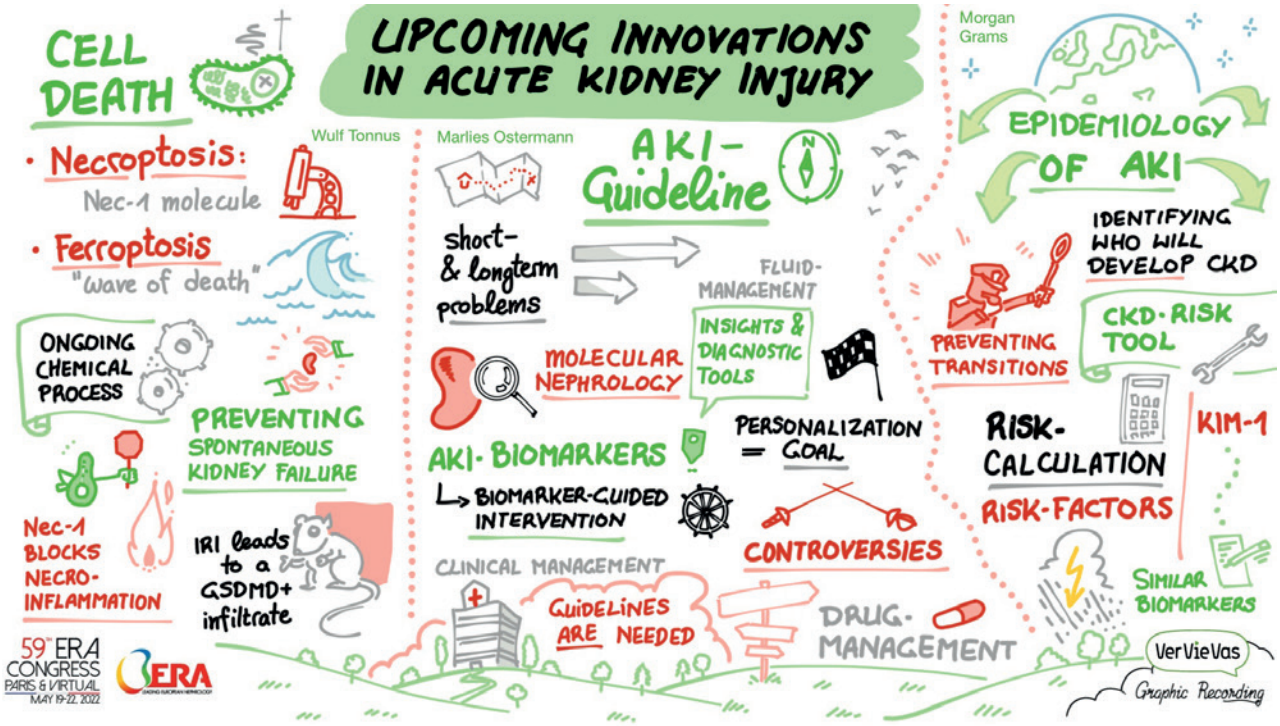
Symposium 8.1
Upcoming innovations in acute kidney injury



Deciphering the molecular mechanisms of necroinflammation in acute tubular necrosis

Wulf Tonnus, Germany

Cell death can occur in both physiological and nonphysiological conditions. Homeostasis is maintained by apoptosis, whereas most pathophysiologically important cell death is necrotic. Necrosis is defined as cell death by plasma membrane rupture, followed by a release of damage-associated molecular patterns (DAMPs) that trigger an immune response, referred to as necroinflammation. Regulated necrosis may come in the different forms including necroptosis, ferroptosis, and pyroptosis. These processes trigger a necro-inflammatory environment which may cause organ failure. Recent studies highlight these pathways as potential, but still neglected, therapeutic targets for the prevention of necrosis, inflammation, and organ failure.

