Endocrinal Emergencies In ICU

An Essay

for Complete fulfillment of Master Degree in Anesthesiology

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Asmaa Mohammed Abdel Fattah

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List of Abbreviations

ABG	arterial blood gases
ACE	angiotensin converting enzyme
ACLS	advanced cardiac life support
ADH	antidiuretic hormone
APACHE	acute physiology and chronic health evaluation
AVP	arginine vasopressin
BUN	blood urea nitrogen
CBC	complete blood count
CHF	congestive heart failure
CI	confidence interval
CPK	creatine phosphokinase
CSF	cerebrospinal fluid
CT	computed tomography
CVP	central venous pressure
DHEA	dehydroepiandrosterone
DKA	diabetic ketoacidosis
DM	diabetes mellitus
DOC	drug of choice
ED	emergency department
EDTA	ethylenediaminetetraacetic acid

ECG	electrocardiogram
FSH	follicle stimulating hormone
GH	growth hormone
GI	gastrointestinal
HEENT	head ,eyes ,ears ,nose and throat
HSV	herpes simplex virus
HU	hounsfield units
IL-2	interleukin-2
LH	leutinizing hormone
LP	lumbar puncture
MEN	multiple endocrine neoplasia
MI	myocardial infarction
MIBG	metaiodobenzyl guanidine
MRI	magnetic resonance imaging
NMS	neuroleptic malignant syndrome
NPH	neutral protamine hagedron
beta- OHBbetahydroxybutyrate	
PCR	polymerase chain reaction
PET	positron emission tomography
PMN	polymorphonuclear neutrophil
PP	pancreatic polypeptide

PRL	prolactin releasing hormone
PTH	parathyroid hormone
PTHrP parathyroid harmone related peptide	
PTU	propylthiouracil
SCII	subcutaneous continuous insulin infusion
TPO	thyroid peroxidase
TRH	thyrotropin releasing hormone
TSH	thyroid hormone releasing hormone
UTI	urinary tract infection
VBG	venous blood gases
WBC	white blood cell

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Anatomy and Function of the Pituitary Gland

The pituitary gland, or hypophysis, is an endocrine gland about the size of a pea and weighing 0.5 gram. It is a protrusion off the bottom of the hypothalamus at the base of the brain, and rests in a small, bony cavity (sella turcica) covered by a dural fold (diaphragma sellae). The pituitary fossa, in which the pituitary gland sits, is situated in the sphenoid bone in the middle cranial fossa at the base of the brain. It is considered a master gland. The pituitary gland secretes hormones regulating homeostasis, including tropic hormones that stimulate other endocrine glands. It is functionally connected to the hypothalamus by the median eminence. Located at the base of the brain, the pituitary is composed of two lobes: the anterior pituitary (adenohypophysis) and the posterior pituitary (neurohypophysis). The pituitary is functionally linked to the hypothalamus by the pituitary stalk, whereby hypothalamic releasing factors are released and, in turn, stimulate the release of pituitary hormones. Although the pituitary gland is known as the master endocrine gland, both of its lobes are under the control of the hypothalamus. If there are problems with the pituitary gland, it can cause an irregular condition known as gigantism ***(Molitch, 2000)***.

Anterior pituitary

The anterior pituitary synthesizes and secretes important endocrine hormones, such as ACTH, TSH, PRL, GH, endorphins, FSH, and LH. These hormones are released from the anterior pituitary under the influence of the hypothalamus. Hypothalamic hormones are secreted to the anterior lobe by way of a special capillary system, called the hypothalamic-hypophyseal portal system ***(James et al., 2006)***.As seen in fig.1

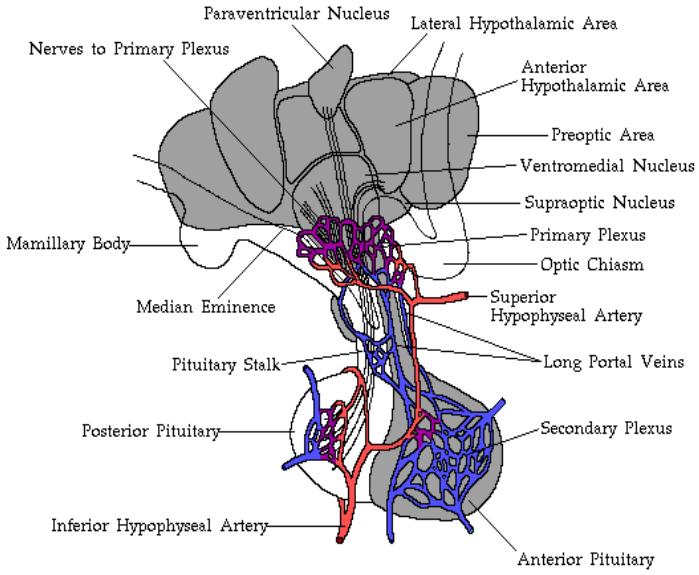

Figure 1. Anatomy and blood supply of pituitary and hypothalamus***(Barkovich, 2000)***.

Posterior pituitary

The posterior pituitary stores and releases Oxytocin, most of which is released from the paraventricular nucleus in the hypothalamus Antidiuretic hormone (ADH, also known as vasopressin and AVP, (arginine vasopressin), the majority of which is released from the supraoptic nucleus in the hypothalamus. Oxytocin is one of the few hormones to create a positive feedback loop. For example, uterine

contractions stimulate the release of oxytocin from the posterior pituitary, which, in turn, increases uterine contractions. This positive feedback loop continues throughout labor ***(James et al., 2006)***.

Anatomy and function of the Pancreas

Insulin is produced from islets of the pancreas, so the anatomy and function of the pancreas are very important. The pancreas is a gland in the digestive and endocrine system of vertebrates. It is both an endocrine gland producing several important hormones, including insulin, glucagon, and somatostatin, as well as an exocrine gland, secreting pancreatic juice containing digestive enzymes that pass to the small intestine. These enzymes help in the further breakdown of the carbohydrates, protein, and fat in the chime ***(Medvei, 1993)***.

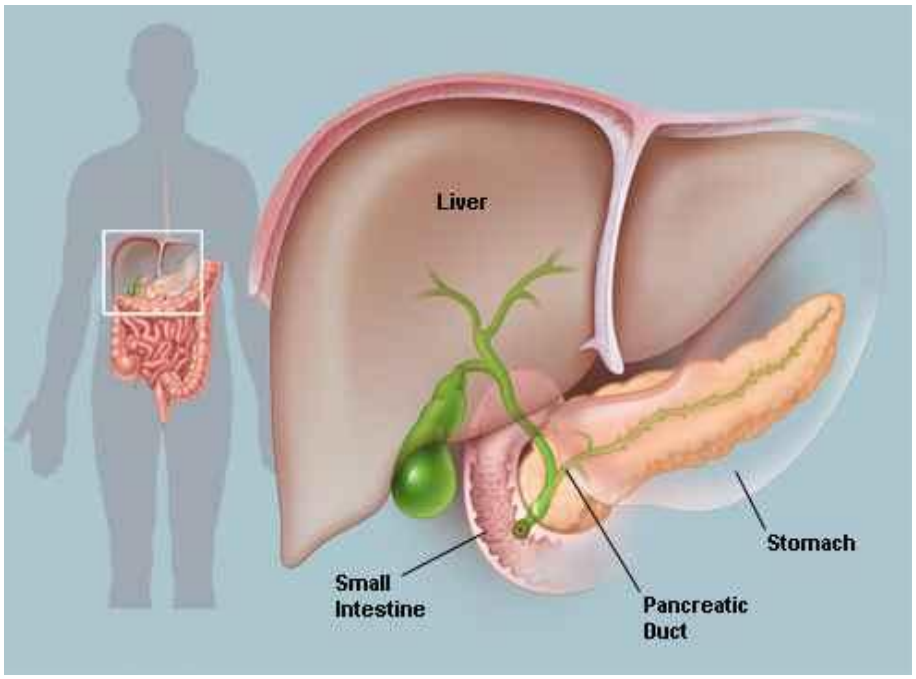

Figure 2 . Anatomy of the pancreas ***(Cabrera et al. 2006)***

Endocrine function :

The part of the pancreas with endocrine function is made up of approximately a million cell clusters called islets of Langerhans. Four main cell types exist in the islets. They can be classified by their secretion: α cells secrete glucagon(increase Glucose in blood), β cells secrete insulin (decrease Glucose in blood), δ cells secrete somatostatin (regulates/stops α and β cells), and PP cells secrete pancreatic polypeptide ***(Rother, 2007).***

Exocrine function:

In contrast to the endocrine pancreas, which secretes hormones into the blood, the exocrine pancreas produces digestive enzymes and an alkaline fluid (referred to as pancreatic juice), and secretes them into the small intestine through a system of exocrine ducts in response to the small intestine hormones secretin and cholecystokinin. Digestive enzymes include trypsin, chymotrypsin, pancreatic lipase, and pancreatic amylase, and are produced and secreted by acinar cells of the exocrine pancreas. Specific cells that line the pancreatic ducts, called centroacinar cells, secrete a bicarbonate- and salt-rich solution into the small intestine ***(Lawrence et al., 2008).***

Anatomy and Function of Thyroid gland

The thyroid gland is one of the largest endocrine glands in the body. This gland is found in the neck inferior to the thyroid cartilage and at approximately the same level as the cricoid cartilage. The thyroid gland is a butterfly shaped organ and is composed of two cone-like lobes or wings: right lobe and left lobe, and is also connected with the isthmus.

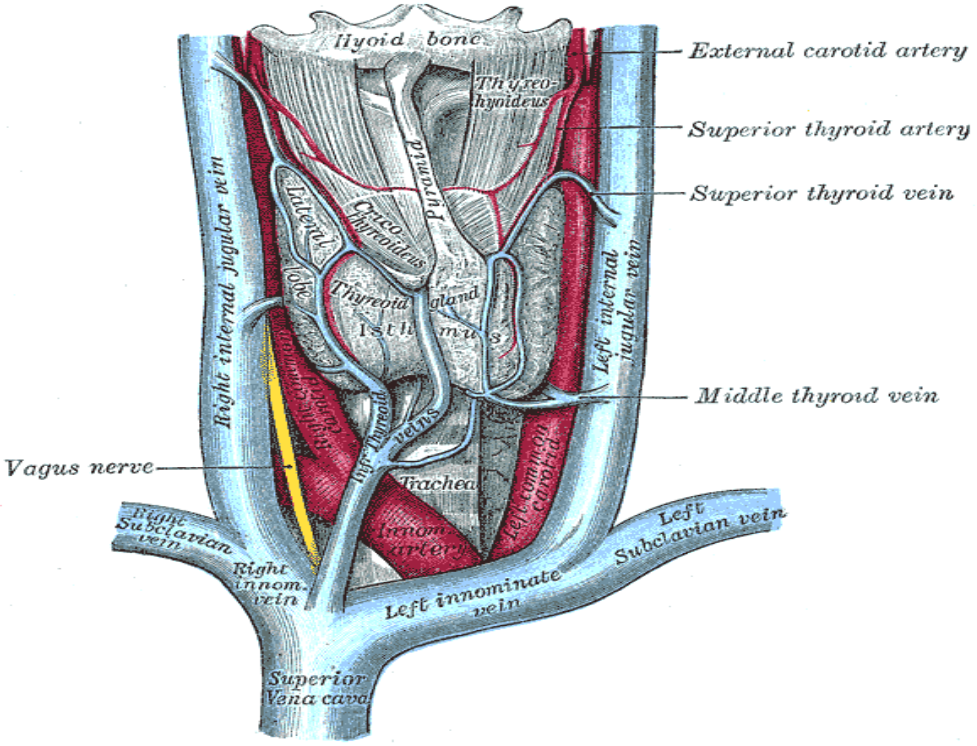

Figure 3. The Thyroid gland and its relations ***(Williams et al., 1995)***

The organ is situated on the anterior side of the neck, lying against and around the larynx and trachea, reaching posteriorly the oesophagus and carotid sheath. It starts cranially at the oblique line on the thyroid cartilage and extends inferiorly to the fifth or sixth tracheal ring. It is difficult to demarcate the gland's upper and lower border with vertebral levels because it moves position in relation to these during swallowing ***(Yalcin and Ozan 2006)*** .

