Acute kidney injury: highlights from the ERA-EDTA Congress in London

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ABSTRACT

The ERA-EDTA 52nd Congress was held in London, 28–31 May 2015. In the scientific programme, overall, during the symposium, there were 18 lectures, 3 minilectures, 15 free communications and 135 poster presentations on acute kidney injury (AKI). Among many excellent reports and presentations, I selected three hot topics on AKI for the readership of Nephrology Dialysis Transplantation.

GLOBAL EPIDEMIOLOGY OF ACUTE KIDNEY INJURY

This critical issue was elegantly discussed by Norbert Lameire (Belgium) in the ‘0by25 symposium’. It was underlined that the incidence of acute kidney injury (AKI) is increasing not only in well-developed [1, 2] but also in developing countries worldwide. This critical finding was confirmed in two recent meta-analyses, which appeared in 2013 [3] and 2015 [4].

The first meta-analysis included more than 49 million patients, primarily in the hospital setting, between 2004 and 2012 [3]. The incidence of AKI showed considerable variation among many regions of the world, from 14 to 32%. Considering 154 studies, including 3 585 911 patients who adopted a KDIGO equivalent AKI definition [5], the pooled incidence rates of AKI were 21.6% in adults and 33.7% in children. In other words, one in five adults and one in three children experienced AKI worldwide during a hospital episode of care [3]. The major limitation of this meta-analysis was that most studies originated from high-income countries (HIC), while very few studies were from low/middle-income countries (LMIC) where 85% of the world population resides.

The second meta-analysis appeared this year in the Lancet, which added >300 reports to the previous one, and increased the sample size from 49 million to >77 million individuals [4]. Importantly, a wider geographic distribution was represented in this new report because it included data from several regions of Africa and Asia [6–9]. Preliminary analysis of this new database revealed that the pooled incidence of AKI, by KDIGO classification, was 21% of all hospital admissions. The overall proportion of patients with AKI who needed dialysis support was small (2% of all hospital admissions and 11% of all AKI patients), whereas 12% of all admissions (80% of all AKI cases) had KDIGO stage 1 disease. The overall pooled mortality rate was quite favourable (21%), very probably due to the predominance of mild stages of AKI. On the other hand, patients with more severe AKI, i.e., KDIGO stage 3 or those who required dialysis, had a higher mortality rate (42 and 46%, respectively) [4].

Interestingly, the features of the patients in HIC and LMIC differed significantly (Table 1).

Most importantly, AKI in LMIC is preventable and very inexpensive to treat, especially in the early stages, which formed the basis for the ‘0by25’ initiative by the International Society of Nephrology (http://www.0by25.org/).

AUTOMATED ELECTRONIC ALERTS (E-ALERTS) FOR AKI

At the London Congress, there were two oral presentations and two lectures on e-alerts. In this review, snapshots from Mark Devonald’s (UK) and P. Wilson’s (US) presentations will be presented.

Electronic alerts automatically and systematically identify all AKI episodes based on changes in serum creatinine and notify especially non-nephrologists about patients with AKI. The main aim of these alerts is to facilitate earlier recognition and treatment of AKI [10]. This system may stratify the patients using KDIGO, AKIN or RIFLE criteria and may also be used in combination with other tools, such as hospital-wide intranet AKI guidelines, an educational programmes and also an AKI care bundle, which may further optimize the treatment.

For assessment of the first serum creatinine (SCr) on admission, a comparison is made against the lowest SCr on record from 7 to 365 days prior to admission. When no SCr is available in this particular period, a comparison is made against a ‘theoretical’ SCr, calculated from the MDRD equation, assuming normal estimated glomerular filtration rate (eGFR) of 75 mL/min [11].

This alert can be conveyed to a clinician by a simple message alerting him/her about ‘high’ serum creatinine: this may be a passive alert (i.e., a page or an e-mail message), or a more active alert (i.e. a telephone call), or alternatively, an interruptive...
and are characterized by a high energy demand, they are one of the major organs in focus for clinical application of rIPC. In clinical practice, ischaemia for IPC can be induced by inflating the cuff of a sphygmomanometer to 200 mmHg or ≥50 mmHg higher than the systolic blood pressure [20].

Currently, the molecular mechanisms of rIPC are not clear; local ischaemia may stimulate a physiological response and activate some pharmacological, autacoid or neural triggers, which in turn may open ATP-sensitive K+ (K<sub>ATP</sub>) channels. This may lead to inhibition of mitochondrial permeability transition pore and reactive oxygen species, hence, protecting the kidneys. Furthermore, an antioxidant and anti-inflammatory response may also contribute to this protection via many other mechanisms [21, 22].

