Neutrophil gelatinase-associated lipocalin: a novel biomarker in laboratory medicine with many faces

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NGAL in Medicine

• Todays problems and the Clinical Challenges

• Actual and Possible Clinical Applications
  – Acute kidney injury (AKI)
  – New use of NGAL in AKI diagnosis – the NGAL ratio
  – ICU (early detection of AKI in sepsis)
  – Chronic kidney diseases (CKD)
  – Proteinuria
  – Quick walkthrough
    - immune mediated diseases
    - cardiovascular diseases
    - metabolic diseases
    - neoplasias
    - anemia

• Economic impact of NGAL measurements

• Search for possible answers to the AKI problem

• Answers and Conclusions
AKI diagnosis with NGAL is possible as early as 6h after the insult

Can Intervention here change the course?

Serum Creatinine
AKI onset
RRT initiation

Urinary NGAL

Surgical patients with/without developed AKI after surgery

Patient 1. 21 days in ICU X 1770 euros per day = 37170
Patient 2. 3 days in ICU X 1770 euros per day = 5130
CLINICAL CHALLENGES
(WHAT THE CLINICIANS ARE FACED WITH)
Why some studies report a moderate or poor performance

- Decisions in all clinical settings are still based on serum creatinine results
- Poor Definitions of AKI
  - do not incorporate a marker of tubular damage
  - dependent on serum Creatinine
- Complexity of clinical populations (ICU, medical, surgical, trauma, cardiac)
- Confounders
  - Presence of sepsis (the production of systemic NGAL in such populations and accumulation in urine while the kidney produces its own NGAL may cause difficulties in evaluation)
  - Creatinine is under produced in sepsis therefore this population may be examined with different criteria.
  - Baseline creatinine is most of the time unknown or difficult to estimate accurately in ICU or ED patients (trauma)
- AKIN criteria may be overly sensitive esp. in those with CKD where small changes in creatinine result in proportionally smaller changes in GFR (that’s why the improved performance in the sub population with GFR>75)
**Table 2: Comparison of biochemical markers between septic patients and nonseptic patients.**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Septic pts (N = 56)</th>
<th>Nonseptic pts (N = 42)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (%)</td>
<td>33.9</td>
<td>66.7</td>
<td>0.0013</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69 (48.7 to 74.2)</td>
<td>67 (59 to 75)</td>
<td>0.83</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.64 (1.04 to 2.97)</td>
<td>1.0 (0.8 to 1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NGAL (ng/mL)</td>
<td>459 (213 to 744)</td>
<td>120 (79 to 174)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AOPP (μmol/L)</td>
<td>505.1 (307.6 to 643.5)</td>
<td>115.7 (79.2 to 181.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>409 (212 to 673)</td>
<td>135 (61 to 275)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sofa score</td>
<td>10 (8 to 12)</td>
<td>5 (4 to 5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Died (%)</td>
<td>32.1</td>
<td>16.7</td>
<td>0.08</td>
</tr>
</tbody>
</table>

NGAL: neutrophil gelatinase-associated lipocalin; AOPP: advanced oxidation protein products; BNP: brain natriuretic peptide; SOFA score: sequential organ failure assessment.
AKI is underestimated by the use of sCreatinine in our AKI criteria
Questions pending

• **Is this the right time to use NGAL in our panel of markers for the evaluation of kidney function pre and post operative in surgical patients?**

• **What information we get from the lab?**

• **What are we planning to do with the information we get?**
NGAL IN ACUTE KIDNEY INJURY
Accuracy of NGAL in diagnosis and prognosis of AKI

- Analyzed data from 19 participants with 23 datasets from 8 countries
- Involved 2538 patients of whom 487 (19.2%) developed AKI
- Settings
  1. **Time of insult known**: cardiac surgery, PCI (contrast administration)
  2. **Time of insult unknown**: ICU patients, emergency department
- Pediatric and adult populations
- **Definition of AKI**: creatinine criteria of the RIFLE classification
- **Endpoints**: AKI development, RRT initiation, in-hospital mortality

Haase et al. (2009 vol54, 1012-1024 Am J Kidney Dis)
Accuracy of NGAL in diagnosis and prognosis of AKI

