC	
	PRE	POST	PRE & POST	CO-CURRENT	COUNTER-CURRENT	HEPARIN	CALCIUM-CITRATE	HEPARIN	CALCIUM-CITRATE
SCUF	-	-	-	-	-	x	x	x	-
CVVH	x	x	x	-	-	x	x	x	-
CVVHD	-	-	-	x	x	x	x	x	-
CVVHDF	-	x	-	x	x	x	x	x	-
TPE	-	-	-	-	-	x	x	x	-

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Confirmation of Hemodialysis Central Venous Catheter Placement Using an Ultrasonographic "Bubble Test"

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Confirmation of Hemodialysis Central Venous Catheter Placement Using an Ultrasonographic "Bubble Test"
Introdution
The insertion of hemodialysis catheter is an integral part of the management of critically ill patients requiring continuous renal replacement therapy (CRRT). Doppler ultrasound imaging guidance for the insertion compared with anatomic landmarks, has benefits with respect to several clinical outcomes, and its routine use is strongly recommended. Traditionally, a postprocedural portable chest radiograph (CXR) is performed for catheter confirmation; however obtaining one can take up to several hours, delaying use of the catheter in critical patients requiring emergent dialysis initiation. The objective was to determine if ultrasound (US) can more rapidly confirm hemodialysis central venous catheter position in comparison to (CXR)

Methods
The study included a convenience sample of critically ill patients requiring CRRT with supradiaphragmatic hemodialysis catheters and a CXR for confirmation. Ultrasound was used for confirmation by visualizing microbubble artifact in the right atrium after injection of saline through the distal port. Blinded chart review was performed to assess CXR timing, catheter position and CVC complications. Student's t test was used to compare US time to CXR performance time and radiologist reading time.

Results
Thirty two patients were included in the final analysis. The visualization of turbulence or microbubbles within the RA within 2 seconds of the distal port flush confirmed adequate CVC placement with a 96% sensitivity and 93% specificity. Mean total US time was 3 minutes (95% confidence interval [CI], CI 2,2-3,9) 24 minutes (CI 16,8-39,4) for CXR performance, with a median diference of 21 minutes (CI 10,8 - 36,5, p<0,001. When comparing only US CVC confirmation time to CXR time, US was an average 24 minutes (CI 12,7 – 35,4, p<0,001) faster. Comparing total US time to radiologist CXR reading time, US was an average of 254 minutes faster (95% CI, -384.5 to -203.5; P < 00001).

Conclusion
The rapid appearance of prominent turbulence or microbubbles in the right atrium on chest ultrasound after CVC saline flush serves as a precise bedside screening test of optimal hemodialysis catheter position and was significantly faster than CXR in our population of critically ill patients requiring CRRT.

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Development and validation of an Acute Kidney Injury prediction model in Intensive Care Unit

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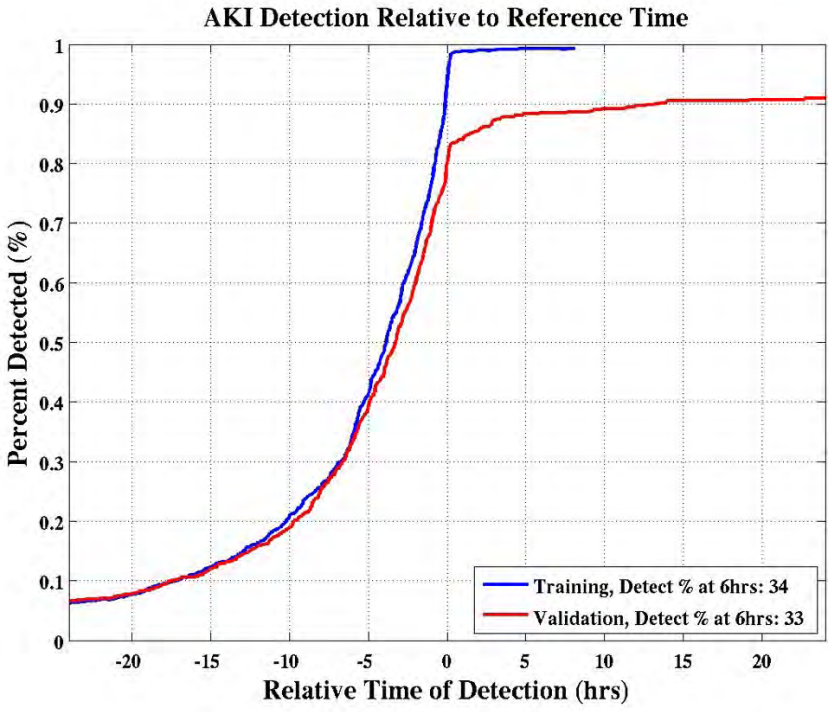
Introduction: Acute Kidney Injury (AKI) is common and life-threatening medical condition seen in the critically ill population. Timely risk stratification of AKI high-risk patients facilitates prevention of its progression. Objective: Over the past few years, standardized diagnostic and staging criteria for AKI standardized AKI detection and its complications. However, these criteria do not have the ability to identify AKI high-risk patients, which could provide the clinicians with an opportunity to develop strategies for prevention, and treatment of AKI. The proposed AKI model is based on random forests approach and uses the signatures of AKI observed in vital signs, laboratory data, and acute conditions to predict AKI.
Methods: This study is conducted in the ICUs of a tertiary care center. The training and validation cohort study subjects were Olmsted County, MN, residents admitted to all Mayo Clinic ICUs from July 1, 2010, through December 31, 2010. The Acute Kidney Injury Network criteria were used to define AKI. The prediction model was developed; its precision and reliability in the prediction of AKI were assessed in both training and validation cohorts. AKI adjudication was performed using a validated electronic surveillance tool which identified patients with AKI using AKIN criteria with a sensitivity of 88% and specificity of 96%.
Results: Out of 7594 screened patients, a total of 6530 patients were included in the study: 5472 for training and 1958 for validation. Following training model in the first cohort, in the validation cohort, sensitivity, specificity and positive predictive value of the AKI prediction model were 93%, 66% and 41% positive predictive value (adjusted to 20% prevalence of AKI in ICU). In addition, the AKI prediction model detects 79% of AKI patients earlier than the reference standard and 33% of AKI patients 6 hours prior to the reference standard.
Conclusion: Acute kidney injury can reliably and accurately be predicted electronically in ICU patients.