The thyroid controls how quickly the body uses energy, makes proteins, and controls how sensitive the body should be to other hormones. The thyroid participates in these processes by producing thyroid hormones, principally thyroxine (T_4) and triiodothyronine (T_3). These hormones regulate the rate of metabolism and affect the growth and rate of function of many other systems in the body. Iodine and tyrosine are used to form both T_3 and T_4. The thyroid

also produces the hormone calcitonin, which plays a role in calcium homeostasis. The thyroid is controlled by the hypothalamus and pituitary. The gland gets its name from the Greek word for "shield", after the shape of the related thyroid cartilage. Hyperthyroidism and hypothyroidism are the most common problems of the thyroid gland ***(Baskin et al., 2002).***

Physiology :

The primary function of the thyroid is production of the hormones: thyroxine (T_4), triiodothyronine (T_3), and calcitonin. Up to 80% of the T_4 is converted to T_3 by peripheral organs such as the liver, kidney and spleen. T_3 is about ten times more active than T_4. Thyroxine (T_4) is synthesised by the follicular cells from free tyrosine and on the tyrosine residues of the protein called thyroglobulin (Tg). Iodine is captured with the "iodine trap" by the hydrogen peroxide generated by the enzyme thyroid peroxidase (TPO) and linked to the 3' and 5' sites of the benzene ring of the tyrosine residues on Tg, and on free tyrosine. Upon stimulation by the thyroid-stimulating hormone (TSH), the follicular cells reabsorb Tg and proteolytically cleave the iodinated tyrosines from Tg, forming T_4 and T_3 (in T_3, one iodine atom is absent compared to T_4), and releasing them into the blood. Deiodinase enzymes convert T_4 to T_3. Thyroid hormone that is secreted from the gland is about 90% T_4 and about 10% T_3 ***(Bianco et al., 2002).***

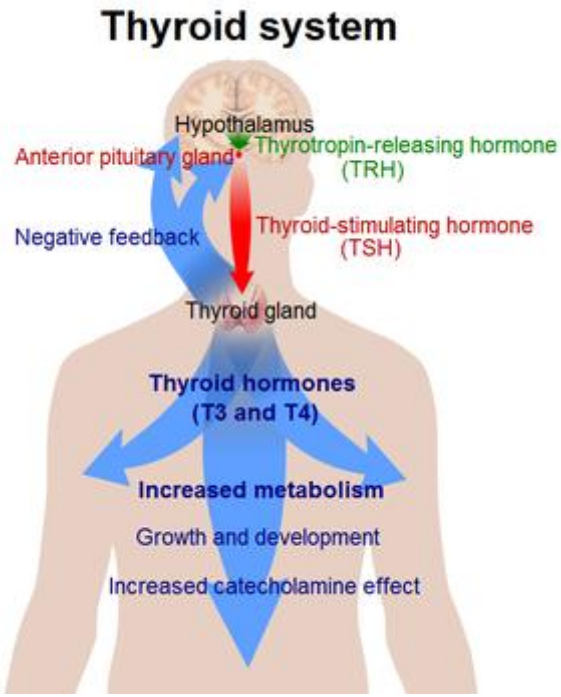

Figure 4. Regulation of the thyroid hormones T_3 and T_4 .***(Hill et al., 1998)***

Cells of the brain are a major target for the thyroid hormones T_3 and T_4. Thyroid hormones play a particularly crucial role in brain maturation during fetal development. A transport protein, organic anion co-transporting polypeptide 1c1 (OATP1C1), has been identified that seems to be important for T_4 transport across the blood brain barrier. A second transport protein, monocarboxylate transporter (MCT8), is important for T_3 transport across brain cell membranes. Non genomic actions of T_4 are those that are not initiated by liganding of the hormone to intranuclear thyroid receptor. These may begin at the plasma membrane or within cytoplasm. Plasma membrane-initiated actions begin at a receptor on the integrin alphaV $beta_3$ that activates ERK1/2. This binding culminates in local membrane actions on ion transport systems such as the Na(+)/H(+) exchanger or complex cellular events including cell proliferation. These integrins are concentrated on cells of the vasculature and on some types of tumor cells which in part explains the proangiogenic effects of iodothyronines and proliferative actions of thyroid hormone on some

cancers including gliomas. T_4 also acts on the mitochondrial genome via imported isoforms of nuclear thyroid receptors to affect several mitochondrial transcription factors. Regulation of actin polymerization by T_4 is critical to cell migration in neurons and glial cells and is important to brain development ***(Jansen et al., 2005).***

T_3 and T_4 regulation : (fig 4)

The production of thyroxine and triiodothyronine is regulated by thyroid-stimulating hormone (TSH), released by the anterior pituitary. The thyroid and thyrotropes form a negative feedback loop: TSH production is suppressed when the T_4 levels are high, and vice versa. The TSH production itself is modulated by thyrotropin-releasing hormone (TRH), which is produced by the hypothalamus and secreted at an increased rate in situations such as cold (in which an accelerated metabolism would generate more heat). TSH production is blunted by somatostatin (SRIH), rising levels of glucocorticoids and sex hormones (estrogen and testosterone), and excessively high blood iodide concentration. An additional hormone produced by the thyroid contributes to the regulation of blood calcium levels. Parafollicular cells produce calcitonin in response to hypercalcemia. Calcitonin stimulates movement of calcium into bone, in opposition to the effects of parathyroid hormone (PTH). However, calcitonin seems far less essential than PTH, as calcium metabolism remains clinically normal after removal of the thyroid, but not the parathyroids ***(Kester et al., 2004)***.

The use of iodised salt is an efficient way to add iodine to the diet. It has eliminated endemic cretinism in most developed countries, and some governments have made the iodination of flour, cooking oil or salt mandatory. Potassium iodide and sodium iodide are typically used forms

of supplemental iodine. As with most substances, either too much or too little can cause problems. Recent studies on some populations are showing that excess iodine intake could cause an inceased prevelence of autoimmune thyroid disease resulting in permanent hypothyroidism ***(Patrick, 2008)***.

Anatomy and physiology of adrenal glands

The adrenal glands each weigh approximately 4 grams in term neonates at birth, which is equivalent to that of adult glands; however, adrenal size decreases by approximately 50% to 60% within the 1st week of life. The adrenal glands are made up of an inner medulla and an outer cortex that are linked by vascular supply and hormonal influence. Within the mature adrenal cortex are 3 functionally distinct zones:

(1) the glomerulosa, comprising approximately 15% of the gland;

(2) fasciculata, the largest zone, comprising approximately 75% of the gland; and

(3) the reticularis, comprising approximately 10% of the gland. The adrenal medulla is regulated by the sympathetic nervous system and secretes catecholamines, whereas the 3 zones of the cortex secrete steroid hormones categorized, respectively, as mineralocorticoids, glucocorticoids, and sex steroids. Mineralocorticoid production, exemplified by aldosterone, is principally regulated by the renin-angiotensin axis and by ambient potassium levels. Mineralocorticoids affect sodium and potassium homeostasis, and deficiencies in their production or action cause hyponatremia, hyperkalemia, and dehydration. Glucocorticoid and adrenal sex steroid production are primarily regulated by pituitary corticotrophin

(adrenocorticotropic hormone [ACTH]) and hypothalamic corticotrophin-releasing hormone, secreted mainly in the early morning hours. Cortisol is the main glucocorticoid, and dehydroepiandrosterone (DHEA) is the main adrenal sex hormone ***(Rozansky, 2006)***.

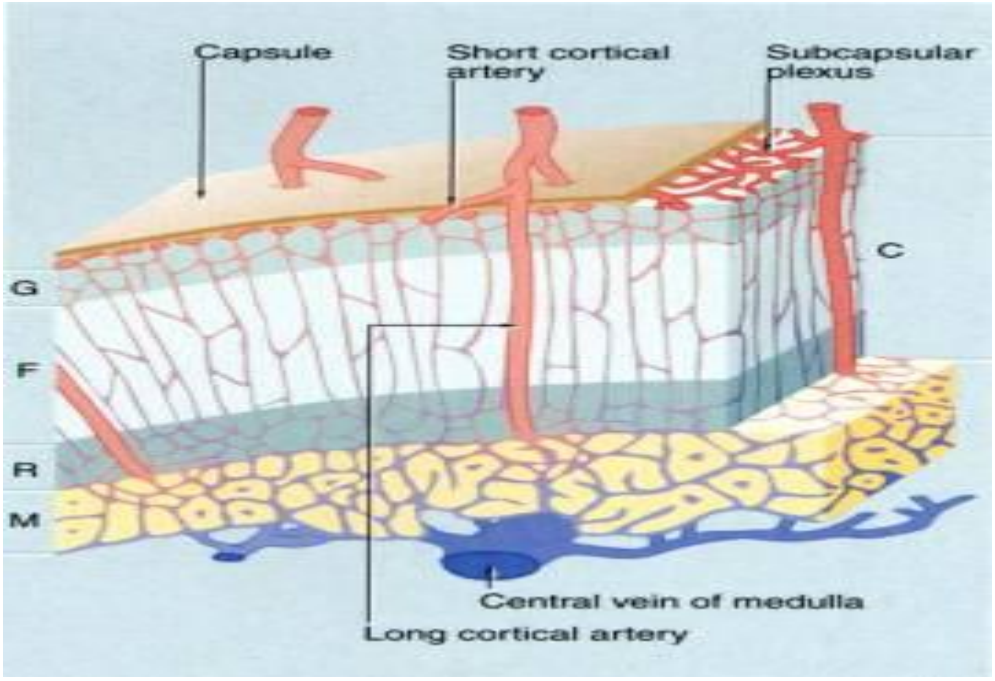

Figure 5. Schematic diagram of the adrenal gland showing its 3 cortical layers and blood supply. G = glomerulosa, F = fasciculata, R = reticularis, M = medulla, C = cortex ***(Barbara and John 2000)***.