For AKI diagnosis

- Urine seems to be the most appropriate sample
- A cut-off value of 150 ng/mL was determined as optimal for AKI diagnosis in this study
- The diagnostic accuracy was better in children than in adults
- But, with no mention of:
  1. on baseline NGAL value,
  2. Biological variation
  3. On other pathological comorbidities or physiological situations that affect the NGAL levels in serum and urine

Haase et al. (2009 vol54, 1012-1024 Am J Kidney Dis)
Accuracy of NGAL in diagnosis and prognosis of AKI

For RRT prediction and in hospital mortality

- RRT incidence was 4.3%
  - AUC-ROC for RRT initiation 0.782
- In-hospital mortality was 5.4%
  - AUC-ROC for in-hospital mortality 0.706
- Optimal cut-off values here were:
  - 278 ng/mL (141-381) for RRT initiation
  - 212 ng/mL (121-506) for in-hospital mortality

Haase et al. (2009 vol54, 1012-1024 Am J Kidney Dis)
The aim of this study was to test the hypothesis that, without diagnostic changes in serum creatinine, increased NGAL levels identify patients with subclinical AKI and therefore worse prognosis.

- We analyzed pooled data from 2,322 critically ill patients with predominantly cardiorenal syndrome from 10 prospective observational studies of NGAL
- We used the terms NGAL(-) or NGAL(+) according to study-specific NGAL cutoff for optimal AKI prediction and
- the terms sCREA(-) or sCREA(+) according to consensus diagnostic increases in serum creatinine defining AKI
The Outcome of Neutrophil Gelatinase-Associated Lipocalin-Positive Subclinical Acute Kidney Injury
A Multicenter Pooled Analysis of Prospective Studies

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Baseline Characteristics of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NGAL(−)/sCREA(−)</td>
</tr>
<tr>
<td>n</td>
<td>1,296 (55.8%)</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>47.2 (4.5–61.6)</td>
</tr>
<tr>
<td>Female</td>
<td>475 (36.7%)</td>
</tr>
<tr>
<td>Chronic kidney disease*</td>
<td>143 (11.0%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>113 (8.7%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>67 (5.2%)</td>
</tr>
<tr>
<td>Peak NGAL, ng/ml</td>
<td>59 (20–97)</td>
</tr>
</tbody>
</table>

n = 2,322. Values given as n (%) or median (25th to 75th percentiles). *As defined by estimated glomerular filtration rate <60 ml/min/1.73 m² with the modification of diet in renal disease study formula (24,25).

Haase et al. (J Am Coll Cardiol 2011;57:1752–61)
The Outcome of Neutrophil Gelatinase-Associated Lipocalin-Positive Subclinical Acute Kidney Injury

A Multicenter Pooled Analysis of Prospective Studies

Figure 3

Incidence of Events

Incidence of RRT initiation, in-hospital mortality, and a combination of both according to NGAL and sCrea. There was a stepwise increase in all outcomes. Abbreviations as in Figures 1 and 2.

Haase et al. (J Am Coll Cardiol 2011;57:1752–61)
The Outcome of Neutrophil Gelatinase-Associated Lipocalin-Positive Subclinical Acute Kidney Injury

A Multicenter Pooled Analysis of Prospective Studies

Figure 4

Median LOS In ICU

Length of stay (LOS) stratified by NGAL and sCREA in the intensive care unit (ICU) (A) and in-hospital (B). There was a stepwise increase in median LOS in ICU and in-hospital. Abbreviations as in Figures 1 and 2.
In the absence of diagnostic increases in serum creatinine, NGAL detects patients with likely “subclinical” AKI who have an increased risk of adverse outcomes.

The concept and definition of AKI needs re-assessment

Haase et al. (J Am Coll Cardiol 2011;57:1752–61)
New use of NGAL in AKI

An unpublished study of stroke patients
Study details

- **Prospective study:** 100 patients with acute stroke (75 ischemic, 25 intracerebral hemorrhages)
- Twenty healthy individuals served as controls.
- Blood samples were taken at the time of admission (1), 24h (2), 48h (3), 72h (4) and finally at performed on day 7 (5) post admission.