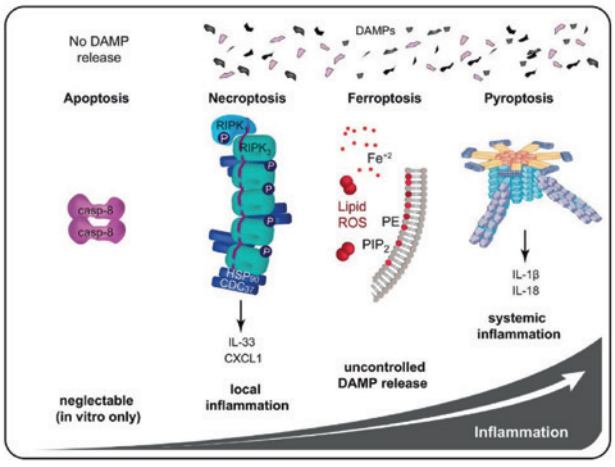


Figure 1.
Types of cell death and their pathways (adopted from: Sarhan M. et al., Physiological Reviews 2018)

The kinase RIPK3 and its substrate MLKL are crucial players in the necroptosis pathway. The phosphorylated MLKL translocates to the plasma membrane and mediates its rupture. Necroptosis was first linked with acute kidney injury (AKI) a decade ago through an observation that treatment with a highly specific receptor-interacting protein kinase 1 inhibitor, necrostatin-1, reduced organ damage and renal failure, even when administered after ischemia-reperfusion injury (IRI). Later studies

corroborated these findings in renal tissue samples from humans with AKI.

Ferroptosis is dependent on iron-mediated lipid peroxidation. The typical feature of a ferroptotic cell is a "wave of death", characterized by a progressive synchronized tubular necrosis, eventually resulting in the formation of granular casts. A lipophilic radical scavenger, ferrostatin-1 (Fer-1), was identified as an effective inhibitor of ferroptosis, blocking the "wave of death", thus attenuating tubular damage and decreasing serum urea and creatinine levels in renal IRI. Genetic evidence for ferroptosis in renal ischemic-reperfusion injury has been substantiated in both glutathione peroxidase 4 (GPX4)-deficient and ferroptosis-suppressor protein 1 (FSP1) knock-out mice. A significant breakthrough was achieved when a combined small molecule inhibitor (Nec-1f), which simultaneously targets necroptosis and ferroptosis and improves survival in mouse models of ischemia-reperfusion injury in AKI, was generated. Nec-1f also reduces the influx of F4/80+ macrophages; thus, ameliorating inflammatory responses related to the IRI.

Pyroptosis is a highly inflammatory form of regulated necrosis and the most potent known trigger of the immune system. Its execution requires caspase activation for cleavage of proinflammatory cytokines IL-1B and IL-18, and gasdermin D (GSDMD). GSDMD is an effector for pyroptosis downstream of the inflammasome signaling pathways and its cleavage leads to the destruction of the cell membrane and lytic cell death. While healthy tubular cells do not express GSDMD, tubular necrosis following IRI leads to a GSDMD-positive infiltrate which is associated with higher tubular damage scores, and increased serum urea and creatinine levels.

These novel pieces of information shall be helpful for clinicians as new inhibitors of necroptosis (necrostatins), ferroptosis (ferrostatins), and inflammasomes are expected to emerge in future clinical trials.

What is to come in the next KDIGO AKI guideline?

Marlies Ostermann, United Kingdom

The previous KDIGO AKI guideline, issued a decade ago, relied on evidence from over 18,000 studies and represented a landmark that steered both clinical practice and research. These guidelines covered four major areas: diagnosis, staging, and risk assessment; prevention and treatment of AKI; drugs and contrast-induced AKI; and dialysis interventions for AKI treatment. The insight into AKI mechanisms, and long- and short-term consequences, have since evolved, thus necessitating an update to inform clinical practice and guide the allocation of health resources.

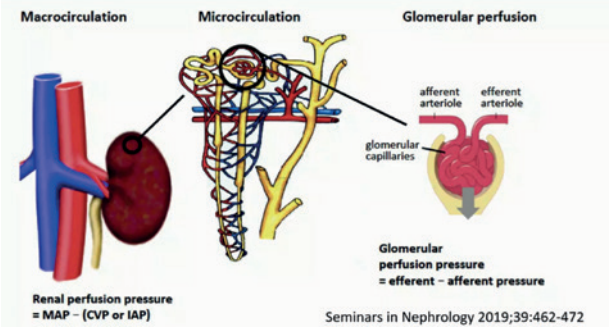


Figure 2.
Relationship between mean arterial pressure (MAP) and renal perfusion pressure