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Better "dose" for CRRT? Deliver the prescribed

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Introduction: historically, assuming the equilibration of low molecular weight solutes between the blood and dialysate, the dose of CRRT has been quantified with the effluent flow rates (the sum of net ultrafiltration, dialysate and replacement fluid) normalized to body weight. It may be reduced by pre-filter administration of replacement fluids or by membrane fouling caused by clotting and by protein concentration polarization. While the literature does not support the concept that more RRT is better, the same data suggest that there must be a lower limit below which mortality will increase. KDIGO AKI guidelines recommend delivering an effluent volume of 20–25 mL/kg/h: prescribing a modestly higher dose of therapy in order to actually deliver the desired target doses; closely monitoring the delivered dose to assure that the targeted dose is actually achieved. 4th generation CRRT machines have becomes multi-organ support technologies that provides a wider range of extracorporeal treatment options. Aim of the present is to evaluate the “Dose” feature, both for prescription and treatment delivery, of the new Kibou (Asahi) CRRT machine.

Methods: the kibou machine is equipped with a “dose” feature capable to calculate and display the instantaneous, the delivered and the target doses. Of the 24 treatment (12 with kibou and 12with others) (4+4 CVVH, 4+4 CVVHD and 4+4 CVVHDF) performed in our semi-intensive care unit, we calculate the number of flows settings changes and the effect on the dose. In addition we evaluate the prescribed vs delivered values.

Results: Excluding blood flow changes we observe 35 (vs 22 others) flows variations when kibou machine were used. Post infusion (22 vs 8) was mainly increased while net UF varied only 8 (vs8) times. 75% (vs 60%) was in a favor of an higher dose. The delivery dose was the 96% of the prescribed for treatments done with Kibou and the 90% for the others. Nurses was comforted on the actual delivery dose displayed in the main page of the machine.

Discussion:

Even if a debate on the better dose for the patient is still open and actual, the delivery of the prescribed amount is mandatory in clinical practice. Our results are in favor with a “dose” feature integrated on the CRRT machine

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Adverse Effects of Hypophosphatemia during Renal Replacement Therapy for Acute Kidney Injury

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Purpose: Hypophosphatemia in critically ill patients is common and may be exacerbated by dialysis. We aimed to identify risk factors and adverse outcomes associated with hypophosphatemia in intensive care unit (ICU) patients treated with dialysis for acute kidney injury (AKI).
Methods: Secondary analysis of data from a single-center prospective cohort study of medical and surgical intensive care patients with acute kidney injury initiated on dialysis for AKI between 18th December 2010 and 3rd April 2013. Patients with premorbid serum creatinine ≥500 μmol/L, received dialysis prior to ICU admission, had incomplete dialysis data or died within 1 day of dialysis initiation were excluded. Demographic, comorbidity, laboratory and dialysis data were retrieved from patient case notes and electronic medical records. Outcomes assessed were hypophosphatemia (serum phosphate <0.94 mmol/L) during dialysis, ICU mortality and duration of mechanical ventilation and vasopressor support.
Results: Median serum phosphate at initiation of acute dialysis was 1.63 mmol/L (IQR: 1.23, 2.43) in 96 patients. Twenty-five patients (26.0%) developed hypophosphatemia. On multi-variate logistic regression, serum phosphate at dialysis initiation [adjusted odds ratio (OR) 0.29 (95% CI (0.09, 0.91, p=0.03] was independently associated with hypophosphatemia during acute dialysis. Patients with hypophosphatemia during dialysis required longer ventilatory support [median 12 (IQR: 8, 17) days vs. 5 (3, 9) days, p<0.001] and vasopressor support [5 (4, 15) days vs. 2 (2, 6) days, p=0.003] compared to those without hypophosphatemia but there was no significant difference in ICU mortality [5 patients (20.0%) vs. 24 patients (33.8%), p=0.20]. Hypophosphatemia during dialysis was independently associated with prolonged mechanical ventilation (≥7 days) [adjusted OR 14.0 (1.37, 143.90), p=0.03].
Conclusions: Mild hypophosphatemia during dialysis was associated with prolonged need for mechanical ventilation in critically ill patients with AKI.

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Pharmacokinetics of Imipenem/Cilastatin in Critically Ill Burn Patients Undergoing High Volume Hemofiltation (HVHF)

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Purpose: High-volume hemofiltration (HVHF) is a modality used in septic burn patients for extracorporeal blood purification, volume removal, and removal of inflammatory mediators. Imipenem-cilastatin (I-C) is an antibiotic routinely used for treatment of severe sepsis in burn patients; however, dosing of I-C in patients undergoing HVHF is based on inference from previous studies assessing substantially different CRRT methods. To address this knowledge gap, we quantified the systemic and extracorporeal clearance (CL) of imipenem and cilastatin in burn patients undergoing HVHF.

Methods: Adult critically ill burn patients receiving I-C for a documented infection and requiring HVHF were eligible for inclusion. I-C dosing and the prescribed HVHF dose were at the discretion of the medical team. Blood and effluent (E) samples for analysis of I-C concentrations were drawn in conjunction with a scheduled dose of I-C. Blood and E samples were collected at time 0 (blood only), 0.25, 0.5, 1, 2, 4, and 6 hours after the infusion and the total effluent was collected for calculation of I-C total CL (CLTotal), CL by HVHF (CL HVHF), half-life during HVHF, and the percentage of drug eliminated by HVHF. Drug concentrations were measured using liquid chromatography-mass spectrometry.

Results: A total of 10 patients were enrolled (mean age 50±17 years, total body surface area burns 24±27%, 80% male). The I-C dose was 1 gram every 6 hours in 9 patients and 0.75 g every 8 hours in 1 patient; mean infusion time 87±10 minutes. The median I-C dose number prior to sampling was 4 (range 1-22). The indication for HVHF was AKI in 9 patients and sepsis in 1 patient. Characteristics of the HVHF procedures were: mean delivered dose 52 ± 14 mL/kg/hr (range 32-74), blood flow rate 318 ± 39 mL/min, effluent flow rate 4.3 ± 1.2 L/hr. The dialyzer used for HVHF was the Purema H polyethersulfone filter with all replacement fluid delivered pre-filter. The pharmacokinetic parameters of imipenem and cilastatin during HVHF are shown in the table.

Conclusion: Removal of imipenem and cilastatin was substantial. More aggressive dosing of I-C in the burn population requiring this CRRT modality may be warranted depending on the infection and pathogen.

