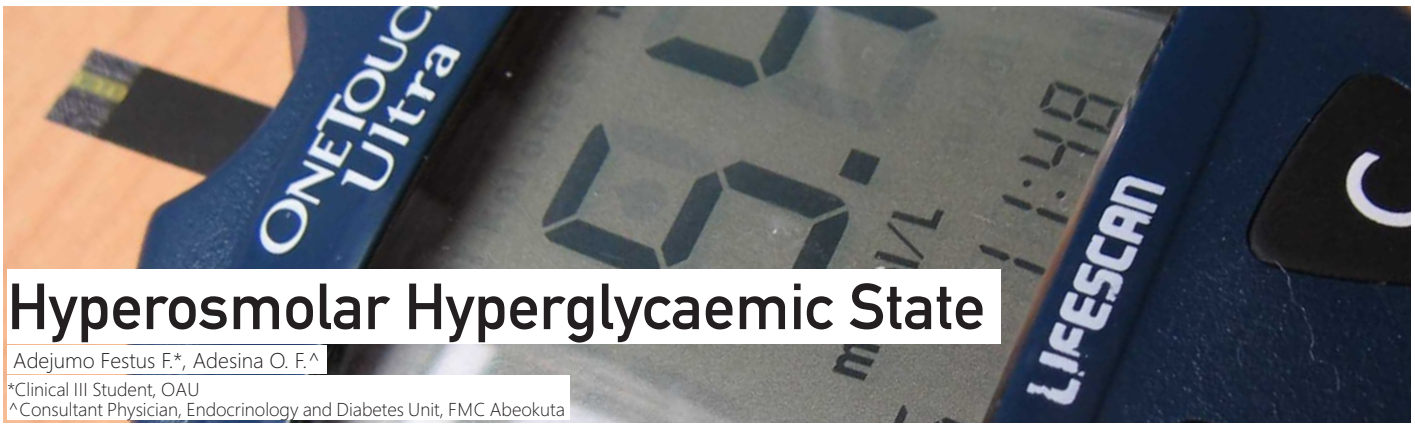

Hyperosmolar Hyperglycaemic State

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INTRODUCTION

Hyperosmolar Hyperglycaemic state (HHS) is one of the serious metabolic derangements that occur in patients with diabetes mellitus (DM) and can be a life threatening emergency. It was previously termed Hyperosmolar Hyperglycaemic Non- Ketotic Coma (HHNC); however, the terminology was changed because coma is found in fewer than 20% of patients with HHS[1]. It most commonly occurs in patients with type 2 DM; however, HHS has also been reported in patients with type 1 DM, in whom Diabetic Ketoacidosis (DKA) is more common. Although typically occurring in the elderly, HHS can also occur in younger adults and teenagers, often as the initial presentation of type 2 DM.

Whilst DKA presents within hours of onset, HHS comes on over many days, and consequently the dehydration and metabolic disturbances are more extreme; hence the higher mortality than that seen in DKA.

DEFINITION

Hyperosmolar hyperglycaemic syndrome (HHS), also known as non-ketotic hyperglycaemic hyperosmolar syndrome (NKHS), is characterized by profound hyperglycaemia (glucose ›600 mg/dL), hyperosmolality (effective serum osmolality ›320 mOsm/kg), and volume depletion in the absence of significant ketoacidosis (pH ›7.3 and HCO3 ›15 mEq/L). It may be the first presentation of type 2 diabetes[13,14]. Although both HHS and diabetic ketoacidosis (DKA) are often discussed as distinct entities, they represent two points on the spectrum of metabolic derangements in diabetes15, HSS and DKA being characterized by relative or absolute insulin deficiency combined with increased counter-regulatory hormones 13, 16. Approximately one third of patients with hyperglycaemic crises present with a mixed picture of DKA and HSS17. Most patients present with severe dehydration and focal or global neurologic deficits[1,2,3].

