WP5 : GESTION RÉNALE ET MÉTABOLIQUE INDIVIDUALISÉE

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Individualized renal management

Factors associated with the occurrence of acute kidney injury

Factors related to the intensive care unit management of septic patients will be studied and will include mechanical ventilation settings, the use of nephrotoxic agents and details about hemodynamics. This will especially focus on the so-called cardio-pulmonary-renal interactions including the relationships between renal perfusion (mean arterial blood pressure, central venous pressure, mean perfusion pressure) and mechanical ventilation

settings (positive end expiratory pressure and plateau pressure). Indeed, renal injury may results from venous congestion lead by decreased venous return and high intra-thoracic pressures as well as decreased renal perfusion by alteration of cardiac output. All these suggestions have been made years ago in animal models. They are quite intuitive in the human setting even if no large study has been provided so far in the field. The goal of such a study is to allow critical care physicians to adjust for individual factors to limit the occurrence of acute kidney injury.

Two studies are currently ongoing on this topic: one has been performed on the MIMIC-III database using landmark models including more than 25,000 ICU patients (Geri G, submitted) and the second one is led by Matthieu Jamme (intensive care unit, Poissy hospital, PhD student at INSERM UMR 1018) on the AP-HP dataset (Entrepôt de données en santé – AP-HP). Regards to the latter, the authorizations have been granted.

Besides ICU interventions, some endogeneous factors have been associated with renal injury. Among those, dyschloremia, and especially hyperchloremia has been associated with tubular injury and renal dysfunction in old animal models. The clinical implication relies on the choice of crystalloids to make fluid expansion. While randomized controlled trials failed to evidence a clinical benefit in terms of acute kidney injury occurrence, observational data strongly suggest a deleterious effect of an increased blood level of chlore in ICU patients.

One study is ongoing (Matthieu Jamme) on the EDS-APHP data looking at 1) the relationship between variations of blood chlore level above and below normal and acute kidney injury occurrence and 2) the relationship between trajectories of blood chlore levels and outcome.

Further validation in studies of AKI are needed to develop a better understanding of uremic toxins levels at the time of AKI diagnosis as well as trends during the course of AKI. To answer this research question, we will collect blood samples at baseline at time of ICU entry, at the time of AKI diagnosis (Diagnosis), and again on the seventh day after AKI diagnosis (Day7) to explore the place of relevant uremic toxins, which accumulate in AKI to predict AKI and/or total mortality in sepsis patients. Relevant uremic toxins and their precursors will be measured in blood (either serum or plasma) samples by ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS). . This analysis will be possible on the existing cohorts (RECORDS) using the available biobank.

Proximal tubular cells are the main target of injury during AKI and their function is poorly

quantified using serum creatinine. Several biomarkers (KIM1, Ngal, TIMP-2, IGFBP7, …) have been proposed to evaluate AKI, however they are mostly markers of cell lesions and do not reflect the functionality of the cells. Their input in the management of AKI is subject of debates since their measurement do not allow diagnosis of proximal tubule early injury. One way to better evaluate proximal functions could be the measurement of renal clearance of some protein-bound solutes such as p-cresol sulfate, indoxyl sulfate, or hippuric acid (hippurate). Renal clearance of these solutes could be performed using plasma and urines (24 hour collection is suitable) concentration of these solutes measured by LC-MS/MS. We propose to prospectively follow tubular function in ICU patients, using plasma and urines samples collected at D0, D2, D4, D7, then every 7 days until the recovery of AKI or exit of ICU. Patients without AKI will serve as control to evaluate the fluctuation of tubular secretion not associated to AKI.

Long-term renal outcome of acute kidney injury in critically ill survivors

Acute kidney injury is a strong risk factor of chronic kidney disease. This has been well demonstrated in nephrology ward patients but few data are to date available in critically ill survivors. This is all the more important that ICU patients must fight renal injury by itself but also multiple systemic threats including ischemia-reperfusion, hypoxia and inflammation phenomena. All these phenomena may worsen renal injury and contribute to the concept of renal scar that could lead to chronic kidney disease occurrence.

The PREDICT study (Geri G, Ann Intensive Care 2018, NCT03282409) will include 1,200 critically ill survivors who will benefit from an active follow-up at day-90 and every year for 3 years. An ancillary study has been pre-planned to organize a passive follow-up (using the National Health Insurance data) for 10 years.

A link between the EDS-APHP-HP data and the national health insurance data (SNDS) is planned. The authorization from the AP-HP has been granted, search for a financial support is ongoing.

Individualized metabolic management

Effect of Vitamin C in sepsis and sepsis related ARDS

A growing body of evidence, suggesting that vitamin C, an inexpensive and readily available intervention, is potentially lifesaving in sepsis. Intravenous vitamin C may be the first therapy to mitigate the dysregulated cascade of events that leads to sepsis.

Inflammation and oxidative stress are among the main mechanisms underlying sepsis-induced organ injury, and death. Vitamin C which cannot be synthesized by humans, scavenges oxygen radicals, limits their production and restores endothelial function. In addition, vitamin C is a cofactor in the synthesis of noradrenaline, cortisol, and vasopressin, hormones that are crucial to maintain adequate vascular tone for organ perfusion.

The aim of LOVIT (Masse MH et al Trials 2020.; NCT03680274, A Multicentre Concealed-Allocation Parallel-Group Blinded Randomized Controlled Trial is to Ascertain the Effect of High-Dose Intravenous Vitamin C Compared to Placebo on Mortality or Persistent Organ Dysfunction at 28 Days in Septic Intensive Care Unit Patients.

A second study, with a similar design, LOVIT-ARDS (Annane D, funded by the French PHRC-N program; NCT04404387) will seek to determine the effect the Effect of High-Dose Intravenous Vitamin C Compared to Placebo on Mortality or Persistent Organ Dysfunction at 28 Days in Septic related ARDS Intensive Care Unit Patients.

Safety and efficacy of an amino acid blend on muscle and gut functionality in ICU patients

Intensive Care Unit (ICU) patients, and especially long stayers exhibit a significant muscle mass loss (hypercatabolism) because muscles are the reservoir of proteins delivering amino acids to the splanchnic area (gut and liver, and also spleen) in response to an important inflammation-related anabolic reaction. It is key to limit muscle losses and improve lean body mass recovery in ICU patients. Indeed, the greater the muscle loss, the longer the recovery period.

The aim of the randomized controlled AMINO5 study (NCT02968836, funded by Nestle, manuscript being drafted) is to determine the safety and efficacy of an amino acid blend on muscle and gut functionality in ICU patients.

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