Glucocorticoids are generally catabolic, promoting protein and lipid breakdown and inhibiting protein synthesis. The effects of cortisol counterregulate those of insulin, increasing the concentration of glucose by stimulating gluconeogenesis and by decreasing glucose utilization in muscle. Amino acids and glycerol produced by catabolic actions of cortisol on protein and fat are used as gluconeogenic substrates. The net effect is increased production and conservation of glucose for use by essential tissues, such as the brain and red blood cells, at the expense of less essential tissues during times of stress or starvation.

Supraphysiological doses of exogenous glucocorticoids suppress growth by antagonizing the production and action of growth hormones (GHs). Cortisol contributes to the maintenance of normal blood pressure through several mechanisms. Under normal baseline conditions, cortisol increases urine flow by stimulating glomerular filtration rate and decreasing water resorption. At high concentrations, cortisol acts as a mineralocorticoid agonist, causing sodium and water retention***(Bradley et al., 2001)***.

Other vascular actions of cortisol include stimulating angiotensinogen synthesis by the liver and increasing vascular sensitivity to vasopressors. In the adrenal medulla, cortisol is required for the enzymatic activity of phenylethanolamine N-methyltransferase, which converts norepinephrine to epinephrine. Epinephrine stimulates cardiac output, as well as hepatic glucose production. Cortisol decreases capillary permeability, as well as the production and activity of nitrous oxide and the vasodilatory kinin and prostaglandin systems during stress, preventing life-threatening hypotension. Cortisol or aldosterone deficiencies, or both kinds, often result in shock if unrecognized and untreated ***(Bradley et al., 2001)***.

DIABETIC KETOACIDOSIS (DKA)

Introduction:

Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) remains a significant complication of diabetes in both the United States and around the world. Diabetic ketoacidosis remains a significant complication of diabetes in both the United States and worldwide with its associated high rates of hospital admissions. Therefore, it becomes vital that the healthcare professional be able to manage the hyperglycemic crises associated with diabetes. Moreover, with increasing healthcare costs and a changing healthcare system, prevention of diabetic ketoacidosis remains essential. Though management of diabetic ketoacidosis has followed a set algorithm for many years, there are exciting management alternatives on the horizon such as subcutaneous insulin administration for uncomplicated DKA patients. By understanding DKA, including its pathogenesis, presentation, treatment, and prevention, admissions may be decreased and length of stay shortened ***(Michael et al., 2013).***

There are two major hyperglycemic crises associated with diabetes: diabetic ketoacidosis and the hyperosmotic hyperglycemic state. There are ~120,000 admissions for diabetic ketoacidosis and hyperglycemic hyperosmolar state per year in the United States alone Diabetic ketoacidosis primarily results from insulin deficiency and hyperglycemic hyperosmolar state (HHS) from severe insulin resistance. Both of the crises result in subsequent glucagon and counter-regulatory hormone excess from lack of suppression from insulin Normally, with elevated blood glucose, as occurs after a digested meal, there is production and

release of insulin by the beta cells in the islets of Langerhans. With this surge of insulin, the production of new glucose is suppressed appropriately. Conversely, in a state of starvation, there is an increase in counter regulatory hormones such as glucagon in which stores are appropriately mobilized and glucose production increased. This is a catabolic state, which allows for sustenance in times when nutrition is not available ***(Christine, Saraceni, et al., 2013).***

Mortality/Morbidity

When diabetic ketoacidosis (DKA) is treated properly, it rarely causes any residual effects. The overall mortality rate from DKA ranges from 1-10% of all DKA admissions, according to hospital facilities and the experiences of people who have dealt with this acute metabolic condition. Better understanding of the pathophysiology of DKA and proper monitoring and correction of electrolytes has resulted in significant reduction in the overall mortality rate from this life-threatening condition in most developed countries. Mortality rates from DKA have markedly decreased from 7.96% 20 years ago to 0.67% ***(Lin, Huang 2005).***

Best results are always observed in patients treated in ICUs during the first 1-2 days of hospitalization.

In contrast, the mortality rate still is high in developing countries and among nonhospitalized patients. This high mortality rate illustrates the necessity of early diagnosis and the implementation of effective prevention programs.

Cerebral edema remains the most common cause of mortality, particularly in young children and adolescents. Cerebral edema frequently results from rapid intracellular fluid shifts. Other causes of mortality

include severe hypokalemia, adult respiratory distress syndrome, and comorbid states (eg, pneumonia, acute myocardial infarction) ***(Zargar et al., 2009).***

Race:

The incidence of diabetic ketoacidosis is higher in whites because of the higher incidence of type 1 diabetes in this racial group
(Zargar et al., 2009).

Sex:

The incidence of diabetic ketoacidosis (DKA) is slightly greater in females than in males for reasons that are unclear. Recurrent DKA is frequently seen in young women with type 1 diabetes mellitus (DM) and is mostly caused by the omission of insulin treatment
(Zargar et al., 2009).

Age:

Among persons with type 1 diabetes, diabetic ketoacidosis is much more common in young children and adolescents than it is in adults***(Zargar et al., 2009).***.

Causes:

Patients with type 1 diabetes

- Diabetic ketoacidosis (DKA) present at diagnosis of type 1 diabetes due to acute insulin deficiency (occurs in 25% of patients).
- Poor compliance with insulin through the omission of insulin injections either due to lack of patient or guardian education or as a result of psychological stress, particularly in adolescents.
- Bacterial infection and intercurrent illness (eg, UTI, vomiting).

- *Klebsiella pneumoniae* (the leading cause of bacterial infections precipitating DKA).
- Medical, surgical, or emotional stress.
- Brittle diabetes.
- Idiopathic (no identifiable cause).
- Insulin infusion catheter blockage.
- Mechanical failure of insulin infusion pump**(Bowden et al., 2008).**

Patients with type 2 diabetes

- Intercurrent illness (eg, myocardial infarction, pneumonia, prostatitis, UTI).
- Medications(eg, corticosteroids,pentamidine,clozapine).

(Potenza et al., 2009).

Pathophysiology:

In diabetic ketoacidosis (DKA), the balance between catabolism and anabolism is, in a sense, broken. With the lack of insulin, there is decreased storage of glucose, increased breakdown of glycogen stores, and increased synthesis of glucose in both the liver and kidney. To add to the overall hyperglycemic state, there is also a concomitant decreased utilization of glucose in peripheral tissues The situation is complicated by the fact that in this more catabolic state there is breakdown of proteins to form new amino acids that in turn are used to build glucose Moreover, the risk of DKA increases with any increased stress state. In a so-called "stressed state," there is a relative abundance of epinephrine and cortisol. Epinephrine acts to block the action of insulin and stimulates the release of glucagon. Growth hormone also has a similar role as epinephrine and cortisol. In a stressed state, such as infection, myocardial infarction,

intoxication, pregnancy, or stroke there is an increased demand for insulin, but a diminished supply by the stress put on the pancreas **(Potenza et al., 2009).**

While elevated blood glucose from the increased glycogenolysis and gluconeogenesis is certainly a major problem, the cornerstone of DKA lies in ketogenesis. Insulin is normally the most important regulator in production and utilization of ketones. Insulin will inhibit lipolysis and oxidation of free fatty acids. Insulin also increases oxidation of ketones in the peripheral tissues Thus there is both overproduction and underutilization of ketones in an insulin-deficient state Also, glucagon itself will stimulate hormone-sensitive lipase, which in turn mobilizes adipose stores and converts triglycerides to free fatty acids These free fatty acids are then transported across the mitochondrial membrane, and they are eventually used for synthesis of ketones, namely in the form of acetoacetic acid, which is oxidized to form betahydroxybutyrate or decarboxylated to form acetone. Unfortunately, with ketone overproduction, peripheral tissues cannot utilize these molecules and ketosis predominates Conversely, in HHS there is usually enough insulin to suppress ketogenesis, but not control blood sugars In HHNK, blood sugars are usually higher as ketoacidosis produces more severe symptoms and presentation is usually earlier **(Potenza et al., 2009).**

Many of the remaining problems with DKA are from the resultant osmotic diuresis. Elevated blood glucose shifts water into the extracellular compartment. However, the expansion of the extra-cellular compartment is short lived as the ability to reabsorb glucose at the level of the renal tubule is limited and osmotic diuresis occurs. Thus, glycosuria and polyuria result. Water losses are typically greater than electrolyte losses, and thus there is an increased serum osmolality

Polydipsia results from the hyperosmolarity after osmoreceptors are triggered in the brain. Many of the other symptoms may result from the pro-inflammatory state of DKA, and elevated cytokines have been documented during diabetic ketoacidosis Sodium tends to be low secondary to the fact that glucose is osmotically active and will draw fluids into the extracellular space. Potassium is variable based on the degree of acidosis and the time of presentation of the DKA

(Potenza et al., 2009).

Management of DKA

Diagnosis:

Symptoms:

- Insidious increased thirst (ie, polydipsia) and urination (ie, polyuria) are the most common early symptoms of diabetic ketoacidosis (DKA).
- Nausea and vomiting usually occur and may be associated with diffuse abdominal pain.
- Generalized weakness and fatigability may occur.
- Altered consciousness in the form of mild disorientation or confusion is a possible symptom. Although frank coma is uncommon, it may occasionally occur when the condition is neglected or if dehydration or acidosis is severe.
- Symptoms of possible associated intercurrent infection may include fever, dysuria, coughing, malaise, and arthralgia, among others.
- Acute chest pain or palpitation may occur in association with myocardial infarction. Painless infarction is not uncommon in patients with diabetes and should always be suspected in elderly patients.

- Patients may present with a history of failure to comply with insulin therapy or missed insulin injections due to vomiting or psychological reasons.
- History of rapid weight loss is a symptom in patients who are newly diagnosed with type 1 diabetes ***(Lin et al., 2005).***

Physical signs:

- Signs of dehydration - Weak and rapid pulse, dry tongue and skin, hypotension, and increased capillary refill time.
- Patient odor - Characteristic acetone odor
- Signs of acidosis - Shallow rapid breathing or air hunger (Kussmaul or sighing respiration), abdominal tenderness, and disturbance of consciousness
- Although these signs are not usual in all cases of diabetic ketoacidosis (DKA), their presence signifies a severe form of DKA.

- Emphasizing that no direct correlation exists between the degree of acidosis, hyperglycemia, and the disturbances in the level of consciousness is important. ***(Lin et al., 2005)***

- Signs of intercurrent illness - Myocardial infarction, urinary tract infection (UTI), pneumonia, and perinephric abscess, among others:
- Noticing that the body temperature may be within the reference range or low, even in the presence of intercurrent infection, is particularly important.

- Search for signs of infection is mandatory in all case ***(Lin et al., 2005)***

Laboratory Studies:

Urine

- This test is highly positive for glucose and ketones by dipstick testing. Rarely, urine is negative for ketones because most of the available laboratory tests can detect only acetoacetate, while the predominant ketone in severe untreated diabetic ketoacidosis (DKA) is beta hydroxybutyrate. When the clinical condition improves with treatment, the urine test result becomes positive due to the returning predominance of acetoacetate.
- Urine culture helps to identify any possible infecting organisms

(Lin et al., 2005).

