Acute kidney injury (AKI)
An imposing medical and diagnostic challenge

- >13 million AKI patients each year
- ~30% with fatal outcome
- Cardiac surgery
  - >1 million patients/year in US and EU alone
  - 20-40% of which suffer from some degree of AKI
The impact of AKI
Current medical practice in England

Complications from AKI
Missed 13%
Avoidable 17%
Badly managed 22%

43% AKI recognition delay post-admission
Unacceptable

50% of AKI care is considered “good”
Unacceptable

36% had inadequate AKI risk assessment
Unacceptable

20% AKI patients missed nephrology referral
Unacceptable

NCEPOD Report 2009
AKI today: An urgent need for earlier identification

Delay in AKI identification

- Acutely unwell patients are not being diagnosed
- Increased hospital stay, re-admissions, and lower patient QOL
- Annual cost of AKI-related inpatient care in England estimated at £1.02 billion

“Annual number of excess inpatient deaths associated with AKI in England may be above 40,000”

*The economic impact of acute kidney injury in England, Kerr et al. 2014*
Rapid Loss of Kidney Function = Acute Kidney Injury or AKI

**Historic definitions**

- AKI – *was* previously known as “acute renal failure” or ARF - defined by a rapid loss of kidney function, which includes:
  - Rapid time course (< 48 hours)
  - Rise in serum creatinine (24-72 hours after AKI)
  - Reduction in urine output (oliguria)
  - More than 90 diagnostic definitions of AKI exists

- Serum creatinine is used as a marker in almost all definitions

**Today’s definitions**

- The gold standard marker is still serum creatinine
  - Responds late (24-72 hours after AKI)
  - As much as 50% of kidney function can be lost at that time
  - Creatinine is insensitive and unspecific
  - Rise in serum creatinine is affected by non-renal factors such as age, gender, weight, race and other factors

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A need for injury-associated biomarkers for AKI

Prof. Dr. Claudio Ronco, Vicenza, Italy
Prof. Dr. Kai M. Schmidt-Ott, Charité, DE
NGALTest – changing diagnosis

Serum Creatinine – standard of care 2015

- >13 million AKI patients each year*
  - ~ 30% with fatal outcome
  - Deadly & Costly
  - Up to 4 million related deaths

Acute Kidney Injury (AKI)

2015: AKI Diagnosed 48-72 hrs. after injury

Early AKI biomarker (2 hours)

NGAL: AKI Diagnosed 2 hours after injury

Early diagnosis

Improved patient management

Individualised therapies initiated

Improved Outcome

Lower hospitalization costs

Improve patient health and QOL

UNIQUE OUTCOME

NGAL

Measure NGAL levels in blood & urine

Diagnosis of patients with or at risk of AKI

Improved Outcome

BioPORTO Diagnostics
2014 – Serum Creatinine used as Acute Kidney Injury biomarker

Serum Creatinine is measured

NO diagnostic measurement
AKI is non-reversible

48-72 Hours

NGAL is measured
NGAL – diagnostic measurements
AKI is reversible

Window of opportunity

Normal → Risk ↑ → Damage → GFR ↓ → Kidney Failure → Death

NGALTest – Changing diagnosis

NGALTest – NGAL used as Acute Kidney Injury biomarker
## Acute Kidney Injury vs. Heart Attack

### Table: Acute Myocardial Infarction vs. Acute Kidney Injury

<table>
<thead>
<tr>
<th>Period</th>
<th>Acute Myocardial Infarction</th>
<th>Acute Kidney Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960s</td>
<td>LDH</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>1970s</td>
<td>CPK, myoglobin</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>1980s</td>
<td>CK-MB</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>1990</td>
<td>Troponin T</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>2000s</td>
<td>Troponin I</td>
<td>Serum creatinine / Cystatin C</td>
</tr>
</tbody>
</table>

### Diagram:

- **Injury biomarkers**
  - Early effective Therapies
  - Mortality

- **Functional biomarkers**
  - Only supportive Care
  - High Mortality
What is NGAL?

