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Biomarkers and Their Impact in ICU Patient Outcomes

The laboratory plays a critical role in ensuring optimal outcomes for ICU patients. Several biomarkers are valuable in this context and can help clinicians achieve improved patient outcomes and decreased expenses for healthcare.

Improving both in-ICU and post-ICU clinical outcomes often depends on actions taken much sooner in a patient's pathway during hospitalisation. Regardless of the underlying diagnosis which brings someone to the ICU, there are a few very common complications in this patient population, which are strongly associated with the overall mortality and morbidity expected during the course of hospitalisation. Among these complications, the most prevalent and significant ones are sepsis and acute kidney injury (Sakr et al. 2018; Case et al. 2013).

Challenges of Sepsis

Sepsis occurs when a patient develops an infection, which triggers an exaggerated, un-controlled and sustained inflammatory response. While a simple infection leads to local damage to the organs and tissues where the offending organism is present, in sepsis the damage is caused by the body's own immune response. It is a systemic disease, possibly affecting all organs in the body, including the most vital ones such as the brain, lungs and kidneys. Sepsis is associated with very high morbidity and mortality (Sakr et al. 2018) - a simple skin infection which would never be life threatening per se can quickly lead to a patient`s demise if this infection triggers sepsis, for example, due to respiratory failure caused by an overwhelming inflammation in the lungs.

Once a septic event is already fully established, there is very little physicians can do to help. It is therefore critical to recognise sepsis early on, when simple measures such as the administration of fluids and broad-spectrum antibiotics have been shown to significantly improve a patient`s mortality and morbidity. The challenge is that early clinical signs and symptoms of sepsis, such as fever, respiratory difficulty, and fatigue, are unspecific and overlap with those of much less severe conditions, such as a simple flu. In this context, treating physicians need additional support beyond their clinical assessment in order to recognise early sepsis and start appropriate interventions at a time when they are most effective. This support is provided by the laboratory through critical biomarkers which can help discriminate sepsis from the myriad of other simpler and less severe clinical conditions which can present with a very similar clinical picture.

Biomarker for Early Sepsis Identification

A biomarker for early sepsis identification is procalcitonin (PCT). While PCT is originally a hormone involved in calcium metabolism, multiple studies have shown how levels increase in the presence of bacterial infection, and this increase is proportional to disease severity and most pronounced when patients develop sepsis. This biological behavior of procalcitonin enables it to answer some key clinical questions critical to the proper management of sepsis which ultimately impact a patient's in-ICU and post-ICU outcomes. These key clinical questions are:

- Early recognition of sepsis when therapies are most effective.
- Discrimination between bacterial and viral infections, guiding the decision whether antibiotics are indicated.
- Establishing when a lower respiratory tract infection has been controlled and antibiotics can be discontinued safely.

Acute Kidney Injury (AKI)

Another common complication in ICU patients which can lead to severe long-term consequences and worsened post-ICU outcomes is acute kidney injury (AKI). This disease is characterised by a rapidly progressive loss of renal function, over days or even a few hours. AKI is classified in 3 different stages of worsening severity, based on criteria relying on levels of urine output and blood concentration of creatinine, a waste product typically filtered by the kidney and which accumulates in renal failure. ICU patients who develop AKI typically have worse mortality, longer duration of stay in the ICU often requiring haemodialysis, and quite often will go on to develop chronic renal failure requiring either dialysis for the rest of their lives, or renal transplantation.

The main risk factors for acute kidney injury are critical diseases very common in ICU patients, such as sepsis, major trauma or surgery, acute heart failure and respiratory failure. Risk factors also include clinical interventions common in ICU patients, such as the use of nephrotoxic antibiotics or contrast media for radiology studies. Taken together, these factors lead to AKI prevalence rates as high as 40% in ICU patients, leading to billions of dollars

in excess expenses to health care systems.

The actions clinicians can take to lower the risk of acute kidney injury among ICU patients are well known and are based primarily in minimising exposure to nephrotoxic measures. The challenge is that these nephrotoxic measures are also beneficial to treat the underlying critical condition the patient is facing. For example, the best antibiotic combination to treat a septic patient may also be the most toxic to the kidney, or the use of contrast media in radiology exams may be critical to diagnose a pulmonary embolus. In this scenario, intensivists are faced with a challenging choice between doing what is best to save a patient's life and protecting their renal health.

Biomarker to Help Prevent AKI

A novel biomarker for acute kidney injury has been introduced into medical practice and is helping physicians navigate this challenging clinical predicament. Nephrocheck is an index biomarker generated by measuring two cell cycle arrest biomarkers, called tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP-7). These proteins are responsible for stopping cellular division and are typically released by renal tubular cells under situations of kidney stress. As such, patients with elevated Nephrocheck values are at higher risk of developing moderate and severe acute kidney injury within 24 hours of testing.

The advent of Nephrocheck enables clinicians to recognise those patients already undergoing renal stress and take decisive action to avoid additional nephrotoxic measures which would take the patient into overt AKI. Using this biomarker, intensivists can make better decisions between when to go full speed ahead and focus on treating the underlying critical condition the patient is facing, versus when to be more conservative to preserve renal function and improve post-ICU outcomes. For example, patients recovering from cardiac surgery often benefit from inhibitors of the angiotensin converting enzyme (ACE inhibitors), but these drugs do increase the risk of AKI. In this scenario, clinicians can rely on Nephrocheck to recognise when it is safe to focus primarily in cardiac recovery and deploy the ACE inhibitors to their patients.

A study with post-cardiac surgery patients at the University of Muenster, Germany, demonstrated how patients screened for higher risk of acute kidney injury using Nephrocheck benefited from a nephroprotective care bundle, consisting of aggressive optimisation of volume status and haemodynamics, avoidance of nephrotoxic drugs and close monitoring for hyperglycaemia (Meersch et al. 2017). Patients randomised to the "care bundle" cohort had a 30% decrease in rates of moderate and severe AKI, when compared with usual care. Patients in the "care bundle" cohort had moderate or severe AKI rates of 29.7%, compared to 44.9% in the control group (Meersch et al. 2017). Most importantly, in this study the majority of patients had Nephrocheck values within normal limits, indicating no need for a change in their routine care. Since the care bundle increases the complexity and cost of care, it is prohibitive to be deployed in all ICU patients. But as demonstrated in this study, use of a biomarker such as Nephrocheck can guide clinicians to identify those patients for whom special attention with their renal function is required. Once they are identified, the deployment of aggressive nephroprotective measures is effective in lowering the rates of moderate and severe AKI, and the in-ICU and post-ICU complications derived from AKI.

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A similar observation was made in a study with patients undergoing major abdominal surgery. Patients were randomised to receive either usual ICU care, or an optimised nephroprotective care bundle as described above. In the overall study population, there were no differences in AKI rates, but in a sub-group analysis including only patients with elevated Nephrocheck values, the incidence of AKI was reduced from 48% in the usual care group, to 27.1% in the "care bundle" group (Goecze et al. 2018). This study offered additional evidence that a nephroprotective care bundle is beneficial to prevent AKI in ICU patients, but only in those with a higher risk of kidney damage, as identified with the use of Nephrocheck.

These are just two examples of how the laboratory plays a critical role in ensuring optimal outcomes for ICU patients. Several other biomarkers are valuable in this context, for example high-sensitivity troponin and NTproBNP, critical for the management of cardiac diseases. Health administrators can greatly benefit by enabling greater communication and collaboration between pathologists and intensivists, leading to improved patient outcomes and decreased expenses for the institutions they manage. ■

References

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