Blood and plasma

- The blood glucose level usually is higher than 250 mg/dL.
- Serum ketones are present. Blood beta-hydroxybutyrate (beta-OHB) levels measured by a reagent strip (Ketostix, N-Multistix, and Labstix) and serum ketone levels assessed by the nitroprusside reaction are equally effective in diagnosing DKA among uncomplicated cases.
- Arterial blood gases (ABG) frequently show typical manifestations of metabolic acidosis, low bicarbonate, and low pH (<7.2).
- Serum potassium levels initially are high or within the reference range due to the extracellular shift of potassium in exchange of hydrogen, which is accumulated in acidosis, in spite of severely depleted total body potassium.
- The serum sodium level usually is low.
- The serum chloride levels and phosphorus levels always are low.
- The anion gap is elevated ([Na + K] - [Cl + HCO3] >13 mEq/L).
- Plasma osmolarity usually is increased (>290 mOsm/L). If plasma osmolarity cannot be directly measured, it may be calculated with this

formula: plasma osmolarity = 2 (Na + K) + BUN/3 + glucose/18. Urine osmolarity also is increased.

- Even in the absence of infection, CBC shows increased WBC count.
- BUN frequently is increased.
- Blood culture findings may help to identify any possible infecting organisms***(Lin et al., 2005)***.

Frequency of laboratory studies

- Blood tests for glucose should be performed hourly (until patient is stable, then every 6 h).
- Serum electrolyte determinations should be obtained hourly (until patient is stable, then every 6 h).
- BUN should be performed initially.
- ABG should be performed initially, followed with bicarbonate as necessary***(Glaser et al., 2008).***

Imaging Studies:

- Plain chest radiograph may reveal signs of pneumonia.
- If it occurs during therapy, magnetic resonance imaging (MRI) is helpful in detecting early cerebral edema and should only be ordered if altered consciousness is present ***(Glaser et al., 2008).***

Other Tests:

Electrocardiogram (ECG) :

- This test may reveal signs of acute myocardial infarction that could be painless in patients with diabetes, particularly in those with autonomic neuropathy.
- T-wave changes may produce the first warning sign of disturbed serum potassium levels.
- Low T wave and apparent U wave always signify hypokalemia, while peaked T wave is observed in hyperkalemia.

- ECG should be performed every 6 hours during the first day, unless the patient is monitored ***(Glaser et al., 2008).***

Treatment:

Immediate medical Care:

Managing diabetic ketoacidosis (DKA) in an ICU during the first 24-48 hours is always advisable. When treating DKA, the points that must be considered and closely monitored include correction of fluid loss with IV fluids; correction of hyperglycemia with insulin; correction of electrolyte disturbances, particularly potassium loss; correction of acid-base balance; and treatment of concurrent infection if present Paying great attention to the correction of fluid and electrolyte loss during the first hour of treatment, followed by gradual correction of hyperglycemia and acidosis, always is advisable. Correction of fluid loss makes the clinical picture clearer and may be sufficient to correct acidosis. The presence of even mild signs of dehydration means that at least 3 liters of fluid already have been lost ***(Glaser et al., 2008).***

Fluids: Initial correction of fluid loss is either by isotonic sodium chloride solution or by lactated Ringer solution.

- Administer 1 liter over the first 30 minutes.
- Administer 1 liter over the second hour.
- Administer 1 liter over the following 2 hours.
- Administer 1 liter every 4 hours, depending on the degree of dehydration and central venous pressure (CVP) readings.
- When the patient becomes euvolemic, the physician may switch to half the isotonic sodium chloride solution, particularly if hypernatremia exists.

- When blood sugar decreases to less than 180 mg/dL, isotonic sodium chloride solution is replaced with 5-10% dextrose with half isotonic sodium chloride solution ***(William et al ,2014)***

When insulin treatment is started in patients with DKA, several points must be considered. A low-dose insulin regimen has the advantage of not inducing the severe hypoglycemia or hypokalemia that may be observed with a high-dose insulin regimen.Only short-acting insulin is used for correction of hyperglycemia. Subcutaneous absorption of insulin is reduced in DKA because of dehydration; therefore, using intravenous routes is preferable. ***(William et al ,2014)***

SC use of the fast-acting insulin analog (lispro) has been tried in pediatric DKA (0.15 U/kg q2h). The results were shown to be comparable to IV insulin, but ketosis took 6 additional hours to resolve. Such technically simplified methods may be cost-effective and may preclude admissions to intensive care units in patients with mild cases. Use of subcutaneous insulin analog (aspart) has been shown to be effective as well in adults.The initial insulin dose is a continuous IV insulin infusion using an infusion pump, if available, at a rate of 0.1 U/kg/h. A mix of 24 units of regular insulin in 60 mL of isotonic sodium chloride solution usually is infused at a rate of 15 mL/h (6 U/h) until the blood glucose level drops to less than 180 mg/dL; the rate of infusion then decreases to 5-7.5 mL/h (2-3 U/h) until the ketoacidotic state corrected. ***(Timothy et al, 2014)***

Larger volumes of an insulin and isotonic sodium chloride solution mixture can be used, providing that the infusion dose of insulin is similar. Larger volumes may be easier in the absence of an IV infusion pump (eg, 60 U of insulin in 500 mL of isotonic sodium chloride solution at a rate of 50 mL/h.The optimal rate of glucose decline is 100 mg/dL/h. Do not

allow the blood glucose level to fall below 200 mg/dL during the first 4-5 hours of treatment. Hypoglycemia may develop rapidly with correction of ketoacidosis due to improved insulin sensitivity***(Timothy et al, 2014)***.

Allowing blood glucose to drop to hypoglycemic levels is a common mistake that usually results in a rebound ketosis derived by counter-regulatory hormones. Rebound ketosis necessitates a longer duration of treatment. The other hazard is that rapid correction of hyperglycemia and hyperosmolarity may shift water rapidly to the hyperosmolar intracellular space and may induce cerebral edema. Although DKA was a common problem in patients with diabetes who were treated with continuous subcutaneous insulin infusion through insulin infusion pumps, the incidence of DKA was reduced with the introduction of pumps equipped with sensitive electronic alarm systems that alert users when the infusion catheter is blocked***(William et al , 2014).***

Electrolyte correction:

Potassium

- If the potassium level is greater than 6 mEq/L, do not administer potassium supplement.
- If the potassium level is 4.5-6 mEq/L, administer 10 mEq/h of potassium chloride.
- If the potassium level is 3-4.5 mEq/L, administer 20 mEq/h of potassium chloride.
- Monitor serum potassium levels hourly, and the infusion must stop if the potassium level is greater than 5 mEq/L.
- Monitoring of serum potassium must continue even after potassium infusion is stopped in the case of (expected) recurrence of hypokalemia ***(William et al , 2014).***

- In severe hypokalemia, not to starting insulin therapy is advisable unless potassium replacement is underway in order to avoid potentially serious cardiac dysrhythmia that may result from hypokalemia.

Correction of acid-base balance:

- Sodium bicarbonate only is infused if decompensated acidosis starts to threaten the patient's life, especially when associated with either sepsis or lactic acidosis.
- If sodium bicarbonate is indicated, 100-150 mL of 1.4% concentration is infused initially. This may be repeated every half hour if necessary.
- Rapid and early correction of acidosis with sodium bicarbonate may worsen hypokalemia and cause paradoxical cellular acidosis ***(Pugliese et al., 2009).***

Treatment of concurrent infection:

- In the presence of infection, administer proper antibiotics guided by the results of culture and sensitivity studies.

  Starting empiric antibiotics on suspicion of infection until culture results are available may be advisable ***(Weber et al., 2009).***

Follow-up:

Further Inpatient Care:

Patients are not usually discharged from the hospital unless they have switched back to their daily insulin regimen without recurrence of ketosis. When the condition is stable, pH is greater than 7.3, and bicarbonate is greater than 18 mEq/L, the patient is allowed to eat a meal preceded by an SC dose of regular insulin. Insulin infusion can be discontinued 30 minutes later. If the patient is still nauseated and cannot eat, continue dextrose infusion and administer regular or ultra–short-acting insulin SC every 4 hours according to blood glucose level, while

trying to maintain blood glucose values at 100-180 mg/dL. In established patients with diabetes, SC long-acting insulin (eg, insulin glargine, Detemir, Ultralente) should be initiated back at the same dose that was used prior to diabetic ketoacidosis. However, if neutral protamine Hagedorn (NPH) insulin was previously used, start back at the usual dose only when the patient eats well and is able to retain meals without vomiting; otherwise, the dose should be reduced to avoid hypoglycemia during its peak efficacy period. In newly diagnosed patients with type 1 DM, a careful estimate of the long-acting insulin dose should be considered. Starting with smaller doses generally is recommended to avoid unneeded hypoglycemia ***(Weber et al., 2009).***

Complications:

The most widely recognized complications of DKA treatment include exogenous insulin-induced hypoglycemia and hypokalemia. The effect of bicarbonate therapy may also worsen hypokalemia. These complications may be avoided with the use of dextrose-containing solutions when blood glucose falls below 250 mg/dL with a concomitant reduction in the rate of insulin delivery as well as the addition of potassium to replacement fluids Additionally, abrupt discontinuation of intravenous insulin therapy after resolution of DKA without overlapping subcutaneous insulin coverage may precipitate hyperglycemia Although rare in adult patients***(Michael et al., 2013).***

cerebral edema is a complication of DKA treatment with significant morbidity and mortality Its hallmarks include rapid deterioration in the level of consciousness and headache. Other manifestations include seizure, bradycardia, incontinence, respiratory arrest, and eventual brain-stem herniation. Theoretically, cerebral edema develops when water is osmotically driven into the central nervous system;

plasma osmolality declines too rapidly during replacement of sodium and water deficits in DKA treatment Gradual correction of the hyperosmolar state in addition to adding dextrose to intravenous fluids when blood glucose falls below 250 mg/dL may avert this risk***(Michael et al., 2013).*** .

Hypoxemia and noncardiogenic pulmonary edema may result secondary to falling colloid osmotic pressure and subsequent increase in lung water content and diminished lung compliance A rare but highly morbid complication of DKA is ARDS Ominous signs include a widened A-a gradient, dyspnea, hypoxemia, rales or infiltrates during routine resuscitation as well as severe acidemia Lastly, vascular thrombosis may occur in the setting of critical illness and low dose heparin or low molecular weight heparin should be considered for prophylaxis ***(Christine, Saraceni, et al., 2013).*** .