AKIN definition
- **abrupt (within 48hours) reduction of kidney function** characterized by
  - an absolute increase in serum creatinine of either >0.3mg/dL (>25μmol/L)
  - or a percentage increase of >50% from baseline
  - or a reduction in urine output (documented oliguria >0.5ml/kg per hour for a period >6hours)

- **Plus:**
  A urinary biomarker of tubular damage to be positive
  NGAL - >150 ng/mL
Incidence of AKI

- A total 24 (24 %) patients developed AKI
  - 5 presented with AKI (on admission)
  - 19 developed AKI during hospitalization
- 11 showed a significant increase in uNGAL without an increase in sCrea
Serial changes of uNGAL and sCrea

- **Means of uNGAL**
  - AKI 0
  - AKI 1
  - AKI 2
  - AKI 3

- **Means of sCrea**
  - AKI 0
  - AKI 1
  - AKI 2
  - AKI 3
Changes of NGAL levels and outcome

<table>
<thead>
<tr>
<th>outcome</th>
<th>No AKI</th>
<th>AKI</th>
<th>sCrea-ve/uNGAL+ve</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Survivors</td>
<td>42</td>
<td>7</td>
<td>7</td>
<td>56</td>
</tr>
<tr>
<td>Non-survivors</td>
<td>21</td>
<td>17</td>
<td>4</td>
<td>42</td>
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<tr>
<td>Total</td>
<td>63</td>
<td>24</td>
<td>11</td>
<td>98</td>
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</table>

Means of uNGAL

Means of sNGAL

Means of SUNR ratio
Changes of NGAL levels and stroke severity

<table>
<thead>
<tr>
<th>mRS_severity group</th>
<th>No AKI</th>
<th>AKI</th>
<th>sCrea-ve/uNGAL+ve</th>
<th>Total</th>
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<tbody>
<tr>
<td>Low</td>
<td>35</td>
<td>6</td>
<td>5</td>
<td>46</td>
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<tr>
<td>Moderate</td>
<td>12</td>
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<td>2</td>
<td>16</td>
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<tr>
<td>high</td>
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<td>16</td>
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<td>36</td>
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<tr>
<td>Total</td>
<td>63</td>
<td>19</td>
<td>11</td>
<td>98</td>
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**Means of sNGAL**

<table>
<thead>
<tr>
<th>mRS_sg</th>
<th>1</th>
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**Means of uNGAL**

<table>
<thead>
<tr>
<th>mRS_sg</th>
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**Means of SUNR**

<table>
<thead>
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<td>3</td>
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ICU (Early detection of AKI)
Septic vs non-septic AKI

- Discrimination of septic and nonseptic AKI may be clinically relevant
- Recent evidence suggested that septic AKI may be characterized by a distinct pathophysiology
- Septic AKI may be unique and, as such, may have differences in clinical outcomes and responses to interventions when compared with nonseptic AKI
- Few clinical studies have focused on the presentation, profile, and outcome of septic AKI
What happens with NGAL in sepsis?

• Sepsis sharply increases the expression of mRNA coding for NGAL in leukocytes

• Severe sepsis resulting in impaired kidney function increases NGAL expression AND in renal epithelial cells very early in the course of acute tubular injury esp. when sepsis is caused by bacterial infection

• Thus NGAL levels increase in both serum and urine in patients with sepsis
Possible use of NGAL in sepsis

PlasmaNGAL/urineNGAL Ratio could be a tool to assess the origin of the NGAL response
   i.e. pre-Renal vs intra-Renal

Needs more investigation in combination with changes to the AKI definitions. UTI’s may confound this use
NGAL in chronic kidney diseases
NGAL in chronic kidney diseases

• **Hypothesis:** chronic renal damage could influence the physiological balance of NGAL in a way similar that observed for acute injury conditions

• **Result:** chronically damaged tubular cells will produce large quantities of NGAL

• Levels of observed NGAL is not the result of decreased protein clearance due to tubular impairment but

• the active chronic-stress induced production of this protein by the same injured cells
The forest fire theory

• In general, to evaluate the severity of renal failure, at least two aspects should be considered
  1. the ratio of functional versus atrophic nephrons (or the results of kidney injury)
  2. and the severity of on-going damage.
Hypothesis: sNGAL may represent a biomarker for quantitation of CKD

Subjects: 45 children with CKD stages 2–4

Measurements: sNGAL, serum cystatin C, GFR by Ioversol clearance, and eGFR by Schwartz formula

Results: sNGAL significantly correlated with cystatin C (r =0.74). Both NGAL and cystatin C significantly correlated with measured GFR (r=0.62, and r=0.71) as well as with eGFR (r=0.66 and r=0.59).

