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The Future of Noninvasive Monitoring:
Optimizing Fluid, Blood and Oxygen

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High-Risk Surgical Patients: Oxygen Delivery and Hemodynamic Strategies

Jean-Louis Vincent, MD, PhD
Professor of Intensive Care Medicine (Université Libre de Bruxelles)
Department of Intensive Care, Erasme University Hospital
President, World Federation of Intensive and Critical Care Societies (WFSICCM)

Oxygen Reserve Index (ORI™): Validation and Application of a New Variable

Thomas W.L. Scheeren, MD, PhD
Professor of Anaesthesiology, Head Cardiothoracic Anaesthesia
Department of Anaesthesiology, University Medical Center Groningen
Groningen, The Netherlands

Oxygen Delivery (DO2): An Oversimplified Concept?

Azriel Perel, MD
Professor of Anesthesiology and Intensive Care
Sheba Medical Center, Tel Aviv University
Tel Aviv, Israel

Location:
N Hall 5, ExCel Congress Center, London

Date and Time:
Sunday May 29th • 12:15pm - 1:45pm

Lunch will be provided

Chairperson:
Prof. Jean-Louis Vincent

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A

acute kidney injury (AKI) has been

recognised as a major public health

problem. It affects >50% of patients in

the Intensive Care Unit (ICU) and is associated

with serious short- and long-term complications,
premature death and high financial healthcare
costs (Mehta et al. 2015; Hoste et al. 2015;
Lewington et al. 2013). The consensus definition of
AKI has emerged from the Risk, Injury, Failure,
Loss, End-stage (RIFLE) criteria in 2004 and
the AKI Network classification in 2007 to the
most recent Kidney Disease Improving Global
Outcomes (KDIGO) classification in 2012
(Kidney Disease: Improving Global Outcomes
2012). Although these consensus criteria should
be considered a major success towards the stan-
dardisation of AKI, they are solely based on
serum creatinine and urine output, i.e. two
markers which are not kidney-specific and have
well-known limitations (Thomas et al. 2015).
In particular, serum creatinine can take 24–36
hours to rise after a definite renal insult, may
increase following administration of medications
that inhibit tubular secretion despite no change
in renal function, and is not reliable in patients
with sepsis, liver disease, muscle wasting or fluid
overload. It also does not provide any informa-
tion regarding the underlying aetiology. As such,
diagnosing AKI can be challenging, especially
in critically ill patients. The failure to detect AKI
early and the inaccuracy of AKI diagnosis are
reasons why the management of AKI is often
delayed and attempts to develop specific thera-
pies for AKI have not been successful. There is
general agreement that better tools are needed
to improve risk assessment, early detection and
management of AKI.

Types of Novel AKI Biomarkers

Biomarkers are defined as “characteristics that are
objectively measured and evaluated as indicators
of normal biologic or pathogenic processes,
or pharmacologic responses to a therapeutic
intervention” (Biomarkers Definition Working
Group 2001). An ideal biomarker for AKI should
be accurate, easy to measure at the point of care,
correlate with severity of injury, be sensitive
to early subclinical renal injury and affordable
(Belcher et al. 2011).

In the last 10 years, numerous different
substances in serum and urine have been iden-
tified and undergone evaluation as potential
biomarkers for AKI (Ostermann et al. 2012;
Charlton et al. 2014). They vary in their
characteristics that are

biomarkers for AKI (Ostermann et al. 2012;
Charlton et al. 2014). They vary in their

application, physiological function,
time of release after the onset of renal injury,
kine

ics and systemic distribution (Table 1).

Based on their physiological role, they can be
divided into markers of glomerular filtration
(i.e. serum creatinine, cystatin C), glomerular
integrity (i.e. albuminuria and proteinuria),
tubular stress [i.e. insulin-like growth factor
binding protein 7 (IGFBP-7), tissue inhibitor
metalloproteinase 2 (TIMP-2)], tubular damage
[i.e. neutrophil gelatinase-associated lipocalin
(NGAL), kidney injury molecule-1 (KIM-1),

liver fatty acid-binding protein (L-FAB) and

intra-renal inflammation (i.e. interleukin-18)
(Table 1).

Potential Benefits of Novel AKI

Biomarkers

Biomarkers for AKI have been studied in various
different patient cohorts, ranging from those
with a clearly defined renal insult (i.e. coro-
nary angiography or cardiac surgery) to patients
presenting to the emergency department or
critically ill patients in ICU where the onset of
renal injury is less clear. Most investigations have
focused on their ability to detect AKI earlier than
serum creatinine. The results are most impres-
sive in paediatric cohorts without comorbidities
suffering from an illness with a defined onset of

AKI, for instance in children after cardiac surgery.
In more heterogeneous populations, where the
onset of renal injury is not usually known and
comorbid factors exist, the performance is more
variable and sometimes equivalent to clinical
evaluation and standard laboratory measurements
(Vanmassenhove et al. 2013). Some biomarkers
have also been shown to correlate better with
severity of renal injury and important outcomes
like mortality and need for renal replacement
therapy than serum creatinine.