AKI is considered a multifactorial condition with variable presentation and outcomes. The underlying pathophysiology may differ even in patients with similar manifestations of the disease. The knowledge of fundamental molecular mechanisms has also expanded recognizing many separate AKI subtypes with distinct patterns of molecular markers of tubular injury, functional dysfunction and trajectories. Many new biomarkers of AKI stemming from different parts of the nephron have been discovered and assessed. Some of them may even predict the development and outcomes of AKI, thus supporting the reassessment of the concept and incorporation of biomarkers in the definition of AKI. It has also been observed that patients with similar serum creatinine levels may have substantially different underlying renal function and hence the risk of developing AKI under certain circumstances. This finding warrants introducing renal function reserve as a novel risk factor for AKI. Measuring patients' renal functional reserve preoperatively offers opportunities to identify those who may benefit from specific preventive measures.

The new AKI guidelines are expected to address the many previously not covered AKI-related issues, such as the newly developed terminologies and defining criteria for recovery from AKI. They are also expected to incorporate new diagnostic and monitoring tools, including potentially e-alerts and digital health. Therapeutic interventions should also be addressed and more precisely described. Several fluid studies have been conducted in the last 10 years with conflicting results on the optimal timing, amount, and fluid type to prevent and treat AKI, as well as on the type and timing of vasopressors to maintain the mean arterial pressure (MAP). Furthermore, the target MAP to support adequate renal function is also elusive, especially since the relationship between the MAP and renal hemodynamics is complex. Very likely, there can be no universal

answer to these questions. It is possible that individually tailored therapies targeted at preserving renal perfusion pressure, which is easily calculated from MAP and central venous pressure, might be the favored approach.

Contrast-induced AKI is another important issue where new evidence has evolved since the publication of the KDIGO guideline in 2012. It appears that the level of risk for developing this condition is decreasing with the growing use of modern contrast agents. Furthermore, recent studies have challenged the renoprotective effect of the commonly used saline, sodium bicarbonate, and/or N-acetylcysteine in the prevention of contrast-induced AKI. The future KDIGO guidelines should also examine the current concept of nephrotoxicity and address the fact that not all drugs that lead to a creatinine rise are indeed nephrotoxic. The timing, prescription, and duration of renal replacement therapy to treat AKI should also be elaborated on relevant to the abundance of recently published data on these points. Finally, the optimal principles of post-AKI follow-up are also expected to be specified in the anticipated new guidelines.

Identifying patients at risk of the AKI-to-CKD transition

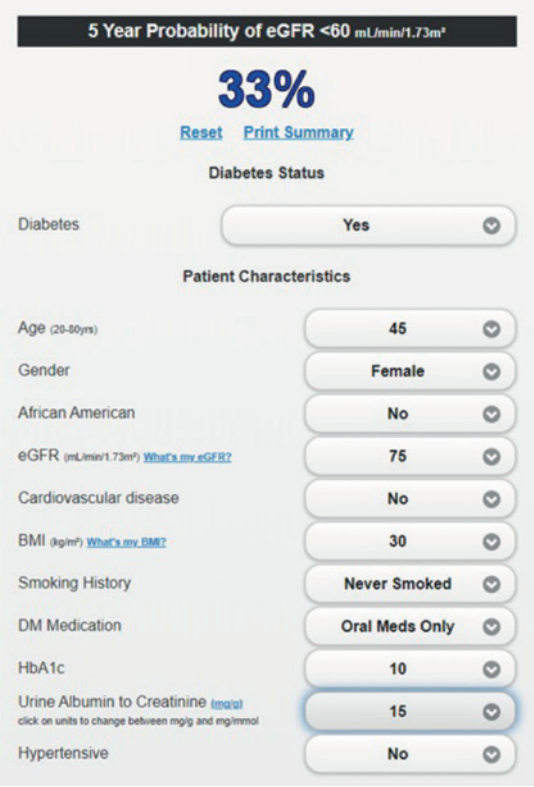
Morgan Grams, USA

AKI is a common condition with higher incidence at older age. Outcomes after AKI hospitalization are poor, especially if patients required acute dialysis. In one study of older patients who survived AKI, as many as 70% progressed to chronic kidney disease (CKD). Moreover, approximately one-third of patients discharged after an AKI hospitalization are readmitted for AKI hospitalization in the next 24 months, presenting yet another risk for worsening kidney function.