Parameter	Imipenem	Cilastatin
CLTotal (mL/min)	120 ± 36	44 ± 20
CL HVHF (mL/min)	54 ± 8	33 ± 9
Half-life (hrs)	1.9 ± 0.4	1.8 ± 0.4
% Removed by HVHF	48 ± 9	84 ± 32

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Continuous renal replacement therapy in the NICU; ten years experience in a single center

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Introduction:
A Japanese clinical guideline of neonatal continuous renal replacement therapy (CRRT) was published in 2013; however, few neonatal intensive care units (NICUs) perform CRRT, and patient mortality remains high. Our objective was to study the clinical course of patients receiving CRRT in the NICU, and to analyze factors associated with mortality.
Methods:
We performed a retrospective observational study of all neonates who received CRRT at our NICU between 2005 and 2014. Patient characteristics, laboratory findings at initiation of CRRT, setting of CRRT, and 3-month mortality were reviewed retrospectively. Survivors and non-survivors were compared using univariate and multivariate analysis.
Results:
Twenty-seven patients received CRRT and had data available for analysis. Median patient age was 2 days (range, 0–210 days), and median body weight was 2.9 kg (range, 1.2–3.8 kg). Diaphragmatic hernia was the most common underlying disease, with associated shock due to persistent pulmonary hypertension of the newborn. No patients had renal or urological disease. The mean catheter size was 5.6Fr, and the insertion sites were femoral, jugular, and umbilical veins. The filter material was polysulfone and polyacryonitrile, and polyether sulfone. The mean membrane surface area was 0.29m2. The priming fluid of circuit was red blood cell in all patients. The anticoagulant was nafamostat mesilate. The mean blood flow was 12±6 mL/kg/min, and the mean CRRT dose was 208±140 mL/kg/h. Median treatment duration was 8 days (range, 2–124 days). Overall survival was 51.9% within 3 months. To compare survivors and non-survivors, univariate and multivariate analysis indicated no risk factors for mortality. Non-survivors tended to have a lower PF ratio (93 versus 163), higher lactate (9.9 versus 4.4 mmol/L) and higher serum creatinine (1.77 versus 0.97 mg/dL), and higher %fluid overload (44.7 versus 11.4%). All survivors recovered to dialysis-independence at hospital discharge. All non-survivors died from their primary disease.
Conclusion:
In neonatal CRRT, the main cause of CRRT is not renal disease but circulatory insufficiency. Central and peripheral circulatory failure, and fluid overload might be risk factors for mortality in neonates. The mortality is high, but all survivors require neither dialysis nor management of chronic kidney disease. The survey of neonatal CRRT should be continued.

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Early versus Late Initiation of Renal Replacement Therapy in Critically Ill Patients with Acute Kidney Injury (The ELAIN-Trial): a randomized clinical trial

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PURPOSE OF THE STUDY The optimal timing of initiation of renal replacement therapy (RRT) in patients with severe AKI but without life-threatening indication is still unknown. This study was performed to determine whether early initiation of RRT in critically ill patients with AKI reduces 90-day all cause mortality.
METHODS In this single-center trial, we enrolled critically ill patients with AKI between August, 2013, and June, 2015. We enrolled 231 patients at a University hospital in Germany and randomized them to early or late initiation of RRT. All patients completed follow-up 90 days after randomization, and were analyzed according to the intention-to-treat principle. RRT was either initiated early (KDIGO stage 2) or late (stage 3). The primary endpoint was survival over the first 90-days after randomization. Secondary endpoints included 28- and 60-day survival, clinical evidence of organ dysfunction, recovery of renal function, requirement of RRT after day 90, duration of renal support, ICU and hospital length of stay and markers of inflammation.
RESULTS Early initiation of RRT significantly reduced 90-day all-cause mortality (44 deaths (39.3%)) compared to late initiation of RRT (65 deaths (54.7%); HR, 0.66; 95% CI, 0.454 – 0.966; P=0.03). More patients in the early group had renal recovered (60 (53.57%), versus 46 (38.66%); OR, 1.83; 95% CI, 1.08 – 3.09; P=0.02). Furthermore, duration of RRT and length of hospital stay were significantly shorter in the early group compared to the late group, but there was no significant effect on requirement of RRT after day 90, organ dysfunction, and length of intensive care stay. Early initiation of RRT significantly attenuated the levels of pro-inflammatory mediators in the plasma of critically ill patients with AKI (interleukin 6 at day 1: early: 399.4 vs late, 989.3 ng/mL; Hodges-Lehmann estimation of location shift, 310.9; 95%CI, 93.3-663.2; P < .001; interleukin 8 at day 1: early: 65.7 vs late, 215.5 ng/mL; Hodges-Lehmann estimation of location shift, 105.9; 95% CI, 52.7-160.6; P < .001). No safety signal was evident in either arm.
CONCLUSION Among critically ill patients with AKI, early initiation of RRT significantly reduced 90-day all-cause mortality. The observed reduction in mortality warrants further investigation.

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Effect of the intensity of Continuous renal Replacement Therapy in Patients With cardiac surgery associated Acute Kidney Injury (CRITERIA STUDY)

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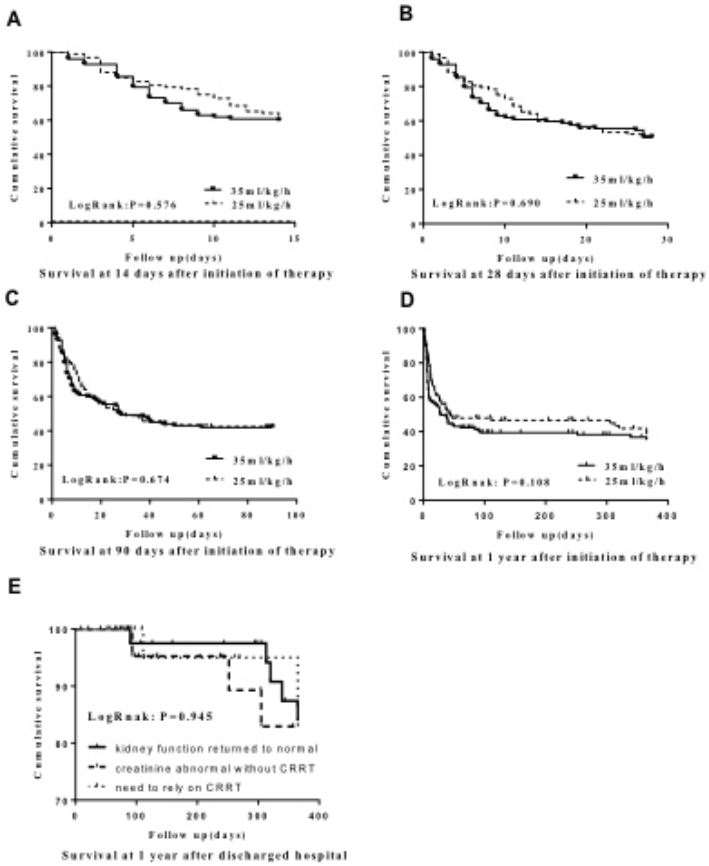
Introduction. Acute kidney injury (AKI) is a major complication in patients with cardiac surgery and is an independent predictor of mortality. However, the optimal intensity of continuous renal replacement therapy(CRRT) for such patients is still controversial. Methods. From 13 April 2011 to 9 August 2015, we randomly assigned 211 patients with Cardiac surgery-associated acute kidney injury (CSA-AKI) to continuous renal replacement therapy with different treatment dose (35ml / kg / h or 25ml/kg／h),The primary study outcome was death from any cause within 14, 28 ,90 and 365 days. Secondary outcomes were length of stay in the ICU and hospital and renal outcome of survivors at 14, 28 ,90 and 365 days after randomization. Results were analyzed by univariate and multivariate methods and by Kaplan–Meier survival curves. Results. A total of 112 patients were given 35ml / kg / h and 99 were given 25ml / kg / h. There were no significant differences between the groups in number of deaths at 14, 28 ,90 or 365 days. There were also no differences between the groups in renal outcome of survivors at 14, 28 ,90 or 365 days. Conclusions. In patients with cardiac surgery associated acute kidney injury, the intensity of renal replacement therapy about 25 and 35 mL/kg/h had no effect on survival at 14, 28, 90 or 365 days.