An important finding has been the identifica-
tion of patients with elevated biomarker levels
but no detectable change in serum creatinine
(Haase et al. 2011). These injury biomarker-
positive, creatinine-negative patients appear to
have a greater risk of complications, a longer
stay in ICU and a higher mortality compared to
patients without elevated biomarker level, which
implies the existence of a state of ‘subclinical
AKI’ where renal injury has occurred but the
glomerular function is still preserved. Whether
this phase of AKI represents a golden window

BIOMARKERS FOR ACUTE

KIDNEY INJURY

WHERE ARE WE NOW?
for effective therapeutic interventions will need to be investigated in future studies.

Finally the discovery of new functional and damage markers has broadened our understanding and provided invaluable insight into the pathophysiological processes involved in AKI from early injury to recovery. For instance, validation studies of the stress biomarkers IGFBP-7 and TIMP2 have highlighted the role of cell cycle and cell cycle arrest in the development and progress of AKI (Gomez et al. 2014).

Limitations of Novel Biomarkers

As indicators of normal biologic and pathogenic processes, the release of biomarkers following the original renal insult is dynamic and temporary. Therefore, the timing of measurement is very important and affects the interpretation of biomarker levels in serum or urine. Studies also vary in their chosen cut-offs for negative and positive predictive events related to AKI, which again contributes to the differences seen between reports. Another important limitation of biomarker research relates to the fact that in most studies the performance of novel biomarkers was compared with that of serum creatinine and oliguria, two markers which are not renal-specific and are considered to be inadequate for the diagnosis of AKI. So far, newer imaging techniques or methods to measure real-time glomerular filtration have not been used for the purpose of evaluating new biomarkers.

Use of Novel AKI Biomarkers in Clinical Practice

Some studies have shown very impressive results and clear indications that novel biomarkers have the potential to transform the way clinicians diagnose and manage patients with AKI. Commercial kits for measurement of cystatin C, NGAL, IGFBP7, and TIMP-2 are now available. However, some biomarkers of AKI, though approved for clinical utilisation, have not been extensively employed in the clinical setting. While reasonably good results are seen in the research setting, their performance in routine clinical practice is influenced by patient case mix, comorbidities, aetiology of AKI, the timing of renal insult, timing of biomarker measurement and the selected thresholds for diagnosis. The scarcity of evidence that biomarkers improve patient outcomes, the prohibitive cost and unavailability of point-of-care testing are additional barriers to their widespread routine use.

In the right setting, the new biomarkers have great potential. However, it is crucial to identify those patients who would benefit most. Some studies advertise the use of biomarkers in situations where the outcome already seems predictable based on clinical evaluation and standard physiological parameters (Vannmassenhove et al. 2013). Clearly, in this case, there is limited added benefit. Biomarkers should be regarded as a complement to routine assessment and be part of a decision tree. Indiscriminate application in patients at low risk of AKI would render the biomarker useless, as well as unnecessarily increase healthcare costs.

Future Roles of AKI Biomarkers

The discovery of new markers of glomerular and tubular function, tubular damage and inflammation allows a much better description and characterisation of AKI than traditional markers of renal function can offer. It is therefore very likely that they will be incorporated into future definitions and classifications of AKI, as proposed at the 10th Acute Dialysis Quality Initiative Consensus (ADQI) Conference (Murray et al. 2014) (Fig. 1).

As indicators of specific pathophysiological processes within the kidney, some of the new biomarkers also offer the opportunity to be used as diagnostic tools to identify the aetiology of AKI. However, a single biomarker is unlikely to be useful. Instead, a panel of functional and damage biomarkers in combination with traditional markers of renal function and clinical judgement will provide best results.
Some of these biomarkers also have the potential to facilitate the development of new drugs by indicating renal injury earlier than conventional methods. Collaborations between international centres and major pharmaceutical companies, the U.S. Food and Drug Administration and the European Medicines Agency have already begun, and rodent urinary and plasma biomarkers have been accepted as surrogates for renal histology for initial evaluation and monitoring of nephrotoxicity in drug development. Finally, there is some hope that some of the novel molecules may not only serve as diagnostic tools but also as potential therapeutic targets for the treatment of AKI.

**Conclusion**

Numerous novel functional and damage biomarkers for AKI have been discovered and validated. Current evidence supports the concept that they have potential to facilitate the early detection, differential diagnosis and management of AKI in appropriately selected patients. More research including intervention studies based on biomarker results, identification of the most appropriate patient groups and standardisation of testing is necessary to incorporate utilisation of biomarkers into routine clinical practice.

**Conflict of Interest**

Marlies Ostermann declares that she has no conflict of interest. Kianoush Kashani declares that he has no conflict of interest.

**Abbreviations**

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<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>AKI</td>
<td>Acute kidney injury</td>
</tr>
<tr>
<td>IGFBP-7</td>
<td>Insulin-like growth factor binding protein 7</td>
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<td>ICU</td>
<td>Intensive care unit</td>
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<td>KDIGO</td>
<td>Kidney Disease Improving Global Outcomes</td>
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<td>RIFLE</td>
<td>Risk, Injury, Failure, Loss, End-stage</td>
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<tr>
<td>TIMP2</td>
<td>Tissue inhibitor metalloproteinase 2</td>
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**References**