Nonspecific myocardial injury may occur in severe DKA, which is associated with minute elevations of myocardial biomarkers (troponin T and CK-MB) and initial ECG changes compatible with myocardial infarction (MI). Acidosis and very high levels of free fatty acids could cause membrane instability and biomarker leakage. Coronary arteriography usually is normal, and patients usually recover fully without further evidence of ischemic heart disease. Regardless of the pathogenesis, the presence of minute biomarker elevations and ECG changes do not necessarily signify MI in DKA ***(Moller et al., 2005).***

Microvascular changes consistent with diabetic retinopathy have been reported prior to and after treatment of DKA; however, the blood-retinal barrier does not experience the same degree of perturbation as the blood-brain barrier does ***(Martin et al., 2005).***

Prognosis:

The prognosis of properly treated patients with diabetic ketoacidosis is excellent, especially in younger patients if intercurrent infections are absent. The worst prognosis is usually observed in patients who are older with severe intercurrent illnesses, eg, myocardial infarction, sepsis, or pneumonia, especially when they are treated outside an ICU. The presence of deep coma at the time of diagnosis, hypothermia, and oliguria are signs of poor prognosis **(Martin et al., 2005).**

THYROID STORM

Introduction:

Thyroid storm is a clinical manifestation of an extreme hyperthyroid state that results in significant morbidity or disability or even death. Previously, thyroid storm was a common complication of toxic goiter surgery during intraoperative and postoperative stages. Preoperative control of the thyrotoxic state and use of radioiodine ablation has greatly reduced this phenomenon. Today, thyroid storm more commonly is seen in a thyrotoxic patient with intercurrent illness or surgical emergency. Early recognition and prompt intervention are necessary
(Migneco et al., 2005).

Epidemiology:

Presently, incidence is less than 10% among patients hospitalized for thyrotoxicosis***(Migneco et al., 2005).***

Mortality/Morbidity:

Thyroid storm, considered a fulminating state, is fatal when untreated. Although methods of diagnosis and management have improved considerably, reported mortality still is 20-30%. Although it can develop in toxic adenoma or multinodular toxic goiter, thyroid storm is more commonly seen in toxicity secondary to Grave's disease ***(Nakamura et al., 2005).***

Sex:

Age and sex predilection depends on the etiology of thyrotoxicity. Graves disease more frequently develops in females (ie, male-to-female ratio ranges from 1:7 to 1:10); multinodular goiter more often manifests in the elderly population ***(Nakamura et al., 2005).***

Causes:

A precipitating factor usually is found with thyroid storm. Presently, the most common cause of thyroid storm is intercurrent illness or infection (ie, medical storm)

Some causes that rapidly increase the thyroid hormone levels include the following:

- Surgery, thyroidal or nonthyroidal.
- Radioiodine therapy.
- Withdrawal of antithyroid drug therapy.
- Vigorous thyroid palpation.
- Iodinated contrast dye.
- Thyroid hormone ingestion.
- Other common precipitants include the following:
- Infection.
- Emotional stress.
- Tooth extraction.
- Diabetic ketoacidosis.
- Hypoglycemia.

- Trauma.
- Bowel infarction.
- Toxemia of pregnancy.
- Pulmonary embolism.
- Cerebrovascular accident ***(Migneco et al., 2005).***

Management of thyroid storm

Diagnosis:

History:

Clinical features form the hallmark in diagnosing thyroid storm. Most patients have goiter, and many of those with Graves disease have concurrent ophthalmopathy. Frequently, a past history of thyroid disease that has been partially treated exists ***(Nakamura et al., 2005).***

Physical examination:

An accentuation of signs and symptoms is seen in uncomplicated thyrotoxicosis. The point of transition from uncomplicated thyrotoxicosis to thyroid storm is difficult to ascertain. Very few criteria define the change. However, certain clinical features (eg, high-grade fever, decompensation of one or more organ systems secondary to the severe state of hypermetabolism) reveal its onset ***(Tietgens and Leinung 2006).***

The Following table presents some changes in the symptoms and signs of thyroid storm when compared with uncomplicated thyrotoxicosis. Importantly, some findings of thyroid storm (eg, atrial dysrhythmia) may also occur in uncomplicated thyrotoxicosis.

Therefore, the table represents only guidelines, not specific criteria to define thyroid storm ***(Tietgens and Leinung 2006).***

Uncomplicated Thyrotoxicosis	Thyroid Storm
1.Heat intolerance, diaphoresis	1.Hyperpyrexia, temperature in excess of 106o F, dehydration
2.Sinus tachycardia, heart rate 100-140	2.Heart rate faster than 140 beats/min, hypotension, atrial dysrhythmias, congestive heart failure
3.Diarrhea, increased appetite with loss of weight	3.Nausea, vomiting, severe diarrhea, abdominal pain, hepatocellular dysfunction-jaundice
4.Anxiety, restlessness	4.Confusion, agitation, delirium, frank psychosis, seizures, stupor or coma

Table (1): Manifestations of thyrotoxicosis versus thyroid storm ***(Tietgens and Leinung 2006).***

Certain unusual presentations include chest pain, acute abdomen, status epilepticus, stroke, acute renal failure due to rhabdomyolysis, and apathetic thyroidism. apathetic thyroidism (ie, masked hyperthyroidism) 60 years ago. Apathetic thyroidism more frequently was seen in elderly patients but since has been described in all ages. Patients in this variant group present without goiter, ophthalmopathy, or prominent symptoms of hyperthyroidism. These patients have a low pulse rate and a propensity to develop thyroid storm due to delay in diagnosis ***(Tietgens and Leinung 2006).***

Differential diagnosis:

Postoperative complications (eg, sepsis, hemorrhage, septicemia, transfusion drug reactions) mimic the thyrotoxic state. Previous history of hyperthyroidism, precipitating factors, increased T_3 and T_4 levels, and decreased thyroid stimulating hormone (TSH) levels help to establish the diagnosis of thyroid storm. ***(Morgan et al., 2006).***

Thyroid storm can be differenciated from malignant hyperthermia by that it is not associated with muscle rigidity, elevated creatine kinase, or a marked degree of metabolic (lactic) and respiratory acidosis.The neuroleptic malignant syndrome (NMS) is a rare, but life-threatening, idiosyncratic reaction to a neuroleptic medication. The syndrome is characterized by fever, muscular rigidity, altered mental status, and autonomic dysfunction. Although potent neuroleptics (eg, haloperidol, fluphenazine) are more frequently associated with NMS, all antipsychotic agents, typical or atypical, may precipitate the syndrome ***(Strawn et al., 2007).***

Laboratory Studies:

- Presently, no specific diagnostic criteria to establish the diagnosis of thyroid storm exist.

- Burch and Wartofsky have constructed an excellent clinical diagnostic point scale to facilitate a semiquantitative distinction between uncomplicated thyrotoxicosis, impending storm, and established thyroid storm. Laboratory findings in thyroid storm are consistent with those of thyrotoxicosis and include the following:

- Elevated T_3 and T_4 levels.

- Elevated T_3 uptake.
- Suppressed TSH levels.
- Elevated 24-hour radioiodine uptake.
- Elevated T_4 and decreased TSH are the only abnormal findings needed for conformation of thyrotoxicosis. Treatment should not be withheld for any laboratory confirmation of hyperthyroidism when thyroid storm is suspected clinically. A 2-hour radioiodine uptake is advisable if thyroid storm is suspected and no past history of hyperthyroidism exists***(Strawn et al., 2007).***

Other abnormal laboratory values that point toward decompensation of homeostasis include the following:

- Increased BUN and creatinine kinase.
- Electrolyte imbalance from dehydration, anemia, thrombocytopenia, and leukocytosis.
- Hepatocellular dysfunction as shown by elevated levels of transaminases, lactate dehydrogenase, alkaline phosphatase, and bilirubin.
- Elevated calcium levels.
- Hyperglycemia ***(Strawn et al., 2007).***

Treatment:

Medical Care:

Management of thyroid storm is a multi-step process. Blocking the synthesis, secretion, and peripheral action of the thyroid hormone is the ideal therapy. Aggressive supportive therapy then is used to stabilize homeostasis and reverse multiorgan decompensation. Additional measures are taken to identify and treat the precipitating factor, followed by definitive treatment to avoid recurrence. Thyroid storm is a fulminating crisis that demands an intensive level of care, continuous monitoring, and vigilance ***(Rosenberg, 2006).***

Blocking thyroid hormone synthesis:

Antithyroid compounds propylthiouracil (PTU) and methimazole (MMI) are used to block the synthesis of the thyroid hormone. propylthiouracil also blocks peripheral conversion of T_4 to T_3 and hence is preferred in thyroid storm over methimazole. methimazole is the common agent used in hyperthyroidism. propylthiouracil and methimazole block the incorporation of iodine into thyroglobulin within 1 hour of ingestion. A history of hepatotoxicity or agranulocytosis from previous thioamide therapy precludes use of propylthiouracil and methimazole. PTU is considered as a second-line drug therapy, except in patients who are allergic or intolerant to methimazole, or for women who are in the first trimester of pregnancy***(Rosenberg, 2006).***

Blocking thyroid hormone secretion:

After initiation of antithyroid therapy, hormone release can be inhibited by large doses of iodine, which reduce thyroidal iodine uptake. Lugol solution or saturated solution of potassium iodide can be used.

Iodine therapy should be administered after approximately 1 hour following administration of PTU or MMI; iodine used alone helps to increase thyroid hormone stores and may increase the thyrotoxic state. The iodinated x-ray contrast agent, sodium ipodate, can be administered instead of iodine and also inhibits peripheral conversion of T_4 to T_3. Potassium iodide (KI) decreases thyroidal blood flow and hence is used preoperatively in thyrotoxicosis. Patients intolerant to iodine can be treated with lithium, which also impairs thyroid hormone release. Patients unable to take PTU or MMI also can be treated with lithium, as use of iodine alone is debatable. Unlike iodine, lithium is not subject to the escape phenomenon; lithium blocks the release of thyroid hormone throughout its administration***(Rosenberg 2006).***

Plasmapheresis, plasma exchange, peritoneal dialysis exchange transfusion, and charcoal plasma perfusion are other techniques used to remove excess circulating hormone. Presently, these techniques are reserved for patients who do not respond to the initial line of management ***(Ingbar, 2000).***

Blocking peripheral action of thyroid hormone:

Propranolol is the drug of choice to counter peripheral action of thyroid hormone. Propranolol blocks beta-adrenergic receptors and prevents conversion of T_4 to T_3. It produces dramatic improvement in clinical status and greatly ameliorates symptoms Propranolol produces the desired clinical response in thyroid storm only after large doses. Intravenous administration of propranolol requires continuous monitoring of cardiac rhythm ***(Ingbar, 2000).***

Presently, esmolol is the ultra-short-acting beta-blocking agent used successfully in thyrotoxicosis and thyroid storm. Noncardioselective beta-

blockers (eg, propranolol, esmolol) cannot be used in patients with congestive cardiac failure, bronchospasm, or history of asthma. Guanethidine or reserpine can be used instead in these cases Successful treatment with reserpine in cases of thyroid storm resistant to large doses of propranolol has been documented. However, guanethidine and reserpine cannot be used in the presence of cardiovascular collapse or shock ***(Ingbar, 2000).***

Supportive measures:

- Aggressive fluid and electrolyte therapy is needed for dehydration and hypotension. This excessive hypermetabolic state, with increased intestinal transit and tachypnea, leads to immense fluid loss. Fluid requirements may increase to 3-5 L/day. Therefore, invasive monitoring is advisable in elderly patients and in those with congestive cardiac failure ***(Ingbar, 2000).***

Pressor agents can be used when hypotension persists following adequate fluid replacement. Add glucose to IV fluids for nutritional support. Multivitamins, especially vitamin B-1, are added to prevent Wernicke encephalopathy ***(Ingbar, 2000).***