At GFR levels of ≥30 ml/min sNGAL, cystatin C, and eGFR were all significantly correlated with measured GFR. However, in subjects with lower GFRs (<30ml/min), sNGAL correlated best with measured GFR (r=0.62), followed by cystatin C (r=0.41).

Conclusion: (a) both sNGAL and cystatin C may prove useful in the quantitation of CKD, and (b) by correlation analysis, NGAL outperforms cystatin C and eGFR at lower levels of measured GFR.

Mitsnefes et al. (2007 vol22, 101-108 pediatric nephrology)
NGAL in chronic kidney diseases

• **Hypothesis:** test the clinical significance of measuring sNGAL and uNGAL on CKD
• **Subjects:** 85 children with renal dysfunction (GFR<90mL/min), proliferative glomerulonephritis steroid sensitive and resistant nephrotic syndrome and tubular dysfunction and 24 controls
• **Results:** uNGAL significantly higher in all these groups compared to controls.
  • Both s and uNGAL showed significant inverse correlations with GFR
  • Proteinouria significantly correlated with uNGAL
  • The highest uNGAL values were observed in the tubular dysfunction group
• **Conclusion:** uNGAL is a better biomarker for CKD than sNGAL.

Nishida et al. (2010 vol52, 563-568 pediatrics international)
Significance of NGAL in CKD

- Increased plasma and urine NGAL is produced by the “inflamed”, but viable, tubular cells
  whereas

- The increased serum creatinine levels and decreased GFR are the passive result of the loss of functional cells or nephrons

- NGAL is a real-time indicator of how much active kidney damage is occurring within the overall condition of CKD
NGAL in proteinuria
NGAL in proteinuria

- Patients with proteinuria have been observed to show increased uNGAL levels even without clinical signs of overt CKD.

- Also reported that patients with persistent severe macroproteinuria can have a stable and significant increase in uNGAL levels up to 500-fold compared with age-matched healthy controls independently of residual renal function.

Bolignano et al. (2008 vol31 255-258 kidney blood press res)
What is the effect of albuminuria in the development and the severity of AKI

- We studied patients undergoing elective surgery of abdominal aortic aneurysm repair.
- Total number of patients = 126
  - Mean age 69.2 years
  - Male= 117
  - Female= 6
Patient follow-up

• A baseline measurement before surgery
  (serum, plasma and urine samples were collected)

• Immediately post-surgery (mean time 2 hours)
  (serum and plasma samples were collected)

• At 6-hours, 24-hours, 48 hours and at the end of the week
  (serum, plasma and urine samples were collected)

• AKI was diagnosed with AKIN criteria

• AKI was diagnosed in 27 patients (21.43%)
Correlation of urine NGAL levels with ACR

- Positive ($r=0.549$) and significant correlation between ACR and uNGAL levels.
Baseline mean urine NGAL levels among the three albuminuria groups in patients who...

Did not develop AKI
1 = ACR < 100
2 = ACR 100-300
3 = ACR > 300

Developed AKI
Changes in urine NGAL levels among the three albuminuria groups in AKI positive patients

- Did not develop AKI
- 1= ACR <100
- 2= ACR 100-300
- 3= ACR >300
- Developed AKI
Baseline mean urine NGAL levels among the two sCrea groups in patients who...

Did not develop AKI
0 = sCrea < 1.0 mg/dL
1 = sCrea > 1.0 mg/dL

developed AKI
Changes in urine NGAL levels among the two sCrea groups in AKI+ and AKI-patients

Means of uNGAL

Did not develop AKI
0 = sCrea < 1.0 mg/dL
1 = sCrea > 1.0 mg/dL

devolved AKI
0 = sCrea < 1.0 mg/dL
1 = sCrea > 1.0 mg/dL
NGAL in
- immune mediated diseases
- cardiovascular diseases
- metabolic diseases
- neoplasias
(- anemia)
NGAL in immune mediated diseases

- **Hypothesis:** uNGAL excretion may represent a novel biomarker for the identification and quantitation of childhood onset of SLE nephritis (relationship between uNGAL and disease activity)
- **Subjects:** 35 (pSLE) and 8 idiopathic arthritis (JIA)
- **Results:** uNGAL were significantly increased in subjects with pSLE compared with those with JIA
- **uNGAL were strongly to moderately correlated with disease activity and renal damage**
- **Levels > 0.6 ng/mg uCrea identified onset of SLE with 90% sensitivity and 100% specificity**
- **Conclusion:** NGAL in urine but not in plasma represents a novel biomarker for renal disease activity in pSLE