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Relationship of Total Parenteral Nutrition Administration and Renal Replacement Therapy in the Intensive Care Unit

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Purpose of the study: Adequate nutritional support is a mainstay of treatment of critically ill patients. In case of contraindications for enteral feeding, total parenteral nutrition (TPN) emerges as the next choice. Some adverse effects of TPN on kidney homeostasis have been reported. We ought to analyze the relationship between TPN and renal replacement therapy (RRT) in the Intensive Care Unit (ICU). Specifically, we hypothesized that TPN is a risk factor to receive RRT during ICU stay.

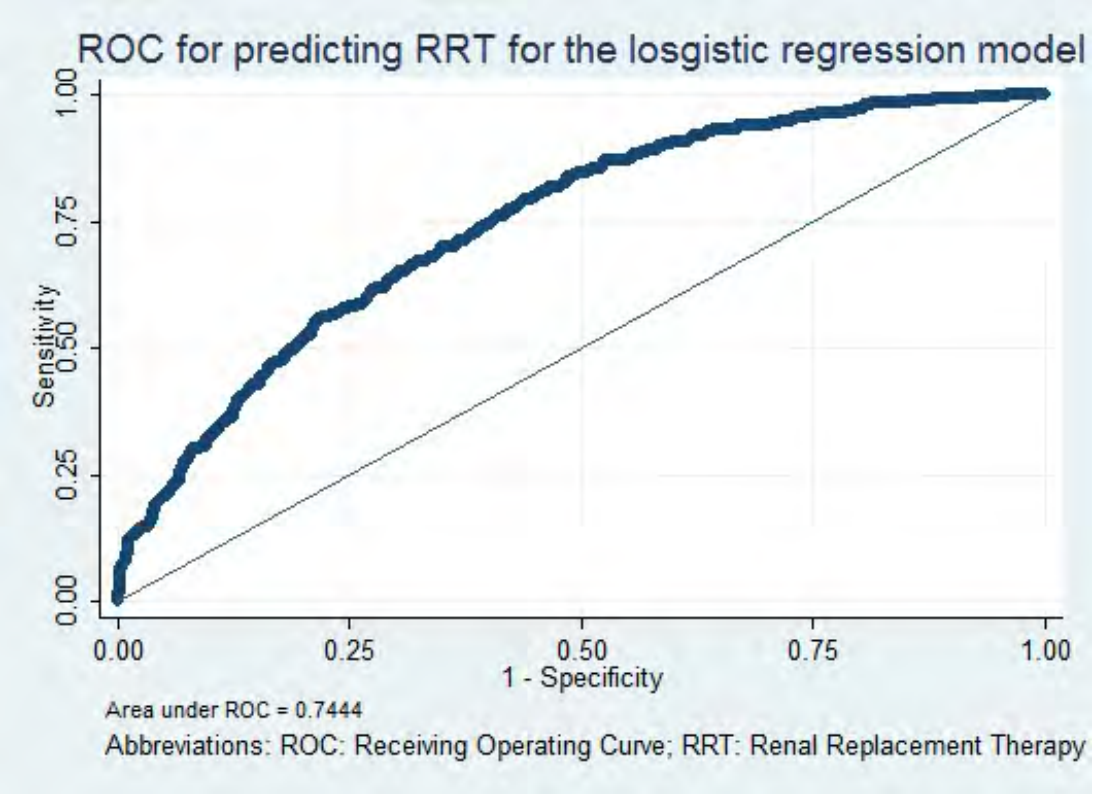
Methods: This was a study in 4 hospitals in Mexico City. We used a prospectively collected administrative database conducted in all the ICUs. We included adult patients admitted between September 2009 and April 2015-Hospital A; January 2009 and December 2014-Hospital B; January 2013 and April 2015-Hospital C; January 2010 and March 2015-Hospital D. We excluded readmissions and transfers. A propensity score (PS) was created by a logistic regression model (LRM) with TPN or No-TPN as the dependent variable. The numeric value of this PS was included as covariable in a LRM with RRT as the outcome. The final model's stability was tested by Hosmer–Lemeshow Goodness of fit test and bootstrapping. Lastly, a receiving operating curve (ROC) for predicting RRT by the final model was created.

Results: In total, 4061 patients were admitted and 570 of them excluded. From the remaining 3491 patients, 250 (7.1%) received RRT. TPN was more frequently administered in those receiving RRT (16.3% vs 6%; $p<0.001$). The variables included in the PS creation were ICU days, enteral feeding, urgent surgical treatment, mechanical ventilation and hospital days. Significant variables related to RRT after LRM were male gender (OR 1.35, CI95% [1.03-1.78]; $p=0.030$), organic failure (OR 5.54, CI95% [2.67-11.5]; $p<0.001$), Saps3 predicted mortality (OR 1.01, CI95% [1.009-1.02]; $p<0.001$) and TPN administration (OR 2.17, CI95% [1.52-3.11]; $p<0.001$). Hosmer-Lemeshow Goodness of fit test resulted in a Chi-2 of 1.84 ($p=0.98$). The area under the ROC for predicting RRT was 0.74.

Conclusion: The administration of TPN was found to be related to RRT even after adjusting for various cofactors, including each patients´ propensity to receive TPN. Within the limitations of this study, results suggest that TPN might be consider a risk factor for RRT during ICU stay. Due to the high frequency which TPN is prescribed, and the still uncertain feasible adverse effects, a well design prospective trial is needed.