Hyperthermia:

is treated through central cooling and peripheral heat dissipation. Acetaminophen is the drug of choice, as aspirin may displace thyroid hormone from binding sites and increase severity of thyroid storm. Cooling blankets, ice packs, and alcohol sponges encourage dissipation of heat. Use of a cooled humidified oxygen tent is advised ***(Rosenberg 2006).***

Use of glucocorticoids in thyroid storm is associated with improved survival rates. Initially, glucocorticoids were used to treat potential relative insufficiency due to accelerated production and degradation owing to the hypermetabolic state. However, the patient may have type 2 autoimmune deficiency, in which Graves disease coexists with absolute adrenal insufficiency . Glucocorticoids reduce iodine uptake and antibody titers of thyroid-stimulating antibodies with stabilization of the vascular bed. In addition, dexamethasone and hydrocortisone have an inhibitory effect on conversion of T_4 to T_3. Therefore, a stress dose of glucocorticoid (eg, hydrocortisone, dexamethasone) now is routine***(Scholz et al., 2003).***

Cardiac decompensation, although seen more frequently in elderly patients, may appear in younger patients and in patients without underlying cardiac disease Digitalization is required to control the ventricular rate in patients with atrial fibrillation ***(Scholz et al., 2003).***

Anticoagulation drugs may be needed for atrial fibrillation and can be administered in the absence of contraindications ***(Martin, 2009).***

Medications:

Antiadrenergic drugs:

Promptly administer antiadrenergic drugs (eg, propranolol) to minimize sympathomimetic symptoms. Propranolol is administered orally or via nasogastric tube at a dose of 60-80 mg every 4-6 hours and the dose adjusted based on heart rate and blood pressure. It may also be given intravenously when necessary for rapid onset of action (0.5-1 mg over 10 min followed by 1-2 mg over 10 min every few hours, adjusted based on vital signs). It is important to avoid propranolol in conditions

such as asthma, chronic obstructive pulmonary disease, peripheral vascular disease, or decompensated heart failure. Cardioselective beta blockers such as atenolol or metoprolol may be administered in patients with reactive airway disease, and calcium channel blockers may be used when beta blockers are contraindicated. The use of intravenous short acting beta-1 blockers, such as esmolol (loading dose of 250-500 mcg/kg, followed by an infusion of 50-100 mcg/kg per minute), allows quick dose titration with minimization of side effects (***Madhusmita et al, 2016).***

Dosing of beta blockers for thyroid storm in a pediatric population:

Propranolol: Neonates: 2 mg/kg per day PO/NGT divided every 6-12 hours; **Children:** 0.5-4 mg/kg per day PO/NGT divided every 6 hours (not to exceed 60 mg per day) or 0.01-0.02 mg/kg IV over 10 minutes (may repeat over 10' every few hours to a maximum cumulative dose of 5 mg) ***(Rosenberg 2006).***

Esmolol:

Loading dose: 250-500 mcg/kg over 1 minute, repeat as needed, maintenance dose: 50-100 mcg/kg per minute IV infusion***(Rosenberg 2006).***

Thionamides:

Correct the hyperthyroid state. Administer antithyroid medications to block further synthesis of thyroid hormones (THs) ***(Rosenberg 2006).***

High-dose propylthiouracil (PTU) is preferred over methimazole for treatment of severe thyroid storm because of its early onset of action and capacity to inhibit peripheral conversion of T4 to T3. Methimazole may be used in less severe cases. Dosing for thyroid storm in adults is as

follows: PTU 200 mg every four hours or methimazole 20 mg orally every four to six hours; these drugs may need to be administered through a nasogastric tube***(Stephen et al, 2016)***.

Dosing of PTU for thyroid storm in children: Neonates: 5-10 mg/kg per day PO/NGT divided every 6-8 hours; Children: 15-20 mg/kg per day PO/NGT divided every 6-8 hours (up to 40 mg/kg per day has been used; not to exceed 1200 mg per day ***(Stephen et al, 2016)***.

The US Food and Drug Administration (FDA) has added a boxed warning, the strongest warning issued by the FDA, to the prescribing information for PTU.

The boxed warning emphasizes the risk for severe liver injury and acute liver failure, some of which have been fatal. The boxed warning also states that PTU should be reserved for use in those who cannot tolerate other treatments such as methimazole, radioactive iodine, or surgery(***Madhusmita et al, 2016).***

The decision to include a boxed warning was based on the FDA's review of postmarketing safety reports and meetings held with the American Thyroid Association, the National Institute of Child Health and Human Development, and the pediatric endocrine clinical community (***Madhusmita et al, 2016).***

The FDA has identified 32 cases (22 adult and 10 pediatric) of serious liver injury associated with PTU. Among adults, 12 deaths and 5 liver transplants occurred; among the pediatric patients, 1 death and 6 liver transplants occurred. ***(Stephen et al, 2016)***. PTU is indicated for hyperthyroidism due to Graves' disease. These reports suggest an increased risk for liver toxicity with PTU compared with methimazole.

Serious liver injury has been identified with methimazole in 5 cases (3 resulting in death***(Stephen et al, 2016)***.

PTU is now considered as a second-line drug therapy for treatment of hyperthyroidism in general (though not thyroid storm), except in patients who are allergic or intolerant to methimazole, or women who are in the first trimester of pregnancy. Rare cases of embryopathy, including aplasia cutis, have been reported with methimazole during pregnancy. For more information, The FDA recommends the following criteria be considered for prescribing PTU. Reserve PTU use for during first trimester of pregnancy or for patients who are allergic to or intolerant of methimazole. Closely monitor patients undergoing PTU therapy for signs and symptoms of liver injury, especially during the first 6 months after initiation of therapy. For suspected liver injury, promptly discontinue PTU therapy and evaluate for evidence of liver injury and provide supportive care ***(Stephen et al, 2016)***.

PTU should not be used in pediatric patients unless the patient is allergic to or intolerant of methimazole and no other treatment options are available. Counsel patients to promptly contact their health care provider for the following signs or symptoms: fatigue, weakness, vague abdominal pain, loss of appetite, itching, easy bruising, or yellowing of the eyes or skin. If the patient is given PTU during treatment of thyroid storm, this should be switched to methimazole at the time of discharge unless methimazole is contraindicated. If methimazole is contraindicated, alternative methods to treat hyperthyroidism should be considered after discharge, such as radioactive iodine or surgery***(Stephen et al, 2016)***.

Iodine compounds:

Administer iodine compounds (Lugol iodine or potassium iodide) orally or via a nasogastric tube to block the release of THs (at least 1 h after starting antithyroid drug therapy). In adults, KI is a given at a dose of 5 drops every 6 hours, or Lugol's iodine at a dose of 10 drops every 8 hours. If available, intravenous radiocontrast dyes such as ipodate and iopanoate can be effective in this regard. These agents are particularly effective at preventing peripheral conversion of T4 to T3***(Stephen et al, 2016)***.

Dosing of iodine compounds for thyroid storm in children:

SSKI (50 mg iodide per drop): Neonates: 2 drops PO/NGT every 6-8 hours; Children: 2-5 drops PO/NGT every 6 hours

Lugol's iodine (8 mg iodine/drop): 10 drops PO/NGT every 8 hours***(Stephen et al, 2016)***.

Glucocorticoids

Administer glucocorticoids to decrease peripheral conversion of T4 to T3. This may also be useful in preventing relative adrenal insufficiency due to hyperthyroidism and improving vasomotor symptoms. Hydrocortisone is administered intravenously at a dose of 100 mg every 8 hours or dexamethasone at a dose of 1-2 mg every 6 hours (***Madhusmita et al, 2016).***

Dosing of glucocorticoids for thyroid storm in children:

Hydrocortisone: 5 mg/kg (up to 100 mg) intravenously every 6-8 hours

Dexamethasone: 0.1-0.2 mg/kg per day divided every 6-8 hours

Bile acid sequestrants prevent reabsorption of free THs in the gut (released from conjugated TH metabolites secreted into bile through the enterohepatic circulation). A recommended dose is 4 g of cholestyramine every 6 hours via a nasogastric tube (***Madhusmita et al, 2016).***

Treatment of the underlying condition, if any, that precipitated thyroid storm and exclude comorbidities such as diabetic ketoacidosis and adrenal insufficiency. Infection should be treated with antibiotics. Rarely, as a life-saving measure, plasmapheresis has been used to treat thyroid storm in adults. Iodine preparations should be discontinued once the acute phase resolves and the patient becomes afebrile with normalization of cardiac and neurological status. Glucocorticoids should be weaned and stopped and the dose of thioamides adjusted to maintain thyroid function in the normal range. Beta-blockers may be discontinued once thyroid function normalizes. If the patient is given PTU during treatment of thyroid storm, this should be switched to methimazole at the time of discharge unless methimazole is contraindicated. If there is a contraindication for the use of methimazole, alternative methods to treat hyperthyroidism should be considered after discharge, such as radioactive iodine or surgery. (***Madhusmita et al, 2016)***

Patients with contraindications to thionamides need to be managed with supportive measures, aggressive beta blockade, iodine preparations, glucocorticoids and bile acid sequestrants for about a week in preparation for a thyroidectomy. Plasmapheresis may be attempted if other measures are not effective (***Madhusmita et al, 2016)***.

Prevention:

Identification of precipitating factors:

- Surgery and anesthesia induction, labor, thioamide withdrawal, and use of radioiodine are known precipitants of thyroid storm. However, these precipitants may not be discovered frequently.
- Precipitating factors are not found in all patients, but a meticulous search improves chances for a successful outcome.
- Chest radiographs and blood, urine, and sputum cultures may be needed to identify intercurrent illness (eg, infection).
- Judicious use of empiric antibiotics is needed if no obvious source is found ***(Stephen et al, 2016)***.

Prevention of recurrence:

- Prevention of a recurrent crisis should be the main objective until completion of definitive therapy.
- Vigilant monitoring of signs and symptoms of hyperthyroidism during preoperative or pre-anesthetic evaluation is paramount. =
- Consider precipitating factors when deciding on treatment modalities.
- Adequate control of the thyrotoxic state prior to initiation of definitive therapy is important. Carry out procedures only after the patient is euthyroid ***(Stephen et al, 2016)***.

MYXEDEMA COMA

Introduction:

myxedema has been applied to several clinical entities and is often used interchangeably with severe hypothyroidism, the common clinical condition in which the thyroid gland produces abnormally low levels of hormones. Myxedema also refers to 2 different dermatologic conditions. Pretibial myxedema, an uncommon skin disorder, occurs not in cases of hypothyroidism but in hyperthyroid states, including, most commonly, Graves disease. The term pretibial is somewhat misleading, because the condition can affect other areas of the body and could more accurately be called localized dermopathy. The other skin condition, called myxedema, occurs in severe, long-standing hypothyroid states and is caused by the deposition of mucopolysaccharides within the dermis. Myxedema coma, an uncommon but life-threatening form of untreated hypothyroidism with physiological decompensation ***(Wall, 2000)***. The condition occurs in patients with long-standing, untreated hypothyroidism and is usually precipitated by a secondary insult, such as climate-induced hypothermia, infection, or another systemic condition, or drug therapy. Patients with myxedema coma have changes in their mental status, including lethargy, stupor, delirium, or coma. A more appropriate term for myxedema coma is myxedema crisis; we often use the term myxedema coma/crisis

(Fliers and Wiersinga 2003).

