

Modern Critical Care Endocrinology

Editor

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Anatole Harrois and James R. Anstey

Diabetes insipidus and the syndrome of inappropriate antidiuretic hormone secretion lie at opposite ends of the spectrum of disordered renal handling of water. Whereas renal retention of water insidiously causes hyponatremic hyponatremia in syndrome of inappropriate antidiuretic hormone secretion, diabetes insipidus may lead to free water loss, hypernatremia, and volume depletion. Hypernatremia and hyponatremia are associated with worse outcomes and longer intensive care stays. Moreover, pathologies causing polyuria and hyponatremia in patients in intensive care may be multiple, making diagnosis challenging. We provide an approach to the diagnosis and management of these conditions in intensive care patients.

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Karim Asehnoune, Mickael Vourc'h, and Antoine Roquilly

Low-dose hydrocortisone reduces the dose of vasopressors and hospital length of stay; it may also decrease the rate of hospital-acquired pneumonia and time on ventilator. No major side effect was reported, but glycemia and natremia should be monitored. Progesterone did not enhance outcome of trauma patients. A meta-analysis suggested that oxandrolone was associated with shorter length of stay and reduced weight loss. Erythropoietin did not enhance neurologic outcome of traumatic brain-injured patients; such treatment, however, could reduce the mortality in subgroups of patients. This review focuses mainly on glucocorticoids, which are the most extensively investigated treatments in hormone therapy.

Classic and Nonclassic Renin-Angiotensin Systems in the Critically Ill	213
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Laurent Bitker and Louise M. Burrell

Classic and nonclassic renin-angiotensin systems (RAS) are 2 sides of an ubiquitous endocrine/paracrine cascade regulating blood pressure and homeostasis. Angiotensin II and angiotensin-converting enzyme (ACE) levels are associated with severity of disease in the critically ill, and are central to the physiology and the pathogenesis of circulatory shock. Angiotensin (1–7) and ACE2 act as an endogenous counterregulatory arm to the angiotensin II/ACE axis. The tissue-based RAS has paracrine effects dissociated from those of the circulating RAS. Exogenous angiotensin II or ACE2 may improve the outcome of septic shock and acute respiratory distress syndrome, respectively.

Angiotensin II in Vasodilatory Shock

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Brett J. Wakefield, Laurence W. Busse, and Ashish K. Khanna

The Angiotensin II for the Treatment of Vasodilatory Shock (ATHOS-3) trial demonstrated the vasopressor effects and catecholamine-sparing properties of angiotensin II. As a result, the Food and Drug Administration has approved angiotensin II for the treatment of vasodilatory shock. This review details the goals of treatment of vasodilatory shock in addition to the history, current use, and recent research regarding the use of angiotensin II. An illustrative case of the use of angiotensin II is also incorporated for understanding the clinical utility of the drug.

Vasopressin in Vasodilatory Shock

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Ida-Fong Ukor and Keith R. Walley

Vasodilatory shock is the final common pathway for all forms of severe shock, with sepsis the most common primary etiology and the leading cause of critical illness-related mortality. The pathophysiology of this condition remains incompletely elucidated. Deficiency of the neuropeptide hormone vasopressin seems to play a significant role. The physiology of vasopressin and its interaction with the pathophysiology of vasodilatory shock are described in this review. A brief review of the major randomized controlled trials assessing the efficacy and safety of vasopressin and its analogs in this complex patient cohort is also provided.

Hydrocortisone in Vasodilatory Shock

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Balasubramanian Venkatesh and Jeremy Cohen

Vasodilatory shock is the most common type of circulatory shock in critically ill patients; sepsis the predominant cause. Steroid use in septic shock gained favor in the 1970s; however, studies of high-dose steroids demonstrated excess morbidity and mortality. Lower dosage steroid use was driven by trials demonstrating improved hemodynamic status and the possibility of relative adrenal insufficiency; however, divergent results led to uncertainty about hydrocortisone treatment. Two recent trials are likely to reinforce the role of steroids in septic shock and change the recommendation in future clinical practice guidelines. Future work could include elucidating mechanisms of shock reversal, interaction of hydrocortisone with other agents, identifying steroid responsiveness using biochemical or gene signatures, and clarifying the role of fludrocortisone.

Erythropoietin in Critical Illness and Trauma

277

Craig French

Erythropoietin (EPO) is a 34kD pleiotropic cytokine that was first identified as being essential for red blood cell (RBC) production. It is now recognized however that EPO is produced by many tissues. It plays a key role in the modulation of the response to injury, inflammation, and tissue hypoxia via the inhibition of apoptosis. Large clinical trials in the critically ill failed to demonstrate a role for EPO as an RBC transfusion sparing agent; however, improved clinical outcomes, attributable to EPO role in tissue protection are observed in critically ill trauma patients. Further research to confirm or refute these observations is required.