According to the consensus statement published by the American Diabetes Association, diagnostic features of HHS may include the following[2,4]:

- Plasma glucose level of 600mg/dl or greater
- Effective serum osmolality of 320mosm/kg or greater
- Profound dehydration, up to an average of 9L
- Serum pH greater than 7.30
- Bicarbonate concentration greater than 15meq/L
- Small ketonuria and absent-to-low ketonaemia
- Some alteration in consciousness

EPIDEMIOLOGY

The precise prevalence and incidence of HHS is difficult to determine because of lack of population-based studies and the multiple co-morbidities often found in these patients. However, the overall prevalence is estimated at less than 1% of all diabetes-related hospital admissions[20, 21]. Incidence of HHS has been estimated at a rate of 17.5 per 100,000 patient years18. It is seen most commonly in older patients and those of African-American ethnicity with diabetes21. Mortality rates in HHS have been reported to be 5% to 20%, and are markedly higher than in diabetic ketoacidosis[14]. Mortality increases significantly above the age of 70 years[22].

AGE RELATED DEMOGRAPHICS

HHS has a mean age of onset early in the 7th decade of life. The average age of patients with HHS is 60 years. Most published series report an average age of 57-69 years at diagnosis[1,3,7]. In contrast, the mean age of onset for DKA is early in the fourth decade of life. HHS may also occur in younger people in particular as rates of obesity increase in children, the prevalence of type 2 DM is also rising in this age group and may lead to an increased incidence of HHS in this population[8,9,10].

SEX RELATED DEMOGRAPHICS

No sex predilection is noted. However, some data suggest that the prevalence is slightly higher in females than in males. In the US National Hospital Discharge Survey, 3,700 persons were male and 7,100 were female.

RACE RELATED DEMOGRAPHICS

African Americans, Hispanics, and most Native Americans are disproportionately affected by HHS as consequence of an increased prevalence of type 2 DM[1]. In the US National Hospital Discharge Survey of 10,800 hospital discharges listing HHS in the United States between 1989 and 1991, there were 6300 white patients and 2900 African American patients.

AETIOLOGY

HHS most commonly occurs in patients with type 2 DM who have some concomitant illness that leads to reduced fluid intake. In general, any illness that predisposes to dehydration or to reduced insulin activity may lead to HHS[1, 3]. A wide variety of major illnesses may trigger HHS by limiting patient mobility and free access to water.

- Acute illnesses: Infection is the major precipitating factor, occurring in 30% to 60% of patients. Urinary tract infections and pneumonia are the most common infections reported[14,19].

In many instances, the trigger is an acute illness, such as cerebrovascular accident (CVA), myocardial infarction (MI), or other medical-surgical illnesses that provokes the release of counter-regulatory hormones (catecholamines, glucagon, cortisol, and growth hormone) and/or compromises water intake[13,14,24].

- Drugs: Drugs that raise serum glucose levels inhibit insulin, or cause dehydration may cause HHS. Examples include the following:

-Atypical antipsychotics (clozapine, olanzapine)
-Alcohol and cocaine
-Antiarrhythmics (e.g. encainide and propranolol)
-Antiepileptics (e.g., phenytoin)
-Antihypertensives (e.g. calcium channel blockers and diazoxide)
-Antipsychotics (e.g. chlorpromazine, clozapine, loxapine, and olanzapine)
-L-asparaginase
-Beta blockers
-Corticosteroids
-Diuretics (eg, chlorthalidone, ethacrynic acid, and thiazides)
-Histamine-receptor blockers (eg, cimetidine)
-Immunosuppressive agents
-Total parenteral nutrition (TPN) solutions and fluids that contain dextrose.

- Noncompliance with oral hypoglycaemics or insulin therapy: Non-adherence to insulin or oral anti-diabetic medications is found in 12% to 25% of patients admitted for HHS[17,18]. This association is much higher in urban African-American patients with diabetes, in whom

non-adherence is the sole reason for HHS in 42% of cases[20]. Alcohol and cocaine abuse is a major contributing factor to non-adherence with diabetic therapy.

· Endocrine disorders: Hyperthyroidism, Acromegaly, Cushing Syndrome (e.g. endogenous, exogenous, ectopic).

· Other conditions and illnesses associated with HHS include: Burns, Gastrointestinal haemorrhage, Trauma, Neuroleptic Malignant Syndrome, Subdural haematoma, Surgery (especially cardiac surgery), Hemodialysis and Peritoneal dialysis, Pancreatitis, Heatstroke.