Brunner et al. (2006 vol54, 2577-2584 arthritis reumatism)
NGAL in immune mediated diseases

**Hypothesis:** NGAL is an early predictive biomarker of disease activity in lupus nephritis

**Subjects:** 85 (pSLE) 50 healthy 30 idiopathic arthritis (JIA)

**Results:** Plasma and urinary NGAL were significantly increased in subjects with pSLE compared with those with JIA or with healthy controls

**pNGAL** increased with worsening disease but to a much lesser degree than **uNGAL**

**Conclusion:** NGAL in urine but not in plasma represents a novel biomarker for renal disease activity in pSLE

Suzuki et al. (2008 vol23, 403-412 pediatric nephrology)
NGAL as a biomarker of cardiovascular disease

- Recent evidence suggests that NGAL plays a crucial role in vascular remodeling and plaque instability in atherosclerosis.
- Recent studies demonstrate that NGAL is upregulated in cardiomyocytes in failing myocardium.
- Elevated NGAL levels have been reported in various cardiovascular conditions, including both acute and chronic heart failure (AHF, CHF), coronary heart disease (CHD), stroke, advanced carotid atherosclerosis, and abdominal aortic aneurysms.
- These findings provide biological plausibility for the potential role of NGAL as a biomarker in cardiovascular disease (CVD).
- The overall relationship between NGAL and CVD remains unclear.

Cruz et al. (Clin Chem Lab Med 2012;50(9):1533–1545)
Makris et al. (Clin Chem Lab Med 2012;50(9):1519–1532)
Clinical studies with NGAL as a biomarker of cardiovascular disease

**Acute heart failure (AHF)**

- The GALLANT study \( n = 186 \) looked at the prognostic value of plasma NGAL at the time of hospital discharge.
- Discharge plasma NGAL level was a stronger predictor of 30-day outcome (all-cause death and HF readmissions) than BNP (adjusted HR for NGAL, 19.91, 95% CI 3.47 – 114.19 vs. adjusted HR for BNP, 2.33, 95% CI 0.93 – 5.79).
- NGAL is not only a risk predictor for renal injury but is an overall strong risk marker for cardiac events in the setting of AHF.

Cruz et al. (Clin Chem Lab Med 2012;50(9):1533–1545)
Makris et al. (Clin Chem Lab Med 2012;50(9):1519–1532)
Clinical studies with NGAL as a biomarker of cardiovascular disease

**Acute heart failure (AHF)**

- There is preliminary evidence that elevated admission serum NGAL levels predict worsening renal function in patients with AHF, with AUC-ROC curve ranging from 0.70 to 0.93.
- sNGAL values observed in HF and CHD patients are relatively lower compared to those seen in AKI, particularly in cardiac surgery and ICU patients.
- **Hint:** Recent evidence suggests that the monomeric molecular form of NGAL is associated more closely with AKI – therefore a more specific assay targeting the monomeric form, with an extended range, may be more appropriate for diagnosing renal injury, particularly in CVD patients.


Aghel A, et al. (J Card Fail 2010;16:49 – 54)
Clinical studies with NGAL as a biomarker of cardiovascular disease

**Coronary heart disease (CHD)**

- NGAL was significantly higher in 49 patients with angiographically confirmed CHD when compared to 42 age-, gender-, and BMI-matched controls (82.6 ng/mL in CHD vs. 43.8 ng/mL in controls, p < 0.001)

- A positive correlation between serum NGAL and body weight, fasting insulin levels and insulin resistance, and a negative correlation with high density lipoprotein (HDL) levels was observed

- Statistically significant correlations between NGAL levels and the number of *diseased vessels* (r = 0.39, p = 0.01) and the severity of CHD, as indicated by the *modified Gensini score* (r = 0.356, p = 0.002)

Cruz et al. (Clin Chem Lab Med 2012;50(9):1533–1545)

Makris et al. (Clin Chem Lab Med 2012;50(9):1519–1532)
NGAL in neoplasia

- Recent evidence indicate that NGAL is induced in a number of human cancers where it often represents a predictor of poor prognosis.
- Lipocalins are overexpressed in a variety of human cancers including breast, colorectal, ovarian and pancreatic cancers.
- Lipocalin ligands have been shown to regulate proliferation, differentiation and protease activities.
- NGAL has been reported to be expressed in malignant tumors arising from several organs including the skin, thyroid, breast, ovary, endometrium, colon, lung, liver, bile ducts, esophagus, stomach and pancreas.
- Several studies have investigated the level of circulating NGAL in the blood (plasma or serum) as a potential marker for the detection and prognostication of both solid tumor and hematologic malignancies.