NGAL - Neutrophil Gelatinase-Associated Lipocalin

- Small secreted protein ~ 25 kDa protein
- Expressed in many tissues
- Protease resistant
- Secretion in high levels into blood and urine upon injury of the kidney (within 2 hours or less)
- Slightly increased expression in inflammation, infection and certain cancers. However, it stays below the cut-off for AKI diagnosis
Clinical application of NGAL

Cardiopulmonary bypass surgery (CPB)
– Monitoring NGAL before and after CPB reveals AKI that may result from the procedure

Renal transplantation
– Post-transplant NGAL levels provide clear predictive evaluation of graft function and survival
Clinical application of NGAL: 1st clinical area of utility

Cardiopulmonary bypass surgery (CPB)

- Monitoring NGAL after CPB represents an early predictive biomarker of AKI

**Neutrophil gelatinase-associated lipocalin (NGAL) for the early detection of cardiac surgery associated acute kidney injury**


**Temporal Relationship and Predictive Value of Urinary Acute Kidney Injury Biomarkers After Pediatric Cardiopulmonary Bypass**

Krawczeski et al 2011 J Am Coll Cardiol 22;58(22):2301-9

**Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study**

NGAL: Classify more patients with AKI

NGAL: Clinical utility

<table>
<thead>
<tr>
<th>NGAL (+) Crea (-)</th>
<th>VS.</th>
<th>NGAL (-) Crea (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 times more likely to need dialysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.6 times more likely to die during hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 extra days in ICU, 8 extra days in hospital</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A re-assessment of the concept and definition of AKI is needed

Haase, Ronco et al., J Am Coll Cardiol. 2011
Clinical application of NGAL: 2nd clinical area of utility

Renal transplantation

- Post-transplant NGAL levels provide clear predictive evaluation of graft function and survival

Reviews on NGAL and renal transplant

Neutrophil Gelatinase-Associated Lipocalin: Ready for Use? An International Perspective

Neutrophil gelatinase-associated lipocalin as a biomarker of acute kidney injury: a critical evaluation of current status

Scientific papers

- Plasma neutrophil gelatinase-associated lipocalin in kidney transplantation and early renal function prediction
- Bataille A et al, Transplantation Nov 15;92(9):1024-30

- Urinary neutrophil gelatinase-associated lipocalin accurately detects acute allograft rejection among other causes of acute kidney injury in renal allograft recipients

- Neutrophil gelatinase-associated lipocalin is a sensitive biomarker for the early diagnosis of acute rejection after living-donor kidney transplantation.

NGAL level early and accurately predicted DGF after renal transplantation.

NGAL...accurately discriminates acute allograft rejection...
# Application Notes

<table>
<thead>
<tr>
<th>Company</th>
<th>Model</th>
<th>Urine</th>
<th>Plasma</th>
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</thead>
<tbody>
<tr>
<td>Roche</td>
<td>Hitachi 917</td>
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<td>Roche</td>
<td>Modular P</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Roche</td>
<td>Cobas c501/c502</td>
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<td>Olympus AU640</td>
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<td>Abbott</td>
<td>Architect</td>
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<tr>
<td>Beckman</td>
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</table>

Draft and customer derived application notes

<table>
<thead>
<tr>
<th>Company</th>
<th>Model</th>
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<th>Plasma</th>
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<tbody>
<tr>
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<tr>
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<td>OCD</td>
<td>Vitros</td>
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<td>?</td>
</tr>
<tr>
<td>Vital Scientific</td>
<td>Junior</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
How to use NGAL?

**NGAL to predict Acute Kidney Injury – Potential applications and limitations**

**Dr. Michael Haase**, Dept of Nephrology and Intensive Care Medicine, Charite University Medicine, Berlin

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**Fig. 4: Implications of urine NGAL**

**Implications of urine NGAL**

**Diagnosis**
- Diagnose AKI early
- Consult nephrologist early
- Admit or delay discharge from hospital

**Therapy**
- Intervene timely in relevant hypotension or hypovolemia
- Optimize hemodynamics after cardiac surgery
- Avoid nephrotoxic medication
- Commence or stop RRT earlier
- Non-invasive monitoring after renal transplantation
- Earlier double blockade of RAAS

**Prognosis**
- Predict clinical outcomes (RRT, DGF, mortality)

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**AKI:** acute kidney injury  
**RRT:** renal replacement therapy  
**RAAS:** renin angiotensin aldosterone system  
**DGF:** delayed graft function
Potential early treatment if NGAL is positive