PATHOPHYSIOLOGY

Relative insulin deficiency and increased concentration of counter-regulatory hormones (catecholamines, glucagon, cortisol, and growth hormone) characterize HHS[13]. Although both HHS and diabetic ketoacidosis (DKA) are often discussed as distinct entities, they represent two points on the spectrum of metabolic derangements in diabetes. Approximately one third of patients with hyperglycaemic crises present with a mixed picture of DKA and HHS[17].

The pathogenesis of HHS is, however, not fully understood[25]. Measurable insulin secretion in patients with HHS is higher than in patients with DKA[26]. This higher insulin concentration is believed to be sufficient to suppress lipolysis and ketogenesis but inadequate to regulate hepatic glucose production and promote glucose utilization. Another potential mechanism for the lack of ketosis in HHS involves the effect of hyperosmolality on inhibiting lipolysis, insulin secretion, and glucose uptake[26]. A reduction in the net effective concentration of insulin owing to any aetiology leads to impaired carbohydrate, lipid, and ketone metabolism in hyperglycaemic crises. Decreased insulin results in increased gluconeogenesis, accelerated glycogenolysis and impaired glucose utilization by peripheral tissues1[3,20,24].

Disturbances in hydration and electrolyte balance are of great importance in the pathogenesis of HHS. Because HHS evolves over several days, continued osmotic diuresis leads to hypernatraemia, particularly in older patients with compromised renal function and/or inability to drink water to keep up with urinary losses. The resulting hypernatraemia and hyperglycaemia, coupled with inadequate water intake and excess water loss, result in profound volume contraction. Hypovolaemia leads to a progressive decline in the glomerular filtration rate, which aggravates the hyperglycaemic state[13,24].

Infection is the major precipitating factor, occurring in 30% to 60% of patients. Counter-regulatory hormones, particularly epinephrine, are increased as a systemic response to infection. They induce insulin resistance, decrease insulin production and secretion, and increase lipolysis, ketogenesis, and volume depletion, thereby contributing to the hyperglycaemic crises in patients with diabetes[13].

CLINICAL PRESENTATION

Most patients with HHS have a known history of DM, usually type 2. In 30-40% of cases, HHS is the patient's initial presentation of DM3.

-Onset: HHS usually develops over a course of days to weeks, unlike DKA, which develops more rapidly, over the course of few days.

-History of a preceding illness or co-morbidity (e.g. dementia, immobility), drug use, poor compliance with hypoglycaemic medications, and dietary indiscretion.

-Symptoms include Polydipsia, Polyuria, Polyphagia, Weight loss, Weakness, Abdominal Pains (more in DKA). A wide variety of focal and global neurologic changes may be present (drowsiness and lethargy, delirium, coma, focal or generalized seizures, visual changes or disturbances, hemiparesis, sensory deficits).

-Physical Examination: Examine for hydration status, mentation, and signs of possible underlying causes, such as a source of infection.

-Vital signs: tachycardia is an early indicator of dehydration; hypotension is suggestive of profound dehydration due to volume loss secondary to osmotic diuresis. Tachypnea may result from respiratory compensation for metabolic acidosis. Abnormally high or low core temperatures (rectal) suggest sepsis as an underlying cause. Lack of fever does not rule out infection

-Body Systems: Check Skin turgor, sunken eyes, and dry mouth for hydration status. Cranial neuropathies, visual field losses, and nystagmus may be appreciated, which are symptoms of HHS. HHS may be associated with several neurologic findings, including seizures, hemianopsia, aphasia, paresis, a positive Babinski sign, myoclonic jerks, change in muscle tone, eye deviation, and gastroparesis. For many patients, these neurologic symptoms and signs could be the manifestation of an underlying cerebrovascular accident.

When HHS causes neurologic dysfunction, treatment results in resolution of signs and symptoms. When neurologic events cause HHS, signs and symptoms fail to improve with correction of the metabolic derangements.

-Assessment of Dehydration: Body weight is the single most important measurement in assessing the degree of hydration. For every 1 L of body fluids lost, 1 kg of body weight is lost. Unfortunately, recently recorded weights are usually not available when patients with HHS are being assessed, and the weight reported by patients may not be accurate.

DIFFERENTIAL DIAGNOSIS

· Diabetic Insipidus
· Diabetic Ketoacidosis
· Myocardial Infarction
· Pulmonary Embolism

INVESTIGATIONS

· Blood:

-Haemoglobin and haematocrit values are usually elevated because of volume contraction. Leukocytosis is frequently present. Stress, dehydration, and demargination of leukocytes contribute to leukocytosis. Given that infections commonly precipitate HHS, consider leukocytosis secondary to an infectious process until proven otherwise.