A meta-analysis of randomized controlled trials (RCTs) compared the incidence of AKI in patients undergoing cardiac and vascular surgery with or without rIPC and found that there was a trend towards decreased AKI in the rIPC cohort; however, this difference was not significant [23]. Therefore, a multicentre RCT was performed, entitled ‘Effect of remote ischaemic preconditioning on AKI among high-risk patients undergoing cardiac surgery’ by Alexander Zarbock (Germany), which was selected among the late breaking clinical trials by the London Congress. Overall, 240 high-risk patients (determined by the Cleveland Clinic Foundation score) undergoing cardiac surgery were included [20]. After randomization, anaesthesia was induced, and 5 min of ischaemia was initiated via inflating blood pressure cuff to 200 mmHg, followed by 5 min of reperfusion in one upper arm. Sham surgery was performed in the control group. The primary outcome was occurrence of AKI within the first 72 h after surgery. The trial revealed that incidence of AKI was significantly less (37.5 versus 52.5%; P = 0.02) in the rIPC group. Also, dialysis was less frequently needed (5.8 versus 15.8%; P = 0.01), and ICU stay was shorter (7 days versus 3 days; P = 0.04) in the intervention group. When the data were stratified by AKI stage, the number of moderate and severe cases of AKI was reduced with no difference in the rate of mild cases [20].

Biomarkers (inducers) of cell-cycle arrest [tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor–binding protein 7 (IGFBP7)] as well as urinary NGAL levels were measured to clarify the underlying mechanisms. Although baseline urinary TIMP-2 × IGFBP7 and NGAL levels were similar, the levels of these biomarkers increased immediately after rIPC (before cardiopulmonary bypass) as compared with the control group; at this stage, urinary NGAL levels did not increase. After the cardiac surgery, however, the urinary levels of all biomarkers decreased significantly in the rIPC arm compared with the sham group. It was suggested that TIMP-2 × IGFBP7 served as ‘alarm’ marker in the pre-surgery period but protected the cells from further damage after the surgery by inducing a transient cell-cycle arrest [20, 25].

In two very recent RCTs, however, upper-limb rIPC did not show a relevant benefit among patients undergoing elective cardiac surgery. Incidence of AKI (analysed either among the individual components of the composite primary end point or secondary end points of the studies) did not differ either [26, 27].

The reasons for the controversy among these three RCTs are obscure; differences in the study populations may be responsible for the inconsistent results.

### Table 1. Features of AKI in high-income and low-income countries

<table>
<thead>
<tr>
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<th>AKI in high-income countries</th>
<th>AKI in low- and middle-income countries</th>
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<tbody>
<tr>
<td><strong>Pattern of occurrence</strong></td>
<td>Occurs mostly in elderly ICU patients with multiple organ failure</td>
<td>Occurs in rural area hospitals; patients are often young, otherwise healthy people</td>
</tr>
<tr>
<td><strong>Disease patterns</strong></td>
<td>Usually associated with multiple organ failure, sepsis and complex surgery</td>
<td>Often caused by a single disease and specific infection (e.g. malaria); multiple organ failure less common</td>
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<tr>
<td><strong>Sufficiency of reporting</strong></td>
<td>Accurately reported</td>
<td>Severely under-reported</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>High mortality</td>
<td>Same or lower mortality than in high-income countries</td>
</tr>
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**EFFECT OF REMOTE ISCHAEMIC PRECONDITIONING ON AKI AMONG HIGH-RISK PATIENTS UNDERGOING CARDIAC SURGERY**

Following ischaemic insult, tissue damage continues after reperfusion [ischaemia reperfusion injury (IRI)]. Transient brief episodes of ischaemia before a prolonged IRI reduce the extent of organ damage [ischaemic preconditioning (IPC)] [17]. Local IPC can also protect distant tissues [remote IPC (rIPC)]. Thus, brief ischaemia induced in non-target tissues, most commonly in the upper arm, confers protection at a remote site such as the brain, lung, intestine, or skeletal muscle [18, 19]. Since kidneys have a very rich microvascular network and are characterized by a high energy demand, they are one of the reasons for the controversy among these three RCTs are obscure; differences in the study populations may be responsible for the inconsistent results.
To conclude, the protective effects of rIPC on AKI development are debated for the time being. If beneficial effects are confirmed, this very simple and potentially safe intervention may be used widely and may be valuable for decreasing morbidity and mortality in patients, who are at risk of developing AKI.

REFERENCES