Table and figure on following page

RRT	OR	p Value	95% CI	95% CI	Bootstrap Bias
Age	1.003	0.442	0.995	1.011	<0.001
Male Gender	1.355	0.030	1.030	1.784	0.002
Organic failure †	5.548	<0.001	2.675	11.509	0.057
Risk of failure †	1.866	0.141	0.813	4.282	0.043
Coronary disease	0.906	0.735	0.514	1.596	-0.042
MV	.838	0.241	0.624	1.125	-0.001
SAPS 3	1.014	<0.001	1.009	1.020	-8.95
TPN	2.177	<0.001	1.52	3.111	0.002
EF	1.245	0.215	0.879	1.763	0.004
PS	1.858	0.270	0.617	5.592	0.031
†. vs Post-surgery care Abbreviations: RRT: Renal replacement therapy; OR: Odds ratio; TPN: Total parenteral nutrition; EF: Enteral feeding; MV: Mechanical ventilation; SAPS 3: Simplified Acute Physiology Score 3, CI: Confidence interval; PS: Propensity					



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Impact of intensity of continuous renal replacement therapy on septic acute kidney injury

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Purpose: The intensity of continuous renal replacement therapy (CRRT) for acute kidney injury (AKI) has been evaluated, but recent randomized clinical trials have failed to demonstrate a beneficial impact of high intensity on the outcomes. High intensity might cause some detrimental results recognized recently as CRRT trauma. This study's aim is to evaluate the association of CRRT intensity with mortality in a population of AKI treated in Japan. Of note, Japanese national insurance system allows relatively lower dose than the international standard dose (20-25 ml/kg/hr).
Method: A retrospective single-center cohort study enrolled 125 AKI patients treated with CRRT in mixed intensive care units of a university hospital in Japan. Subanalysis was conducted for septic and post-surgical AKI.
Result: The median value of the prescribed total effluent rate was 20.1 (IQR 15.3-27.1) ml/kg/hr. Overall, univariate Cox regression analysis indicated no association of the CRRT intensity with the 60-day in-hospital mortality rate (hazard ratio 1.006; 95%CI 0.991-1.018; p=0.343). In subanalysis with the septic AKI patients, multivariate analysis revealed two factors associated independently with the 60-day mortality rate: the SOFA score at initiation of CRRT (hazard ratio 1.152; 95%CI 1.025-1.301; p=0.0171) and the CRRT intensity (hazard ratio 1.024; 95%CI 1.004-1.042; p=0.0195). Trough concentration of teicoplanin in higher intensity group and in lower intensity group were 17.0±7.2μg/ml and 24.2±10.1μg/ml (p=0.028) respectively, and trough concentration of vacomycin were 13.3±4.0μg/ml and 15.9±3.1μg/ml (p=0.075), respectively.
Conclusion: The CRRT intensity was associated significantly with higher 60-day in-hospital mortality in septic AKI, suggesting that several detrimental effects by high intensity CRRT including unexpected antibiotics removal might worsen the outcomes of septic AKI patients.

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Predictive models of flow-induced hemolysis in pediatric CVC

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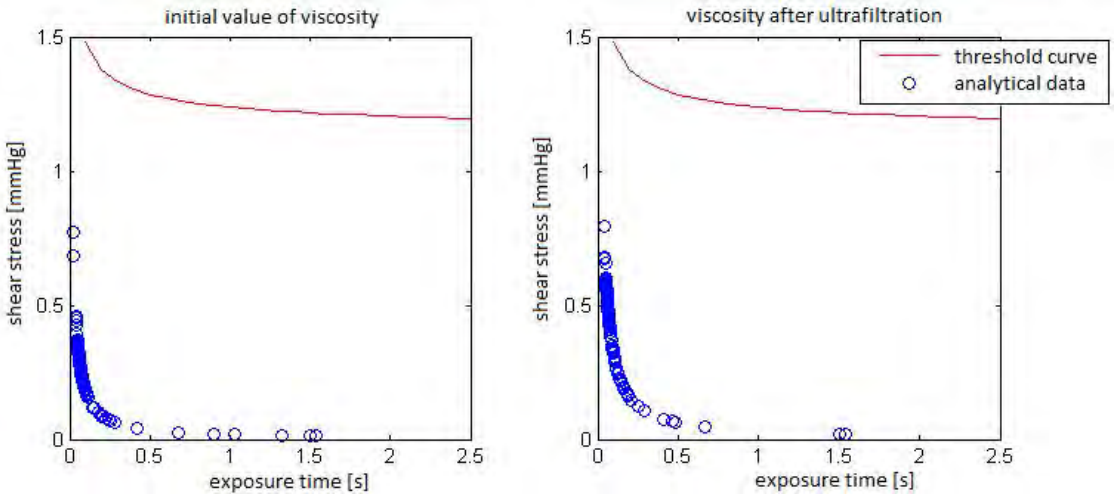
Background:Blood is damaged when it is subjected to non-physiological stress inside medical devices; in a dialysis extracorporeal circuit red blood cells are particularly damaged by catheter, peristaltic pump and filter. The index of hemolysis (HI) gives an experimental quantification of the hemolytic event, but for the optimization and prediction of the hemolytic potential of medical devices, mathematical models are required.We identify four classes of predictive models of hemolysis: power-law, threshold, strain-based and numerical models.Aim of our study is to evaluate these models with our experimental data;in particular, we are interested in the estimation of hemolysis induced by a 4 French catheter when it is inserted in an extracorporeal

circulation system, with a blood flow equal to 10mL/min and two different pump types (adult's and pediatric).This configuration may represent the optimal setting for CRR in newborns with dedicated machines.
Methods:With a simplified version of an extracorporeal dialysis system we collect pressures and flows for different test conditions (4,5 or7 Fr catheters; two roller or pediatric three roller peristaltic pumps).Pressures are measured at access and return points of the catheter, for blood flux of 7,10,15,30 mL/min.With a second testing circuit (where blood circulates without the use of a pump) we obtain an estimation of the release of hemoglobin induced by the 4 Fr catheter only. With data from the first circuit we evaluate power-law and threshold predictive models; analytical results from the specific configuration of 4 Fr catheter and 10 mL/min blood flux are then compared with the variation of free hemoglobin estimated with the second circuit.
Results:Figure1 shows our analytical data of shear stress and exposure time compared with a threshold curve of hemolysis: all the point are below the threshold but they are interested by sub-lethal trauma.Results confirm that the increase of blood viscosity due to ultrafiltration is related to more hemolysis in the circuit.The variation of plasma free hemoglobin induced by the catheter is greater with the adult's pump in the circuit (Table1).Data of one single test is a limit for this preliminary results
Conclusions:there aren't yet some shared "guide lines" for the estimation of hemolysis induced by medical devices. For our specific working conditions and theoretical assumptions, power-law model is suitable for the description of hemolytic phenomenon inside the catheter

	Free Hb mg/dl PowerLaw	Free Hb mg/dl Experimental
Adult	2.58	3.35
Pediatric	1.32	2.03



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Quality Indicators in Continuous Renal Replacement Therapy (CRRT) care in Critically Ill Patients: A Systematic Review

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Purpose: Continuous renal replacement therapy (CRRT) is the most common modality of renal support provided to critically ill patients. Prior data have suggested there is considerable variation in the prescription and delivery of CRRT. This may relate to a paucity of evidence-based quality and performance measures to guide practice. Accordingly, we performed a systematic review and evidence synthesis (PROSPERO No. CRD42015015530) to identify and appraise quality indicators (QIs) of CRRT care in critically ill patients.