-Serum Glucose: Greater than 600mg/dl. The concentration of glucose in the plasma is directly proportional to the degree of dehydration. Higher concentrations of glucose relate to higher degrees of dehydration, higher plasma osmolality, and a worse prognosis.

-Serum Osmolarity: Greater than 320mOsm/kg. In HHS, higher serum osmolality relates to greater impairment of the level of consciousness.

-Serum Electrolytes: Hyponatraemia or Hypernatraemia, Hypokalaemia or Hyperkalaemia may be present. Serum bicarbonate greater than 15meq/L with wide anion gap reflects metabolic acidosis.

-Serum Ketosis: Mild degree of ketosis is observed in any patient who is dehydrated

-Serum Enzymes: Dehydration causes a rise in the plasma levels of albumin, amylase, bilirubin, calcium, total protein, lactate dehydrogenase, transaminases, and creatine kinase (CK). Up to two thirds of patients with HHS have elevated serum enzyme levels. Accordingly, serum levels of CK and isoenzymes should be measured routinely because both MI and rhabdomyolysis can trigger HHS and both can be secondary complications of HHS11.

-Blood Gas: Arterial pH greater than 7.30.

-Blood culture: For bacteraemia.

· Urine: Urinalysis can reveal elevated specific gravity (evidence of dehydration, low specific gravity in diabetes insipidus), glycosuria, small ketonuria, and evidence of urinary tract infection (UTI). Urine cultures in UTI, because they may be undetected by urinalysis alone.

· Cerebrospinal Fluid Studies: Indicated in patients with an acute alteration of consciousness and clinical features suggestive of possible central nervous system (CNS) infection.

· Radiography of Chest and Abdomen: Chest radiography for Pneumonitis and cardiomegaly. Abdominal radiography is indicated if the patient has abdominal pain or is vomiting

· Computed Tomography of the Head: Indicated in patients with focal or global neurologic changes to exclude haemorrhagic strokes, subdural haematoma, intracranial abscesses, and intracranial masses.

· Electrocardiography: Electrocardiography (ECG) is indicated in all patients with HHS because myocardial infarction (MI) and pulmonary embolism (PE) frequently precipitate HHS.

DIAGNOSTIC CRITERIA

Diagnostic features of hyperosmolar hyperglycaemic syndrome (HHS) [13,14,24]

Plasma glucose: ≥600 mg/dL
Arterial pH: ≥7.30
Serum bicarbonate: usually ≥15 mEq/L
Urine ketone: negative or small
Serum ketone: negative or small
Beta-hydroxybutyrate: ≤3 mmol/L
Effective serum osmolality: ≥320 mOsm/kg
Variable anion gap: usually <12 mEq/L
Mental status: lethargy/stupor/coma.

Criteria for resolution of HHS [24]

Plasma glucose <250 to 300 mg/dL
Plasma effective osmolality <315 mOsm/kg
Improvement in haemodynamic and mental status.

TREATMENT

The main goals in the treatment of hyperosmolar hyperglycemic state (HHS) are as follows:

- To vigorously rehydrate the patient while maintaining electrolyte homeostasis
- To correct hyperglycaemia
- To treat underlying diseases/precipitating causes
- To monitor and assist cardiovascular, pulmonary, renal, and central nervous system (CNS) function

Although it is possible to manage mild HHS without admission to the ICU, many cases will require ICU care. Successful treatment requires frequent monitoring of clinical and laboratory parameters to achieve resolution criteria.

Rapid and aggressive intravascular volume replacement is always indicated as the first line of therapy for patients with HHS. Isotonic sodium chloride solution is the fluid of choice for initial treatment because sodium and water must be replaced in these severely dehydrated patients. A reasonable goal of treatment is to replace half of the estimated volume deficit in the first 12 hours of therapy. The remainder of the volume deficit may then be replaced over the second 12-hour period.

Although many patients with HHS respond to fluids alone, IV insulin in dosages similar to those used in diabetic ketoacidosis (DKA) can facilitate correction of hyperglycaemia[12]. Insulin used without concomitant vigorous fluid replacement increases the risk of shock. Insulin or oral hypoglycaemic therapy should be adjusted on the basis of the patient's insulin requirement once serum glucose level has been relatively stabilized.