Makris et al. (Clin Chem Lab Med 2012;50(9):1519–1532)
NGAL in anemia

- It has been shown that there is a close link between human lipocalin and several white blood cell disorders
- Recent studies demonstrated that NGAL plays a key role in the physiology and pathophysiology of red blood cells
- Recent reports have implicated NGAL upregulation as a mechanism that contributes to anemia in the setting of chronic inflammation (CI)
- Several systemic diseases are associated with the presence of secondary anemia (CKD, HF, CI)

Bolignano et al. (Med Sci Monit 2010;16(6):RA131-135)
Makris et al. (Clin Chem Lab Med 2012;50(9):1519–1532)
Association between sNGAL and anemia relative hypochromia and inflammation in chronic systolic HF

- Plasma NGAL levels were inversely correlated with indices of anemia

Shrestha et al. (Congest Heart Fail 2012;18:239-244)
Economic considerations of AKI
Impact of AKI: Health resources / costs

Treatment of AKI: $8 billion / year in US

NHS Kidney Care

Estimated costs of AKI to the NHS in England 2009 – 2010:

- Acute admissions: £151m - £203m
- Critical Care: £141m - £217m
- Renal replacement therapy: £142m - £200m
Costs and projected cost savings by testing NGAL on admission to the ED

- Search for possible answers to the AKI problem-
Possible treatments

• Furosemide in Early Acute Kidney Injury (SPARK)
• Recombinant Human Erythropoietin Use in Intensive Care Unit (ICU) Patients: Does it Prevent Acute Renal Failure
• Fenoldopam for Prevention of Acute Kidney Injury (FANCY)
• Efficacy of Erythropoietin to Prevent Acute Kidney Injury in Chronic Kidney Disease Patients Undergoing Cardiac Surgery

www.clinicaltrialals.gov
Clinical studies with NGAL as a biomarker of AKI

**When the time of injury is known**
- Cardiac surgery
- Vascular surgery (programmed abdominal aortic aneurysm repair)
- Administration of contrast media (CIN) or toxic drugs.

**When the time of injury is not known**
- AKI in ICU patients
- After multiple trauma
Clinical trials that use NGAL in order to prove the efficacy of treatment

- Early detection and intervention using NGAL may improve renal outcome of acute contrast media nephropathy (anti-CIN study)

Study protocol published in BMC nephrology 2011 12:39
Saving Patients and Money with NGAL

<table>
<thead>
<tr>
<th>Serum Creatinine</th>
<th>Urinary NGAL</th>
</tr>
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<tbody>
<tr>
<td>AKI onset</td>
<td>AKI onset</td>
</tr>
<tr>
<td>diagnosis</td>
<td>diagnosis</td>
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<tr>
<td>RRT initiation</td>
<td>Can Intervention here change the course?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICU Price 1770 per day - sCreat diagnosis</th>
<th>Clinical impact</th>
<th>Economic Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 days in ICU = Total 37170</td>
<td>Early detection – stop sCreat from rising</td>
<td>Up to 35410 Euro saved</td>
</tr>
<tr>
<td>3 days in ICU = Total 5130</td>
<td>Early dismissal from hospital/ward</td>
<td>Up to 3540 Euro saved</td>
</tr>
</tbody>
</table>
Answers and Conclusions

• Urine NGAL results need careful interpretation

• “Low” NGAL levels can be used safely to dismiss patients – a diagnostic exclusion criteria

• In cases where uNGAL seems to be elevated compared to baseline or elevated at admission serum levels must be checked

• Inflammation and various comorbidities that affect systemic levels must investigated
Answers and Conclusions

• plasmaNGAL to urineNGAL Ratio seems to be useful in certain indications

• The use of creatinine is completely inaccurate in several clinical settings e.g. ICU patients with sepsis and therefore useless

• The time seems right for a biomarker, which is specific for tubular damage, to be included in the diagnostic criteria of AKI

• We need studies with therapeutic interventions where the endpoints are going to be evaluated with NGAL