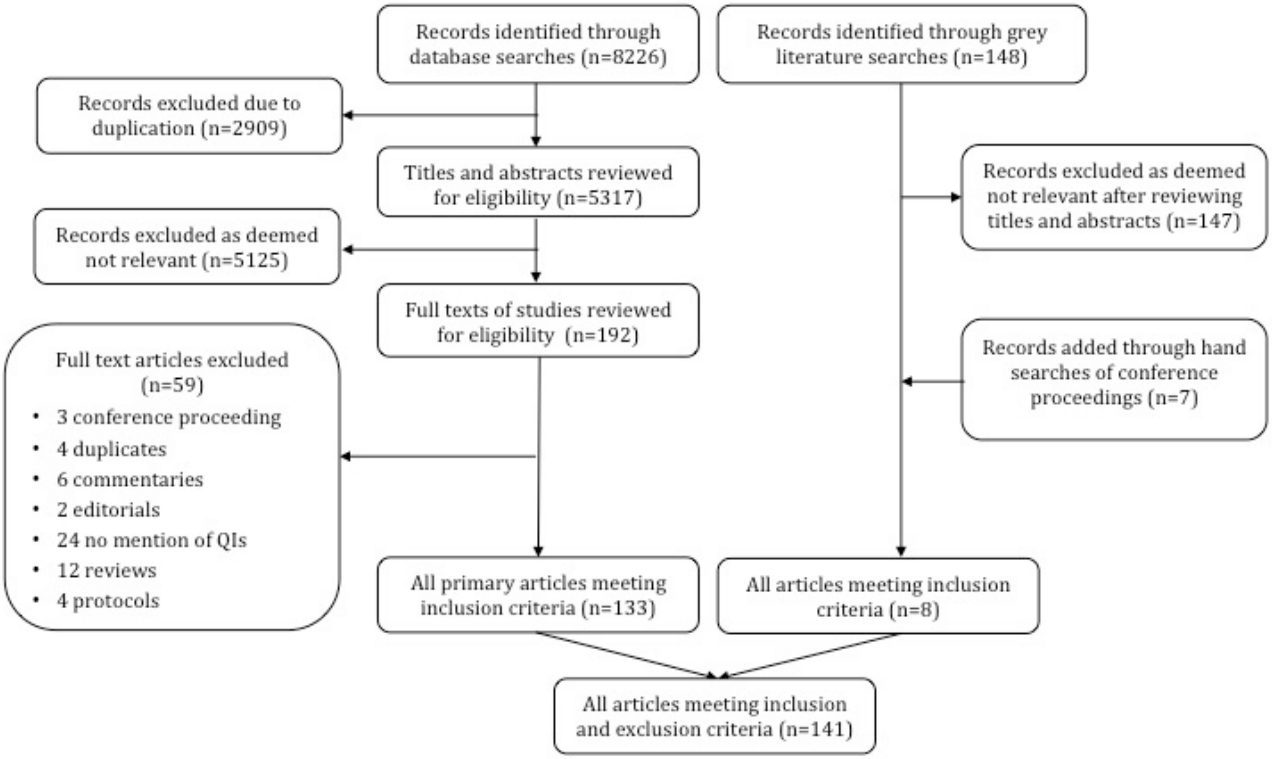
Methods: A comprehensive search strategy was developed and performed, in consultation with a research librarian, of four citation databases (MEDLINE, EMBASE, CINAHL, and Cochrane Library) and select grey literature sources. Studies were included if they mentioned all of the following terms: quality measure, intensive care, CRRT, language of study being English, French, German, Italian or Spanish, publication after 1990 and were either primary studies, secondary analyses or evidence syntheses. Two reviewers independently screened, selected and extracted data using standardized forms. Each retrieved citation was appraised for quality using the Newcastle-Ottawa Scale (NOS) and Cochrane risk of bias tool. Data are summarized narratively.

Results: Our search yielded 8,374 citations, of which 141 fulfilled eligibility and were included (see Figure 1). Overall, the quality of retrieved studies was generally low and associated with a high risk of bias. In total, a QI was mentioned in 257 instances. Identified QIs were further classified as related to: structure (n=100; 38.9%), care processes (n=108; 42.0%) and outcomes (n=48; 18.7%). The most commonly identified QIs focused on: filter lifespan (n=58), urea clearance (n=42), bleeding (n=33), circuit lifespan (n=21), creatinine clearance (n=18), circuit clotting (n=17), therapy interruptions (n=13) and delivered dose (n=11) (see Table 1). Across studies, the definitions used for QIs evaluating similar constructs varied considerably. In terms of their relevance as quality measures, QIs were most commonly described as important (n=98), scientifically acceptable (n=26) and useable and feasible (n=16).

Conclusions: We identified numerous potential QIs of CRRT care characterized by heterogeneous definitions, low quality of derivation and limited evaluation. Further study is needed to prioritize a concise inventory of QIs to measure, improve and benchmark CRRT care for critically ill patients.

Structure	Process	Outcome
Filter life (58)	Clearance - urea (42)	Bleeding (33)
Circuit life (21)	Clearance - creatinine (18)	VTE events (4)
Circuit clotting (17)	Downtime (13)	CRBSIs (3)
Blood flow (2)	Delivered Dose (11)	Catheter Colonization (3)
	Anticoagulation monitoring (4)	
	Clearance - B2 microglobulin (3)	
	Clearance - phosphate (3)	
	Clearance - pH change	
	Treatment interruption (2)	

Figure 1. PRISMA flow diagram of retrieved and included records



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Probability of Target Attainment for Gentamicin Dosing in Modeled Critically Ill Patients Receiving Prolonged Intermittent Renal Replacement Therapies

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Purpose: Prolonged intermittent renal replacement therapy (PIRRT) is growing in clinical practice to treat acute kidney disease (AKI) in critically ill patients, but it is administered in many different forms and durations. Gentamicin pharmacodynamic (PD) research suggests that greatest efficacy is associated with peak concentration/minimal inhibitory concentration (CMax/MIC) ratio of > 10 and the mean 24-hour area under the curve (AUC24) between 70-120 mg*h/L. The challenge in dosing gentamicin in patients with AKI is the high risk of nephrotoxicity at AUC24 above 120 mg*h/L. Using Monte-Carlo Simulations (MCS), we determined the probability of target attainment (PTA) of gentamicin in various dosing regimens in patients receiving daily PIRRT.