Frequent reevaluation of the patient's clinical and laboratory parameters are necessary. Recheck glucose concentrations every hour. Electrolytes and venous blood gases should be monitored every 2-4 hours or as clinically indicated.

Diagnosis of precipitating factors, such as urinary-tract infection (UTI), pneumonia, or causative medications, and appropriate treatment with antibiotics, and removal of the offending medication should be initiated[23].

Fluid therapy

Patients with severe volume depletion (100 mL/kg or approximately 7 to 9 L, orthostatic or supine hypotension, dry mucous membranes, and poor skin turgor) should receive fluid resuscitation in addition to maintenance fluid therapy. Hydration status should be continuously evaluated clinically. In the absence of cardiac compromise, patients should receive 0.9% normal saline at a rate of 15-20 mL/kg/hour or 1.0 to 1.5 L during the first hour[14].

Maintenance fluid therapy is based on the corrected serum sodium level. Corrected sodium (mEq/L) = measured sodium (mEq/L) + 0.016 (glucose (mg/dL)-100). In hyponatraemic patients, subsequent fluid therapy may be continued with 0.9% NaCl at 250 to 500 mL/hour; when plasma glucose reaches 300 mg/dL, fluid therapy should be changed to 5% dextrose with 0.45% NaCl at 150 to 250 mL/hour[13,14,15,19,24].

In hypernatraemic or eunatraemic patients, subsequent fluid therapy should be changed to 0.45% NaCl at 250 to 500 mL/hour; when plasma glucose reaches 300 mg/dL, it should be changed to 5% dextrose with 0.45% NaCl at 150 to 250 mL/hour[13,14,15,19,24].

In most patients, adequate monitoring of the volume status entails the use of a urinary catheter. In patients with pre-existing or acute cardiac disease or with diseases in which third-spacing is a problem, use findings from pulmonary capillary wedge pressure monitoring to guide rehydration therapy. Patients with hypotension may require pressor support in the ICU while rehydration is being accomplished. Norepinephrine or dopamine are considered first-line drugs. Dopamine increases stroke volume and heart rate and norepinephrine increases mean arterial pressure

Insulin Therapy for Correction of Hyperglycaemia

All patients with HHS require intravenous (IV) insulin therapy. However, the use of IM insulin therapy in our environment is associated with a rate of fall of Plasma Glucose Level that is more gradual and more predictable. Therefore in settings such as ours where most hyperglycaemic emergency patients are managed outside the tertiary health centers, IMIT protocols should be the preferred route in the management of HEs.[25]

Immediate treatment with insulin is contraindicated in the initial management of patients with HHS. The osmotic pressure that glucose exerts within the vascular space contributes to the maintenance of circulating volume in these severely dehydrated patients. Institution of insulin therapy drives glucose, potassium, and water into cells. This results in circulatory collapse if fluid has not been replaced first. Infuse insulin separately from other fluids, and do not interrupt or suspend the infusion of insulin once therapy is started.

The following steps may be used as a guideline for insulin infusion:

Begin a continuous insulin infusion of 0.1 U/kg/h
Monitor blood glucose by means of bedside testing every hour; if glucose levels are stable for 3 hours, decrease the frequency of testing to every 2 hours
Set the target blood glucose level at 250-300 mg/dL; this target level may be adjusted downward after the patient is stabilized
For a blood glucose concentration lower than 250 mg/dL, decrease the insulin infusion rate by 0.5 U/h
For a blood glucose concentration of 250-300 mg/dL, do not change the insulin infusion rate.
For a blood glucose concentration of 301-350 mg/dL, increase the insulin infusion rate by 0.5 U/h
For a blood glucose concentration higher than 350 mg/dL, increase the insulin infusion rate by 1 U/h
Do not discontinue the insulin drip
If the blood glucose concentration decreases by more than 100 mg/dL between consecutive readings, wait to increase the insulin infusion rate

When the glucose level has been between 200 and 300 mg/dL for at least 1 day and the patient's level of consciousness has improved, glycaemic control may be tightened. The recommended level of glycaemia for most patients with type 2 diabetes mellitus (DM) is 80-120 mg/dL. This correlates to the haemoglobin A1c value of 7% recommended by the American Diabetes Association.