Pharmacological interventions

- (Prolonged) Application of sodium bicarbonate?
- Prolonged Application of high-dose N-acetylcysteine in CIN?
- Natriuretic peptide, Fenoldopam, Sodium Nitroprusside or Clonidine?
- Statins?
- Avoidance/withdrawal of nephrotoxins like:
  - Aminoglycosides (e.g. Gentamicin)
  - Glycopeptide antibiotics (e.g. Vancomycin)
  - ACE inhibitors
  - NSAID’s
- Shock (loss of blood volume ~ perfusion)
  - Hemorrhagic
  - Hypovolemic
  - Septic

Non-pharmacological interventions

- Low threshold for
  - Nephrologist’s consultation
  - Hemodynamic monitoring
  - Hospitalization
- Optimization of cardiac index and mean arterial pressure
- Avoidance of cardiopulmonary bypass in cardiac surgery
  - Miniaturized cardiopulmonary bypass
- Earlier hemofiltration, extracorporeal blood purification
  (e.g. mediator removal in sepsis using large-pore membranes or new adsorbers)
- Non-invasive monitoring after kidney transplantation

NGAL to predict Acute Kidney Injury – Potential applications and limitations
Dr. Michael Haase,
Dept of Nephrology and Intensive Care Medicine, Charite University Medicine, Berlin
What if NGAL is negative?

A valuable component in decision-making on -

- Discharge home
- Transferral from ICU to normal ward or care
- Effective, inexpensive antibiotics
- Less frequent measurement of serum creatinine and urea
- Elaborate/arterial revascularization during cardiac surgery
- Guiding/waiving protocol biopsies in renal transplant patients
- Differential diagnosis of serum creatinine increase (AKI vs. prerenal azotemia and chronic kidney disease)

NGAL to predict Acute Kidney Injury – Potential applications and limitations

Dr. Michael Haase,
Dept of Nephrology and Intensive Care Medicine, Charite University Medicine, Berlin
NGAL reduces delayed AKI diagnosis and treatment

Hypothetical cohort of 10,000 patients with AKI

- **NYP-Allen Hospital**
  - uNGAL+Scr resulted in 1,578 fewer patients with delayed diagnosis and treatment than Scr alone (2,013 vs. 436 pts)

- **SIUH Hospital**
  - uNGAL+Scr resulted in 1,973 fewer patients with delayed diagnosis and treatment than Scr alone at (2,227 vs. 254 patients)
NGAL reduces overall costs

Although NGAL increases the initial evaluation costs with $50 USD overall costs are reduced

**NYP-Allen Hospital:** $408 saved per patient

**SIUH hospital:** $522 saved per patient
NGAL: Addressing the importance of early detection of AKI

NGAL

SERUM CREATININE

Normal → Increased risk → Damage → GFR↓ → Kidney failure → Death

Window of opportunity

INJURY → FAILURE
NGAL: Addressing unmet needs in early AKI detection

- AKI is a severe condition that may significantly worsen patients clinical outcomes
- AKI may significantly predisposes for progression towards ARF
- NGAL is an early urinary and plasma AKI biomarker
- NGAL levels rise 24-48 hrs. before serum creatinine
- NGAL is useful in ruling out AKI (very low NGAL) or ruling in AKI (very high NGAL)
NGAL: Clinical application and usefulness as expressed by experts

Prof. Dr. Kai M. Schmidt-Ott, Charité, DE

- NGAL measurements help guiding clinical decision-making in:
  - Patients undergoing CPB
  - Patients after kidney transplantation
  - Acutely admitted patients
    - In the ICU
    - In the ED

- NGAL is useful in ruling out (very low NGAL) or ruling in (very high NGAL) AKI
NGAL: Clinical application and usefulness as expressed by experts – CONCLUSIONS ED study

Prof. Dr. Kai M. Schmidt-Ott, Charité, DE

- Biomarkers identify patients with intrinsic AKI and predict poor outcomes
- NGAL shows the most consistent association with intrinsic AKI, severity of AKI and duration of AKI
- NGAL and KIM-1 perform best in identifying patients at risk of death or RRT requirement
- Combination of sCr with either uNGAL or uKIM-1 improves risk assessment in the ED
- > 220 patients at increased risk had low sCr, but high biomarker (uNGAL/uKIM-1)