Methods: A one compartment pharmacokinetic model with first order elimination was developed in 8-10 hour daily PIRRT with dialysate flow rates of 5L/hr and 4L/hr respectively for the first 48 hours of therapy. Gentamicin was infused over 30 minutes; either 1 hour (early) or 14-16 hours (late) before PIRRT commenced.

MCS evaluated PTA of each dosing regimen in sets of 5,000 unique virtual patients constructed using published mean±SD (range) demographic and pharmacokinetic parameters [Weight = 86.6±29.2 kg (40-150), Volume of distribution = 0.373±0.102 L/kg (0.09-1.19), Non-renal clearance = 9.2±6.3 mL/min (1.4-34.5), and Dialysate saturation coefficient = 0.79±0.05 (0.7-0.91)]. Goal PTA was for 90% of virtual patients to achieve a CMax/MIC ratio of >10 with an AUC24 < 120 mg*h/L.

Results: No gentamicin dosing scheme met both the efficacy and toxicity target profiles for 90% of patients infected with organisms with MIC > 1mg/L. Both 8 and 10-hour PIRRT MCS had similar pharmacokinetic profiles. A day 1 gentamicin loading dose of 6 mg/kg followed by a day 2 maintenance dose of 5mg/kg given one hour prior to PIRRT achieved the PTA goal of 90% for MIC = 1 mg/L on both day 1 and day 2. No regimen could attain 90% PTA in “late PIRRT” regimens due to very high AUC24 values when goal CMax/MIC ratios were reached. The “best” 48 hour dosing interval regimen required a 10 mg/kg dose in early PIRRT, but the AUC24 fell below the efficacy target to a mean AUC24 value of 63 mg*h/L on day 2.

Conclusion: MCS suggests that it is difficult to reach 90% PTA with gentamicin in critically ill AKI patients receiving PIRRT, but if used, doses should be given an hour before daily PIRRT for best PD effect.

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Coagulopathy Reduces Dialyzer Clotting in CRRT

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Introduction: CRRT needs continuous systemic anticoagulation to maintain extracorporeal circuit because the circuit is frequently interrupted by dialyzer clotting. We aim to investigate which conditions contribute to frequent dialyzer clotting and dialyzer lifespan. Methods: We investigated retrospectively the medical records of thirty patients who had been received CRRT from March to September in 2015. CRRT modes were all veno-venous hemodiafiltration. Heparin was used primarily for circuit anticoagulation in 4 patients, and nafamostat mesilate was used alternatively in 26 patients with high risk of bleeding. We investigated clinical situations, CRRT prescriptions and basic blood tests including DIC(disseminated intravascular coagulation) profile. Dialyzer lifespan was calculated as: CRRT maintenance time (hours) divided by the frequency of dialyzer membrane clotting. Results: The results showed that D-dimer and FDP(fibrin degradation product) had significant positive correlations with dialyzer lifespan respectively ($r = 0.38$, $p = 0.048$ / $r=0.40$, $p = 0.041$), while hemoglobin concentration, platelet count, PT(prothrombin time) and activated PTT(partial thromboplastin time) did not show the relationship with diaylzer lifespan. Transfusion of packed RBC(red blood cell), FFP(fresh frozen plasma) and platelet concentrate did not show the relationship with dialyzer lifespan, and clinical severity including initial mean blood pressure, urinary amount and APACHE(Acute Physiology And Chronic Health Evaluation) score also had no relationship. CRRT prescription including CRRT dose, blood flow and type of anticoagulation had no correlation with diaylzer lifespan. When compared with non-DIC group (n=20), DIC group (n=10) had longer dialyzer lifespan, but not statistically significant (DIC vs. non-DIC, 47.98±19.48 vs. 33.38±18.25 hours, p=0.052). When compared with non-sepsis group (n=11), sepsis group (n=19) had shorter dialyzer lifespan significantly (sepsis vs. non-sepsis, 32.15±16.12 vs. 48.77±21.34 hours, p=0.022). Conclusion: Our study indicates that CRRT dialyzer could be longer used without clotting in the case of coagulopathy, while dialyzer clotting is more frequent in sepsis. Transfusion, clinical severity and CRRT prescription had no relationship with dialyzer clotting. Although, based on these results, we believe that bleeding diathesis by coagulopathy reduces the dialyzer clotting, further investigation is required to determine clinical implication.

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Risk factors associated with Mortality in patients using Nafamostat mesilate as an Anticoagulant during CRRT

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Introduction: NM (nafamostat mesilate), a synthetic serine protease inhibitor is a commonly used anticoagulant in patients receiving CRRT (continuous renal replacement therapy) with a high risk of bleeding. However there are limited randomized studies on risk factors associated with mortality in these patients.
Methods: AKI (acute kidney injury) patients on CRRT with a high risk of bleeding were randomized into NM and NA (no anticoagulant) groups. We examined the mortality and rate of renal function recovery as well as factors associated with mortality.
Results: Fifty four patients were included in this study (NM group=31, NA group=23). The mortality rate was 77.8 % and the most common cause of AKI was sepsis (50 %). There was no significant difference in mortality between the NM and NA groups (56.4% vs 43.6%, p= 0.09). Among the 12 patients discharged, 6 patients showed complete renal function recovery, 4 patients showed incomplete recovery of renal function (eGFR below 60 mL/min/1.73m2) and 2 patients were on maintenance dialysis. Multivariate analysis revealed longer duration on CRRT as an independent factor protective of death (odds ratio [OR] = 0.97, 95% confidence interval [CI] 0.948-0.996), p= 0.023).
Conclusion: The use of NM does not affect mortality in AKI patients on CRRT with high risks of bleeding. Due to the severity of the AKI patients on CRRT using NM as an anticoagulant longer CRRT duration is a positive factor on mortality.