Epidemiology:

hypothyroidism is a common disorder in the older population; in the United States, the condition is present in 8% of women and 2% of men older than 50 years. Myxedema coma is a rare consequence of

untreated hypothyroidism. In areas in which the population ingests sufficient iodine, the most common cause of hypothyroidism is autoimmune thyroid disease and thyroid ablation therapy, with a prevalence of approximately 8% of women aged 50 years or older ***(Kwaku and Burman 2007)***.

In regions where not enough iodine is ingested, the most common cause of hypothyroidism is iodine deficiency, with the prevalence of hypothyroidism correlating with the iodine content of the diet. Severe hypothyroidism (neonatal thyrotropin [TSH] >5 mU/L in >40% of births) and cretinism are observed with severe iodine deficiency (< 20 mcg/dL). Iodine deficiency of this magnitude is generally observed only in isolated, mountainous regions of South America, Africa, and Asia. The prevalence of myxedema coma/crisis in the populations of these areas is unknown ***(Rodriguez et al., 2004)***.

Mortality/Morbidity:

Myxedema coma/crisis is a metabolic and cardiovascular emergency. If the condition is not promptly diagnosed and treated, the mortality rate is approximately 50% or more. Even with immediate recognition and appropriate medical intervention, mortality rates of up to 25% are observed. Factors suggesting a poor prognosis are a body temperature of less than 93° F, persistent hypothermia that is unresponsive to 72 hours of therapy, advanced age, bradycardia (< 44 beats per min), sepsis, myocardial infarction, and hypotension. In addition, a study found that the patient's admission level of consciousness, as well as his/her score on the Glasgow Coma Scale and on the Acute Physiology and Chronic Health Evaluation (APACHE) II, were most predictive of survival ***(Rodriguez et al., 2004)***.

Race

No studies suggest a race or ethnic predilection to myxedema coma/crisis***(Rehman et al., 2005)***.

Sex

Myxedema coma/crisis is approximately 4-8 times more common in women than in men, corresponding to the increased incidence of hypothyroidism in women***(Rehman et al., 2005)***.

Age

The incidence of hypothyroidism increases with age; the physiological decompensation of severe hypothyroidism, myxedema coma/crisis, occurs primarily in the elderly ***(Rehman et al., 2005)***. However, this condition should not be automatically ruled out in young adults***(Rehman et al., 2005)***.

Causes:

Myxedema coma/crisis is a physiologic decompensation of severe primary or secondary hypothyroidism that is usually caused by additional physiologic stress. Specific types of such stress are as follows:

- Infection/systemic illness.
- Cold environmental temperatures.
- Trauma.
- Burns.
- Decreased cerebral blood flow/cerebrovascular accident.

- Decreased cardiac output/congestive heart failure.
- Respiratory acidosis (increased P_{CO2}, decreased P_{O2}).
- Drugs: Tranquilizers, Sedatives, Anesthetics, Analgesics/ narcotics, Amiodarone, Rifampin, Beta blockers, Lithium, Phenytoin, Diuretics.
- GI hemorrhage.
- Hypoglycemia ***(Rehman et al., 2005)***.

Pathophysiology:

Myxedema coma/crisis is a form of decompensated hypothyroidism in which adaptations are no longer sufficient Essentially, all organ systems are affected. Myxedema coma/crisis occurs most commonly in older women with long-standing, undiagnosed or undertreated hypothyroidism who experience an additional significant stress, such as infection, a systemic disease, certain medications, and exposure to a cold environment.When hypothyroidism is long-standing, physiologic adaptations occur. Reduced metabolic rate and decreased oxygen consumption result in peripheral vasoconstriction, which maintains core temperature. The number of beta-adrenergic receptors is reduced, usually with preservation of alpha-adrenergic receptors and circulating catecholamines, causing beta/alpha-adrenergic imbalance, diastolic hypertension, and reduced total blood volume***(Wall, 2000)***.

Metabolic

Thyroid hormones are critical for cell metabolism and organ function. With an inadequate supply, organ tissues do not grow or mature, energy production declines, and the action of other hormones is affected. Although weight gain is common, severe obesity is rarely secondary to

hypothyroidism alone. However, long-standing, untreated hypothyroidism may result in years of inactivity, eventually with a large increase in weight. Because of decreased drug metabolism, overdoses of medications (eg, morphine, hypnotics, anesthetic agents, sedatives) can occur and can even precipitate myxedema crisis ***(Michiels et al., 2006)***

Neurologic

Although the condition is called myxedema coma, the absence of coma does not exclude the diagnosis of this disorder. The presenting mental status may be lethargy or stupor. The exact mechanisms causing changes in mental status are not known. Brain function is influenced by reductions in cerebral blood flow and oxygen delivery, a lack of thyroxine (T4) and triiodothyronine (T3), and reductions in oxygen and glucose consumption; all of these factors are probably involved. Hyponatremia brought on by renal dysfunction may be an additional cause of altered mental function ***(Michiels et al., 2006)***

Cardiovascular

The heart is profoundly depressed, with bradycardia and decreased contractility causing low stroke volume and cardiac output. These changes are caused by decreased production of myocyte contractile proteins and enzymes, including NA^+/K^+ adenosine triphosphatase (NA^+/K^+ ATPase), as a result of low levels of gene transcription in the absence of T3. Increased systemic vascular resistance occurs; although the causes appear to be multifactorial, a study suggests that in many cases, the increase is secondary to decreased T3 levels. Nonspecific ST- and T-wave inversion changes, low voltage, and ventricular arrhythmias may be noted. Plasma volume is decreased, and capillary permeability is

increased, leading to fluid accumulation in tissue and spaces and possibly causing pericardial effusions. ***(Michiels et al., 2006)***

Pulmonary

Typically, the lungs are not severely affected. Respiratory muscle dysfunction may be compromised, and depressed ventilatory drive and increased alveolar-arterial oxygen gradient are common. Fluid accumulation may cause pleural effusions and decreased diffusing capacity. Ventilation-perfusion mismatch is common, contributing to hypercapnia. Dysfunction of other organ systems may have profound effects. Severe obesity, if present, causes decreased lung volumes, diffusion capacity, and flow rates and may be the primary cause of the hypoventilation, hypoxia, hypercarbia, and depressed respiratory drive that is often noted in these patients. However, hypothyroidism may also have a direct impact, because the condition can cause obstructive sleep apnea that resolves with thyroid replacement (even without weight loss). ***(Michiels et al., 2006)***

Renal

Kidney function may be severely compromised, partly because of low cardiac output and vasoconstriction that causes a low glomerular filtration rate. Reduced levels of NA^{+}/K^{+} ATPase decrease sodium reabsorption and impair free water excretion, resulting in hyponatremia, which is usually present in myxedema coma ***(Michiels et al., 2006)***.

Gastrointestinal

Severe or even mild hypothyroidism decreases intestinal motility. Patients with myxedema coma can present with gastric atony, megacolon, or paralytic ileus. Malabsorption has also been reported. Ascites, while

uncommon, may occur due to increased capillary permeability, congestive heart failure, or other mechanisms.

Diagnosis:

History:

Although most patients with myxedema coma/crisis have a long history of hypothyroidism, undiagnosed or undertreated myxedema coma/crisis may be the initial manifestation of a hypothyroid state. A history of generalized fatigue, cold intolerance, constipation, and dry skin (common features of long-standing hypothyroidism) are usually present. These features slowly progress to lethargy, delirium, or coma.Faster progression may occur, precipitated by overmedication, stroke, congestive heart failure, trauma, exposure to cold environmental temperatures, or an infection, such as pneumonia. Relatives or friends who know the patient may be able to report a history of long-standing fatigue, weight gain, hair and skin changes, edema, constipation, and cold intolerance. Most cases of myxedema coma/crisis occur during the winter in women aged 60 years or older, although a case of a woman presenting in labor has been reported ***(Sheu et al., 2007)***.

Physical signs:

- Hypothermia is usually present in myxedema coma/crisis. If mercury thermometers are used, the degree of hypothermia may not be recognized unless the temperature of the thermometer is lowered before checking the patient's temperature. Moreover, use of special thermometers that record well below 90°F may be necessary in order to determine the patient's actual temperature and to monitor rewarming.
- Absence of fever in the presence of infection can be expected.

- The following features are extremely common, although some are not invariably present:
- Hypotension/shock.
- Hypothermia.
- Decreased pulse pressure, normal systolic pressure, elevated diastolic pressure, slow pulse and respiration rates.
- Periorbital, nonpitting edema; facial swelling or coarseness; macroglossia; enlargement of the tonsils, nasopharynx, and larynx; coarse or thinning hair ***(Sheu et al., 2007).***
- Thyroid - Enlarged, not palpable, scar suggesting previous thyroidectomy.
- Lungs - Slow respiration rate, hypoventilation, congestion, pleural effusions, consolidation.
- Heart - Soft or distant heart sounds, diminished apical impulse, bradycardia, enlarged heart, pericardial effusion.
- Abdomen - Distension secondary to ileus and/or ascites, diminished or absent bowel sounds. ***(Sheu et al., 2007).***
- Bladder distension.
- Extremities - Cold, nonpitting edema of the hands and feet.
- Skin/nails - Cool, pale, dry, scaly, thickened skin; dry, brittle nails; ecchymoses, purpura, sallowness due to carotenemia.
- Neuromuscular - Confusion, stupor, obtundation, coma, slow speech, seizures, reflexes with a slow relaxation phase ***(Sheu et al., 2007)***.

Laboratory Studies:

Laboratory values are essential for the workup of myxedema coma/crisis; however, if the condition is suspected, treatment must be initiated immediately without waiting for the results ***(Sheu et al., 2007)***.

- Free T4 and T3 levels are low or undetectable.
- The TSH level may be elevated, indicating a primary thyroid disorder.
- A low or normal TSH level with low levels of T4 and T3 may indicate central (pituitary) hypothyroidism or the suppression of TSH production by severe illness or drugs, such as dopamine or high-dose glucocorticoids. A serum cortisol level should be determined before beginning intravenous steroids ***(Sheu et al., 2007)***.
- Serum electrolytes and serum osmolality - Hyponatremia with low serum osmolality is common.
- Serum creatinine - Because of decreased renal perfusion, the levels are usually elevated.
- Serum glucose - Hypoglycemia is common but may also suggest adrenal insufficiency.
- Complete blood count (CBC) with differential - Bands and/or a left shift may be the only sign of infection.
- Creatine kinase (CK) - CK levels are often elevated, and fractionation indicates skeletal (not cardiac) muscle injury unless a myocardial infarction was the precipitating event.
- Arterial blood gases - Increased P CO2 and decreased P O2 are found.
- Pan-culture for sepsis ***(Sheu et al., 2007)***.