The transition from AKI to CKD remains incompletely understood but involves numerous complex mechanisms. Animal models have implicated maladaptive repair as a major underlying factor, with cell death, endothelial dysfunction, tubular epithelial cell senescence, and inflammatory processes driving the transition. These alterations eventually may progress to scarring, with the secretion of profibrotic factors, collagen deposition, accelerated aging, and CKD.

Preventive therapy of the AKI-to-CKD transition may be most easily deployed during or after the AKI episode. Many suggest that renin-angiotensin-aldosterone system blockade could be helpful. Research on animal models showed that pre-AKI treatment with losartan prevented the development of proteinuria and creatinine clearance decline, while post-treatment with spironolactone prevented tubulointerstitial fibrosis, glomerulosclerosis, proteinuria, and decrease in renal blood flow.

Efficient targeting of AKI-to-CKD transition further requires timely identification of patients at risk of developing CKD. Several models that have been developed to predict risk for CKD occurrence in the general population may be helpful in the AKI setting as well. The Incident CKD Risk Tool predicts the risk of eGFR decline below 60 mL/min at 5 years based on demographics, comorbidities, body mass index, smoking history, current eGFR, and albumin to creatinine ratio. For patients with diabetes, the model also includes diabetes medications and HbA1c. The Risk of Decline in eGFR by 40% Tool uses similar, readily available patient characteristics to estimate the probability of eGFR decline within the next 3 years. Finally, the Kidney Failure Risk Equation estimates the risk of progression to end-stage kidney disease in 2 and 5 years based on age, sex, eGFR, albuminuria in people with eGFR below 60 mL/min/1.73 m2.. All these tools are user-friendly and publicly available online for everyday practice. Similar risk factors are relevant when assessing AKI-to-CKD transition. As seen in the recent ASSESS-AKI study, the strongest predictor of a 50% decline in eGFR in the post-AKI period was albuminuria and lower eGFR.



Biomarkers may add to risk prediction tools. Certain urine biomarkers correspond to specific kidney compartments, which may help distinguish the type of injury, and both blood and urine biomarkers have been investigated with respect to disease outcomes. For example, basic fibroblast grown factor (bFGF), N-terminal pro-B-type natriuretic peptide (NT-proBNP), kidney injury molecule-1 (KIM-1), and tumor necrosis factor receptor 1 (TNFR1)) biomarkers were predictive of the AKI to CKD transition following cardiac surgery. TNFR 1 and 2 as well as KIM-1 have also been tested in the general population, with evidence that they may add information to the current models for predicting CKD progression based on clinical variables

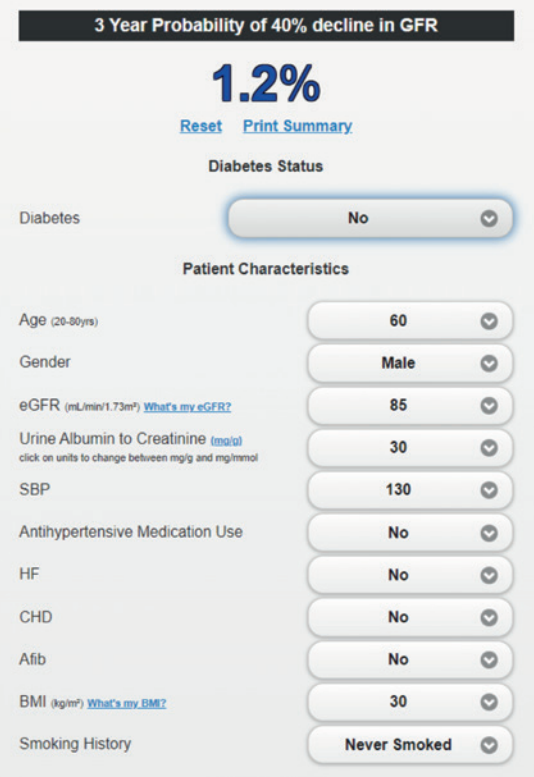


Figure 3.
The Incident CKD Risk Tool and the Decline in eGFR by 40% Risk Tool (available at ckdpcrisk.org)

Further readings

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Written by Jasna Trbojevic-Stankovic.
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