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Pressure and Hemolysis in Pediatric CVCs with Different Peristaltic Pumps

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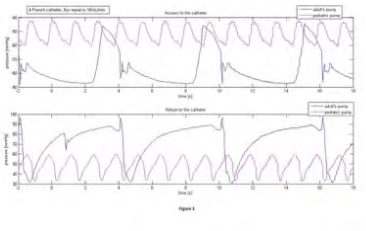
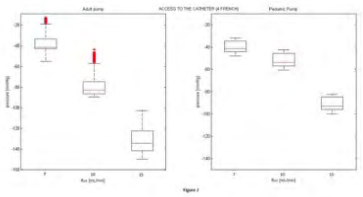
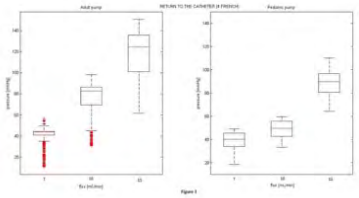
Background:Continuous Renal Replacement Therapies(CRRT)for pediatric patients with renal diseases offer accurate management and control of ultrafiltration flows and accurate fluid balance.On the other hand,the administration of CRRT to pediatrics with adult's machine leads to several problems:vascular access site and catheter dimension have to be adequate both for the needful blood flow and the size of the patient;catheterization with larger catheters may lead to venous damage and thrombosis;a large percentage of patient's blood volume(10-15%)can circulate in the extracorporeal circuit. Information concerning pediatric CRRT are lacking:data about children are limited and referred to particular clinical situations;moreover,knowledge acquired from adult patients cannot be easily shifted in pediatric area. Our aim is the estimation of hemolysis, flow and pressures related to central venous catheters of 4,5,7Fr;analysis are conducted with pediatric dedicated pumps(CARPEDIEM) and adult's pumps in order to study the influence of pump type on pressure in the catheter.
Methods:With a simulated extracorporeal dialysis system we collect pressures and flows for different test

conditions(4,5,7Fr catheters;two roller pump or pediatric three roller peristaltic pump). Pressures are measured at access and return points of the catheter, for blood flux of 7,10,15ml/min. Secondly,we perform an estimation of hemolysis induced by the extracorporeal circuit;we use two separated lines,one with adult's pump and the other with CARPEDIEM pump,both with 4Fr.
Results:In general mean pressure and the amplitude of the oscillation is lower with the pediatric pump in comparison with the adult's one(Figure1).Pressure at the access and return points of the catheter increases with flux.The magnitude of the amplitude also reflects this trend(Figures2 and 3).Hemolysis is slightly greater in the circuit with pediatric pump(Table).Data of one single test is a limit for these preliminary results.
Conclusions:Lower pressures in the catheter translate into reduced stresses on patient's vascular access.The management of the pressure control done by the machine is also more accurate when the signal vary in a narrow range.Hemolysis,an important factor in dialysis treatment,has never been compared when different pumping systems are used with the same small catheter. Results suggest that a slightly greater hemolysis with pediatric pump may have strong advantages on vessel and pressure management.

	Free hemoglobin in 2 hours (mg/dl)
Adult	11.06
Pediatric	14.92







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Combined Continuous Renal Replacement Therapy(CRRT) and Therapeutic Plasma Exchange(TPE): An Alternative Methods in Dual Therapies

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[1]*UCSD Apheresis*

Introduction:
Studies by other investigators have concluded that Continuous Renal Replacement Therapy (CRRT) concurrently with Therapeutic Plasma Exchange (TPE) is achievable. Limiting disruptions and time off the machine produces the best outcomes for CRRT patients. Continuation of the CRRT while provide TPE without disruption minimizes hemodynamic instability and fluid stability. For pediatric patients it also reduces the amount of blood exposure than if the treatments were done separately.

There are two techniques for providing both therapies without interruption: In Parallel" and "In Series". The difference between the two is the way in which the blood flow is routed between the CRRT and TPE equipment. We tested to see which technique was most effective.

Methods:
The data was gathered as part of a performance improvement project. The skills and techniques used provide optimal patient outcomes while receiving CRRT and Therapeutic Plasma Exchange. Sodium citrate anticoagulant is used for both techniques and calcium gluconate replacements are given via central line.

Results:
In Parallel with TPE and In Series with TPE
Ionized Calcium
Pre 1.2 1.13
Mid 1.19 1.2
Post 1.19 1.2
Fibrinogen
Pre 243 323
Post 121 78
Sieving Coefficient
Pre 100% 100%
Post 100% 100%

Both techniques were shown to be adequate in that the fibrinogen levels dropped greater than 50% and the CRRT sieving coefficient was maintained at 100% pre and post levels.

Conclusion:
This study demonstrates that TPE can be concurrently performed safely with CRRT. In series and In Parallel processes are both effective methods to connect CRRT to TPE. The CRRT Sieving Coefficients were 100 percent pre and post results in both techniques and the CRRT treatment was not disrupted. TPE was completed with no access or clotting issues.

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Independently Implementing Slow Low Efficiency Dialysis in a Critical Care Unit

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Intensive Care Units (ICUs) across Ontario predominantly utilize a nursing partnership model to provide intermittent acute dialysis modalities such as Slow Low Efficiency Dialysis (SLED) to critically ill patients who develop Acute Kidney Injury (AKI). This model requires a dialysis nurse to run the dialysis treatment and an ICU nurse to address all other aspects of care. The degree of involvement varies across units and organizations. North York General Hospital (NYGH) Critical Care Unit (CrCU) has established a unique program in which CrCU nurses are successfully providing all aspects of dialytic care to critically ill patients that develop AKI without the support of a dialysis program. Prior to this program, critically ill patients who develop AKI requiring dialysis were transferred to tertiary care ICUs, exposing patient to the risks of inter facility transport, and disrupting care for patient and families. Staff training and education curriculum was created in partnership with Nephrologists, Intensivists, Clinical Nurse Educators and Clinical experts from our industry supplier. Education and certification include lectures as well as simulation. Annual competency sessions are scheduled to help with continued competency.

Since the inception of the program in 2009, 93 patients have received dialysis for a total of 704 SLED treatments. Overall survival to ICU discharge is 61 percent, and a number of aborted due to technical complication is 74. Although there have been a number of challenges related to variable patient volumes, maintenance of competence and access to chronic dialysis facilities for patient who do not recover renal function ,our program has significant strengths. These include high staff satisfaction, tremendous cost efficiency due to a single nurse providing all aspects of care during dialysis treatment, and the ability to avoid costly and disruptive transfers of unstable patient with AKI to other facilities. Given the comparable survival of our patient to that in the literature, our program demonstrates that ICU nurses are able to safely and independently provide intermittent dialysis to critically ill patient with AKI. This model should be considered in other hospitals that lack a chronic dialysis program.