

Editorial

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Copeptin in critical illness

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In this issue of *Clinical Chemistry and Laboratory Medicine* (CCLM), Bolignano and colleagues present an extensive review on copeptin, the C-terminal fragment of the pro-vasopressin peptide (CTproAVP), as a surrogate biomarker of arginine vasopressin [1]. Copeptin is co-released from the hypothalamus in an equimolar ratio with the hypothalamic stress hormone vasopressin, and hence secretion is activated not only by changes in plasma osmolality and circulating blood volume, but also by stress and inflammatory states.

Copeptin reflects the stress response during critical illness. Its plasmatic concentration has been associated with mortality in several acute disease states. The acute-phase response to critical illness is characterized by an abrupt and massive release of stress hormones, including adrenocorticotrophic hormone and cortisol, catecholamines, vasopressin, glucagon, and growth hormone [2]. In the acute stage of critical illness, this response can maintain effective circulation and tissue oxygenation, and increase the production of energy substrates. Persistent systemic inflammation may result in tissue hypoxia and cell damage causing multiple organ dysfunctions and failure. With the body primed by this persistent pro-inflammatory state with hypercatabolism, several drugs, such as propofol, glucocorticoids and catecholamines may further enhance the tissue damage [3]. In the chronic stage of critical illness, the hormonal profile changes substantially with inappropriately low vasopressin levels, onset of the sick euthyroid syndrome, and reduced adrenal responsiveness to adrenocorticotrophic hormone, often despite hypercortisolemia. In sepsis, few endocrine systems are so rapidly activated and then are so rapidly exhausted as the vasopressin axis [4].

Copeptin plasmatic levels correlate with the release of acute phase cytokines interleukin (IL)-1 β , IL-6, tumor necrosis factor (TNF)- α , and have been used to improve prognostication in several neurological and non-neurological acute diseases in the intensive care unit [5] or to improve patients' triage in the emergency department [6, 7]. In community-acquired pneumonia, copeptin has

been shown to be a good predictor of short- and long-term all-cause mortality, superior to inflammatory markers, and at least comparable to “the confusion, respiratory rate, blood pressure, and age over 65 years (CRB-65)” score [8, 9]. In severe chronic obstructive pulmonary disease, copeptin is an independent predictor of acute exacerbation together with chronic obstructive pulmonary disease assessment test (CAT). Importantly, copeptin and CAT scores are both independent predictors of 6-month mortality in such patients. In ventilator-associated pneumonia, a major complication in critically ill patients undergoing mechanical ventilation, copeptin is significantly elevated in non-survivors and moderately predicts survival [10]. In patients with sepsis, copeptin concentration gradually increases with the severity of the disease [11]. Plasma concentrations in septic shock can be more than 30-fold higher than in healthy individuals and more than six-fold higher than in patients with systemic inflammation not related to infection [11]. However, these findings are not uniformly reported. Despite vasopressin levels being expected to increase early in septic shock because hypotension is the most potent stimulus of increased synthesis and release of vasopressin, vasopressin plasma concentrations may not be different in adult patients with and without shock, indicating that the vasopressin system is dysfunctional in severe sepsis [12]. In this condition, the correlation between the vasopressin and copeptin plasmatic levels can be suboptimal, possibly as a consequence of renal dysfunction [12], or reduced vasopressin synthesis and secretion [13]. In children with septic shock, vasopressin and copeptin levels may not robust markers for severity and clinical outcomes [14]. Copeptin is also increased in several acute neurological illnesses, such as acute ischemic stroke [15, 16], spontaneous cerebral hemorrhage [17–19] and brain trauma [20]. Copeptin, measured within the first 24 h after stroke onset, improves neurologic prognostication after ischemic stroke adding predictive information for functional outcome and mortality at 3 months beyond age and stroke severity measured with the NIH Stroke Scale score [16]. In patients with severe brain trauma, copeptin does not reflect the urinary sodium excretion or sodium plasma levels, indicating an uncoupling of

copeptin-vasopressin release and renal water excretion, but is correlated with injury severity [21]. Copeptin combined with high-sensitive cardiac troponin T may help in ruling out acute myocardial infarction in patients with acute chest pain of early onset [22, 23] and non-ST-elevation myocardial infarction (NSTEMI) in older patients [24], facilitating safe early discharge from the hospital [25]. The relevancy of copeptin measurement is debated in NSTEMI patients with troponin I below the 99th centile at presentation [26]. Copeptin may help prognostication in patients presenting with dyspnea in the emergency department [27] or in patients with non-ST-segment elevation acute coronary syndrome [28].

Copeptin plasmatic levels reflect the severity of illness rather than changes in plasma osmolality; as such, copeptin is a promising prognostic biomarker in critical illness. However, the way for biomarkers towards impacting on clinical practices is like long-distance running; few biomarkers reach the finish line [29]. Future studies should evaluate if copeptin measurement adds predictive information to established standard risk markers, allowing *clinical risk reclassification* of patients into higher or lower risk categories [30].

Conflict of interest statement

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