After maintaining adequate glycaemic control with insulin for several weeks after HHS, consider switching patients to an oral regimen.

Lispro Insulin has also been found as a viable alternative to regular insulin in the management of hyperglycaemic emergencies. A study from Ile-Ife concluded that it is not inferior to soluble insulin in the correction of hyperglycaemia, neither does it cause more episodes of hypoglycaemia and hypokalaemia.[26]

ELECTROLYTE REPLACEMENT

Potassium therapy

Insulin therapy and correction of hyperosmolality drive potassium into cells, which may cause serious hypokalaemia. The goal is to maintain potassium levels within the normal range in order to prevent complications of hypokalaemia, including respiratory paralysis and cardiac dysrhythmia. Choices include potassium chloride or potassium phosphate. To avoid excessive chloride administration, one third of the potassium replacement should be administered as potassium phosphate. The choice is also guided by the serum phosphate level. An adequate urine output of >50 mL/hour should be ensured while the patient is on potassium therapy and the hydration status should be continuously evaluated clinically.

- If baseline serum potassium is <3.3 mEq/L, insulin therapy should be delayed until 40 mEq/L of potassium has been given.
- Potassium replacement should be started at 20 to 40 mEq/L if the baseline serum potassium level is between 3.3 to 5.3 mEq/L.
- If the baseline serum potassium level is >5.3 mEq/L, potassium replacement is not needed but levels should be checked every 2 hours[13, 24].

Phosphate, magnesium, and calcium are not replaced routinely, but a patient who is symptomatic with tetany requires replacement therapy.

ON-GOING THERAPY

Management and monitoring should continue until resolution of HHS. Criteria for resolution of HHS are as follows [24]:
Plasma glucose <250 to 300 mg/dL
Plasma effective osmolality <315 mOsm/kg
Improvement in haemodynamic and mental status.
Once HHS is resolved and the patient is able to tolerate oral intake, transition to subcutaneous insulin needs to be made. Patients should be given subcutaneous insulin 1 to 2 hours before the termination of insulin infusion to enable sufficient time for subcutaneous insulin to start work.

COMPLICATIONS

- Cerebral Oedema: Cerebral oedema is rare in HHS and is usually observed in patients much younger than the average age of 60 years. However, it may occur from rapid lowering of glucose levels and an ensuing rapid drop in plasma osmolarity. Brain cells, which trap osmotically active particles, preferentially absorb water and swell during rapid rehydration. Cerebral oedema follows, and, given the constraints of the cranium, uncal herniation may be the cause of death in persons with HHS. However, death from cerebral oedema due to HHS is rare, presumably because the older population that it affects has underlying cerebral atrophy.
- Acute Respiratory Distress Syndrome: Although the precise mechanism by which ARDS develops in persons with HHS remains unclear, a likely scenario is that rapid correction of hyperglycaemia and hyperosmolarity gives rise to pulmonary oedema in much the same manner as it gives rise to cerebral oedema. To compensate for hypoxia and mild acidosis, an increase in the minute ventilation with tachypnoea develops. Continuing pulmonary disease may lead to acute respiratory failure that necessitates full respiratory support, including mechanical ventilation.
- Vascular Complications: The severe dehydration of HHS leads to hypotension and hyperviscosity of the blood, both of which predispose patients to thromboembolic disease of the coronary, cerebral, pulmonary, and mesenteric beds. Disseminated intravascular coagulation (DIC) also may complicate HHS. Together, these vascular syndromes account for much of the morbidity and mortality in HHS. Low-dose subcutaneous heparin is advisable for all patients without a contraindication.

PROGNOSIS

Overall mortality for HHS is typically 10-20%, though figures as high as 58% have been reported. Older age, the presence of concurrent illnesses, and severity of the metabolic derangements (especially dehydration) contribute to this high mortality, as do delay in establishing the diagnosis and failure to treat HHS aggressively from the outset also may contribute to this high mortality rate. In children, mortality from HHS also appears to be higher than mortality from DKA, but too few cases have been reported to allow accurate calculation of paediatric mortality.

CONCLUSION

HHS as one of the major complications of DM is a life threatening medical emergency and management involves a multi-disciplinary approach (an endocrinologist, a neurologist, a critical care specialist and a dietician) for better outcome.

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