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Clinical Reviews

HYPERGLYCEMIC CRISIS

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☐ **Abstract—Background: Hyperglycemic crisis is a metabolic emergency associated with uncontrolled diabetes mellitus that may result in significant morbidity or death. Acute interventions are required to manage hypovolemia, acidemia, hyperglycemia, electrolyte abnormalities, and precipitating causes. Despite advances in the prevention and management of diabetes, its prevalence and associated health care costs continue to increase worldwide. Hyperglycemic crisis typically requires critical care management and hospitalization and contributes to global health expenditures. Objective: Diagnostic and resolution criteria and management strategies for diabetic ketoacidosis and hyperosmolar hyperglycemic crisis are provided. A discussion of prevalence, mortality, pathophysiology, risk factors, clinical presentation, differential diagnosis, evaluation, and management considerations for hyperglycemic crisis are included. Discussion: Emergency physicians confront the most severe sequelae of uncontrolled diabetes and provide crucial, life-saving management. With ongoing efforts from diabetes societies to incorporate the latest clinical research to refine treatment guidelines, management and outcomes of hyperglycemic crisis in the emergency department continue to improve. Conclusion: We provide an overview of the evaluation and treatment of hyperglycemic crisis and offer a concise, targeted management algorithm to aid the practicing emergency physician.** © **2013 Elsevier Inc.**

☐ **Keywords—diabetes; diabetic ketoacidosis; hyperglycemic crisis; hyperglycemic emergency; hyperosmolar hyperglycemic state; metabolic acidosis**

INTRODUCTION

Hyperglycemic crisis includes diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS). Both are extreme metabolic derangements associated with uncontrolled types 1 and 2 diabetes mellitus that may result in shock, coma, or death. These life-threatening endocrine emergencies demand swift, repeated clinical and laboratory assessment; monitoring; correction of hypovolemia, acidemia, hyperglycemia, ketonemia, and electrolytes; and treatment of the precipitating causes. Consensus statements provided by the American Diabetes Association (ADA) for the care of adult patients with hyperglycemic crisis and by the International Society for Pediatric and Adolescent Diabetes (ISPAD) for the care of children and adolescents with DKA are excellent primary resources for diagnosis and management (1,2).

As of 2010, >285 million adults worldwide have diabetes, with estimated yearly global health expenditures totaling >$376 billion (3). In the United States (US), the number of Americans with diabetes has more than quadrupled, from 5.6 million in 1980 to 25.8 million in 2010, with direct and indirect health care costs of >$174 billion (3,4). The incidence of type 1 diabetes is increasing globally, particularly in children <5 years of age, and the earlier onset of type 2 diabetes is a growing concern (5). In a multicenter, population-based study of

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patients <20 years of age who were diagnosed with diabetes, the prevalence of DKA at the initial diagnosis was >25% (6). US population–based studies report the annual incidence of DKA to range from four to eight episodes per 1000 diabetic patient admissions, with an average duration of hospital stay of 3.6 days (4,7). Hyperglycemic crises often require critical care management and are associated with significant health care costs, morbidity, and mortality. The mortality rate from DKA in children ranges from 0.15% to 0.30%, with cerebral edema responsible for 60% to 90% of these deaths (2). Among adults, DKA-associated mortality is often attributable to precipitating or concurrent events, such as sepsis, pneumonia, hypokalemia, acute myocardial infarction (MI), and acute respiratory distress syndrome (8).

Improved understanding of pathophysiology and advances in diabetes prevention and management has resulted in sharply declining death rates in the United States (9). In 1980, among the 0- to 44-year-old age group, 45.5 deaths per 100,000 diabetic patients were attributable to hyperglycemic crisis, compared with 26.2 in 2005 (4). In patients >75 years of age, even greater improvement was observed, with 20.5 deaths per 100,000 in 2005 compared with 140.2 per 100,000 in 1980 (4). Ongoing research holds promise for further decreases, including the early identification and management of patients at risk, improvements in the accuracy and efficiency of acidosis measurement, and trials of alternative insulin regimens for acute management (10).

DISCUSSION

Diagnostic Criteria for DKA and HHS

The diagnosis of hyperglycemic crisis is possible within minutes of a diabetic patient's presentation to the emergency department if classic signs and symptoms are appreciated and point-of-care testing is used. DKA is distinguished by a blood glucose of >250 mg/dL, moderate ketonuria or ketonemia, arterial pH of <7.3, and a bicarbonate of <15 mEq/L (1). A diagnosis of HHS may be presumed in a diabetic patient with an altered sensorium, severely elevated glucose (usually >600 mg/dL), minimal or no ketonuria or ketonemia, serum osmolality >320 mOsm/kg, arterial pH (typically) >7.3, and a bicarbonate of >15 mEq/L (1). Distinct pathophysiologic features account for the laboratory findings that define both DKA and HHS.

Pathophysiology

Diabetes mellitus (DM) is a broad term for diseases distinguished by insufficient endogenous insulin that result in hyperglycemia. The role of insulin is crucial to understanding the pathophysiology of diabetes and hyperglycemic crisis. Insulin stimulates hepatocellular glucose uptake, glycogen storage, and lipogenesis. Opposite to glucagon, insulin inhibits hepatic glycogenolysis and gluconeogenesis. Type 1 DM is defined by progressive and irreversible autoimmune-mediated destruction of pancreatic beta cells, typically leading to absolute insulin deficiency (11). Type 2 DM is distinguished by a progressive insulin resistance and defects in insulin secretion leading to a relative insulin deficiency that may eventually require exogenous insulin (11).

DKA and HHS are severe complications of DM. A combination of hormonal imbalances causes DKA. In the setting of insulin deficiency, increased glucagon, catecholamines, cortisol, and growth hormones lead to increased extracellular glucose, decreased glucose use, and hyperglycemia (1). These counter-regulatory and stress hormones stimulate lipolytic pathways, and the resultant free fatty acids are oxidized to ketone bodies, such as acetone, acetoacetate, and beta-3-hydroxybutyrate. Beta-3-hydroxybutyrate contributes most prominently to an anion gap metabolic acidosis.

In contrast, patients with HHS have some pancreatic beta cell function, and the degree of lipolysis required to produce a measurable ketonemia may not occur. Significantly higher hyperglycemia (>600 mg/dL) is often observed in comparison with DKA. HHS is characterized by severe hyperglycemic diuresis and dehydration, hypernatremia, minimal to absent ketonemia, and serum osmolality of >320 mOsm/kg. Because of severe hypernatremia and elevated serum osmolality, HHS patients more often present with severe mental status changes, including coma (1).

Hyperglycemia itself imposes an osmotic load that favors an intravascular fluid shift, osmotic diuresis, and dehydration. Nausea and vomiting induced by ketonemia also contributes to fluid losses and a profound hypovolemic state. The typical total body water deficit is 6 L in DKA and 9 L in HHS (1). In addition, there are total body losses of key minerals and electrolytes, including sodium, chloride, potassium, phosphate, calcium, and magnesium. Serum electrolytes measured in the setting of intravascular contraction may offer falsely normal results and not accurately represent total body depletion. The net result of these combined biochemical imbalances is an acutely ill, acidotic, ketonemic, hyperglycemic, dehydrated, and electrolyte-depleted patient.

Risk Factors for Hyperglycemic Crisis

Usher-Smith et al. reviewed 46 studies in 31 countries to identify factors associated with the presence of DKA at diagnosis of diabetes among children and adolescents.