Hemoglobin A1c and Permissive Hyperglycemia in Patients in the Intensive Care Unit with Diabetes 289

Anca Balintescu and Johan Mårtensson

Glycated hemoglobin A1c can be used to assess intensive care unit patients' level of chronic glycemic control. Compared with patients with normal glycated hemoglobin A1c, patients with elevated glycated hemoglobin A1c seem to better tolerate hyperglycemia and large glucose fluctuations during critical illness. The risks associated with hypoglycemia are markedly greater among patients with elevated glycated hemoglobin A1c. Observational studies suggest that more liberal targets further decrease the occurrence of hypoglycemia in patients with diabetes with elevated glycated hemoglobin A1c. Whether glycated hemoglobin A1c should be used to individualize glucose control during critical illness should be assessed in randomized trials.

Osteoporosis and the Critically Ill Patient 301

Neil R. Orford, Julie A. Pasco, and Mark A. Kotowicz

Improved survival after critical illness has led to recognition of impaired recovery following critical illness as a major public health problem. A consistent association between critical illness and accelerated bone loss has been described, including changes in bone turnover markers, bone mineral density, and fragility fracture rate. An association between accelerated bone turnover and increased mortality after critical illness is probable. Assessment of the effect of antifracture agents on fracture rate and mortality in the high-risk population of postmenopausal women with prolonged ventilation is warranted.

New Agents for the Treatment of Type 2 Diabetes 315

Renata Libianto and Elif I. Ekinçi

The Renaissance of glucose-lowering therapies has arrived with multiple agents that lower blood glucose and demonstrate cardiovascular and renal benefits in people with type 2 diabetes. This article summarizes these new classes of therapies, including the sodium glucose co-transporter-2 inhibitors, glucagon-like peptide-1 agonists, and dipeptidyl peptidase-4 inhibitors. Their cardiovascular safety profile, effects on glycemic, weight, and renal outcomes are discussed. As more options become available to treat type 2 diabetes, clinicians need to be aware of the advantages of each class of medications, beyond their glycemic lowering effects. The safety profiles are summarized in this article.

Melatonin in Critical Care 329

Annachiara Marra, Tracy J. McGrane, Christopher Patrick Henson, and Pratik P. Pandharipande

Melatonin is involved in regulation of a variety of physiologic functions, including circadian rhythm, reproduction, mood, and immune function. Exogenous melatonin has demonstrated many clinical effects. Numerous clinical studies have documented improved sleep quality following administration of exogenous melatonin. Recent studies also demonstrate the analgesic, anxiolytic, antiinflammatory, and antioxidative effects of

melatonin. This article reviews the principal properties of melatonin and how these could find clinical applications in care of the critically ill patients.

Incretin Physiology and Pharmacology in the Intensive Care Unit

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Mark P. Plummer, Jeroen Hermanides, and Adam M. Deane

In health, postprandial glycemic excursions are attenuated via stimulation of insulin secretion, suppression of glucagon secretion, and slowing of gastric emptying. The incretin hormones, glucagon-like peptide-1 and glucose-dependent insulintropic polypeptide, are primary modulators of this response. Drugs have recently been developed that exploit the incretin-axis for the management of type 2 diabetes. There is burgeoning interest in the potential of incretin therapies for the management of acute hyperglycemia in the critically ill. This article outlines basic incretin physiology, highlights relevant pharmacology, and briefly summarizes the literature on incretins for glycemic control in the critically ill.

Therapeutic Opportunities for Hepcidin in Acute Care Medicine

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Lakhmir S. Chawla, Blaire Beers-Mulroy, and George F. Tidmarsh

Iron homeostasis is often disrupted in acute disease with an increase in catalytic free iron leading to the formation of reactive oxygen species and subsequent tissue-specific oxidative damage. This article highlights the potential therapeutic benefit of exogenous hepcidin to prevent and treat iron-induced injury, specifically in the management of infection from enteric gram-negative bacilli or fungi, malaria, sepsis, acute kidney injury, trauma, transfusion, cardiopulmonary bypass surgery, and liver disease.

Thyroid Hormones in Critical Illness

375

Matthew J. Maiden and David J. Torpy

Thyroid hormone is integral for normal function, yet during illness, circulating levels of the most active form (triiodothyronine [T3]) decline. Whether this is an adaptive response in critical illness or contributes to progressive disease has remained controversial. This review outlines the basis of thyroid hormone changes during critical illness and considers the evidence regarding T3 replacement.

Hormonal Therapy in Organ Donors

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Helen Ingrid Opdam

Optimal supportive treatment of brain dead potential organ donors maximizes donation and transplant outcomes. Brain death is associated with activation of inflammatory pathways and loss of autoregulatory brain functions that may include hypothalamic-pituitary dysfunction. As well as general supportive care, specific treatment to counter the common sequelae of brain death such as hypotension, hypothermia, and diabetes insipidus is required. In addition, the provision of specific hormonal therapy (thyroid hormone, vasopressin, and steroids) has been proposed but is controversial due to lack of high level evidence to support its efficacy.