Imaging Studies:

Chest radiographs: Obtain chest radiographs for all patients. Cardiomegaly, pericardial effusion, congestive heart failure, and/or pleural effusion are observed ***(Sheu et al., 2007)***.

Cardiological Studies:

Electrocardiogram: Sinus bradycardia, low-amplitude QRS complexes, a prolonged QT interval, and flattened or inverted T waves are noted***(Sheu et al., 2007)***.

Treatment:

Management of airway and airway protection from aspiration in case of patients with poor consciousness level should be the utmost priority. Endotracheal intubation or tracheostomy with mechanical ventilation may be performed. Arterial blood gas should be monitored frequently to ensure adequate oxygenation and correction of hypercarbia. Sedatives and other drugs may exacerbate the respiratory depression and may delay the weaning of ventilator support ***(Vivek Mathew et al., 2011)***

Medical Care:

Myxedema crisis/coma is a life-threatening condition; therefore, patients with this disorder must be stabilized in an intensive care unit. The first 24-48 hours are critical. If the diagnosis is considered likely, immediate and aggressive administration of multiple interventions is necessary to lower an otherwise high rate of mortality. Initial priorities include the following: Mechanical ventilation if respiratory acidosis/hypercapnia/hypoxia is significant.Immediate intravenous thyroid hormone replacement while awaiting confirmatory test results (T4

and TSH), even if the diagnosis of myxedema coma is only probable. Because GI absorption is compromised, intravenous therapy is mandatory. Whether to use T4 alone, combined T4 and T3, or T3 alone remains a subject of controversy. Deiodinase conversion of T4 to the active hormone T3 is reduced in these patients, and T3 administration may be advisable. However, T3, because of its more immediate action and short half-life, may be more likely to cause arrhythmias, particularly if myocardial function is compromised. The usual conversion to an intravenous dose of T4 is approximately one half to two thirds of the oral dose. An intravenous loading dose of 500-800 mcg of levothyroxine is followed by a daily intravenous dose of 50-100 mcg; the daily dose is administered until the patient is able to take medication by mouth. Use caution in elderly persons and in patients with coronary artery disease or myocardial infarction, because full-dose T4 therapy may worsen myocardial ischemia by increasing myocardial oxygen consumption. Some authorities advocate the use of additional intravenous T3, at 10-20 mcg every 8-12 hours, especially in young patients with low cardiovascular risk. Because of the rarity of the condition, randomized trials comparing different treatment modalities are not available. Observational studies are not in agreement regarding whether low or high dose T4 or T3 replacement reduces mortality ***(Rodriguez et al., 2004)***.

In light of the possibility of adrenal insufficiency, stress steroid replacement after a cortisol level is obtained .After a baseline cortisol level is ascertained, initiate hydrocortisone at 5-10 mg/hr. Continue therapy unless the random cortisol level on admission indicates adrenal function without abnormalities, in which case, hydrocortisone may be stopped without tapering. ***(Jordan, 1995).***

- Passive rewarming using ordinary blankets and a warm room (rapid and external rewarming are contraindicated).
- Treatment of associated infection.
- Correction of severe hyponatremia (sodium level < 120 mEq/L) with saline, free water restriction.
- Broad-spectrum antibiotics with modification of the antibiotic regimen based on culture results.
- Correction of hypoglycemia with intravenous dextrose.
- Treatment of severe hypotension with cautious administration of 5-10% glucose in half-normal or normal saline (or hypertonic saline if severely hyponatremic, ie, < 120 mEq/L) .
- Dose adjustment of any medication to compensate for decreased renal perfusion, drug metabolism, etc***(Taguchi et al., 2007)***.

Infection:

- The precipitating event in myxedema coma/crisis is often overt or occult bacterial infection.
- Fever and elevated white blood cell (WBC) count are usually absent, although a left shift and/or bands may be observed.
- Pan-culture and initiate empiric broad-spectrum antibiotic treatment, which can be narrowed if the source of infection is identified.
- If culture results remain negative, antibiotics may be discontinued***(Taguchi et al., 2007)***.

Myocardial ischemia

- Myocardial infarction may be the precipitating event in older patients, or it may subsequently occur ***(Taguchi et al., 2007).***

Troponin tests are also sometimes used to evaluate people for heart injury due to causes other than a heart attack or to distinguish signs and symptoms such as chest pain that may be due to other causes. Testing may also be done to evaluate people with angina if their signs and symptoms worsen.

Troponin tests are sometimes ordered along with other cardiac biomarkers, such as CK–MB or myoglobin. However, troponin is the preferred test for a suspected heart attack because it is more specific for heart injury than other tests (which may be elevated in the blood with skeletal muscle injury) and remain elevated for a longer period of time. A high troponin and even slight elevations may indicate some degree of damage to the heart. When a person has significantly elevated troponin levels and, in particular, a rise in the results from a series of tests done over several hours, then it is likely that the person has had a heart attack or some other form of damage to the heart. Levels of troponin can become elevated in the blood within 3 or 4 hours after heart injury and may remain elevated for 10 to 14 days. In people with angina, an elevated troponin may indicate that their condition is worsening and they are at increased risk of a heart attack. ***(American Association for Clinical Chemistry, 2016)***.

A test called high-sensitivity troponin detects the same protein that the standard test does, just at much lower levels. Because this version of the test is more sensitive, it becomes positive sooner and may help detect heart injury and acute coronary syndrome earlier than the standard test.

The troponin test may also be positive in people with stable angina and even in people with no symptoms. When it is elevated in these individuals, it indicates an increased risk of future heart events such as heart attacks. Currently, this test is not approved in the U.S., but research is ongoing and it may become available in the near future. It is already routinely used as a cardiac biomarker Serial CK determinations with fractionation assist in the diagnosis and treatment of an acute coronary event. CK levels are often elevated in myxedema coma/crisis but are usually of muscle origin***(American Association for Clinical Chemistry, 2016)***

If ischemia or infarction is diagnosed, or if the patient has significant risk factors for coronary artery disease, institute thyroid replacement at low doses***(American Association for Clinical Chemistry, 2016)***.

Fluid management

the choice is between fluid supplementation for hypotension and fluid restriction for hyponatremia. A pragmatic approach in mild hyponatremia will be to advice fluid restriction with replacement to cover the daily losses taking care to supplement glucose, sodium, and potassium In a situation of severe hyponatremia, it may be prudent to administer 3% sodium chloride along with furosemide, so that serum sodium may be elevated by 3-4 meq/L to tide over the immediate crisis A rapid correction of chronic hyponatremia might put patients at risk for central pontine myelinolysis Treatment with furosemide will prevent fluid overloading associated with hypertonic saline. In experimental hypothyroidism, the impaired response to an acute water load was shown to be reversed by a Vasopressin receptor antagonist (V2R antagonist) Future research with

V2R antagonists in treating hyponatremia associated with myxedema crisis may prove to be interesting***(Raiz Misgar, et al., 2011)***

Hypothermia

It may be managed by external warming, but the accompanying vasodilatation may precipitate hypotension. Hypotension requires careful infusion of dextrose saline solutions and vasopressors if required. A search for other causes of hypotension like sepsis, myocardial infarction, pericardial effusion, and occult bleeding should be initiated. In a setting of concomitant adrenal insufficiency, hydrocortisone supplementation is also required for correction of hypotension.***(Sujoy Ghosh et al., 2011)***

Hypocortisolemia

It may be due to primary or secondary adrenal insufficiency. The clinical features of myxedema crisis and cortisol deficiency may overlap. Hyperpigmentation, hyperkalemia, hypercalcemia, and previous history of on and off steroid use must be sought. Thyroid hormone replacement may increase cortisol clearance and may aggravate cortisol deficiency. If the facilities for HPA axis evaluation are not available on an emergency basis, steroid therapy may start and a formal evaluation of axis is done at a later date when patient is stable. Intravenous hydrocortisone is preferred at a rate of 50 mg every 6 hours ***(Kaushik Pandit et al., 2011).***

It cannot be overemphasized that the precipitating factors require urgent attention with antibiotics in case of infection, hemodialysis for associated renal failure, and comprehensive care of multiorgan dysfunction. ***(Sheu et al., 2007).***

Volume status:

- Intravenous glucose and normal saline should be carefully administered, because patients are usually volume overloaded and prone to congestive heart failure from the reduced cardiac function of hypothyroidism. If severely hyponatremic (sodium level < 120 mEq/L), consider administration of small amounts of hypertonic saline followed by intravenous furosemide to improve volume status. Generally, hypotension is resistant to the usual drugs until thyroid hormone and glucocorticoids (if insufficient) are administered. If hypotension does not improve with prudent fluid replacement, whole blood can be transfused. Finally, cautious administration of dopamine can be used ***(Rimar et al., 2007)***.

Surgical Care:

Stabilize patients in myxedema coma on T4 and glucocorticoids prior to surgical procedures. In life-threatening situations, administer a loading dose of T4 and glucocorticoids before induction of anesthesia. Careful cardiovascular monitoring with a Swan-Ganz catheter is required.

- Endotracheal intubation - Decreased ventilatory drive, CO 2 retention, and hypoxemia all necessitate mechanical respiratory assistance to prevent cardiovascular collapse and worsening of hypoxia and hypercapnia.
- Cardiac monitoring in an intensive care unit ***(Taguchi et al., 2007).***
- Myxedema coma/crisis is a medical emergency and requires close monitoring and stabilization.
- Patients are at risk of myocardial ischemia.

Central venous pressure or Swan-Ganz catheter monitoring - Hypotension signifies loss of blood volume from bleeding or vascular redistribution and must immediately be corrected. Temperature monitoring - This requires the use of a rectal probe to determine true core temperature and to monitor rewarming***(Rimar et al., 2007)***.

Diet:

Motility of the GI tract is usually decreased; therefore, withhold food until the patient is alert and extubated and normal bowel sounds are present; at that time, gradually introduce soft foods.

Activity:

Once stable, patients may progress to usual activity as their strength allows. Physical therapy may be useful for patients who are debilitated.

Medications:

The goals of pharmacotherapy are to increase thyroid hormone levels, reduce morbidity, and prevent complications.

Thyroid hormones:

Immediate administration of intravenous levothyroxine is necessity if myxedema coma/crisis is considered likely. Controversy exists regarding whether additional treatment with T3 is necessary. When the patient is eating and ambulating, oral T4 may be substituted.

Levothyroxine (Synthroid, Levoxyl):

In active form, influences growth and maturation of tissues. Involved in normal growth, metabolism, and development. IV dosage form has a long half-life (may be administered qd and is the preferred route of

administration in patients with myxedema coma/crisis because GI tract absorption may be compromised). Preferred by many authorities, because the onset of action is slow and sustained, making adverse effects less likely to occur and serum levels easier to monitor. Administering only T4 assumes normal conversion to T3 by deiodinase activity, which is usually compromised in severe illness. IV dose of T4 is approximately one half to two thirds of the PO dose. Lower doses recommended if patient has uncontrolled atrial arrhythmia or recent MI ***(Brent et al., 2008).***

Liothyronine (Cytomel, Triostat)

Synthetic form of the natural thyroid hormone, T3, converted from T4. T3 is the active form, but because peripheral conversion of T4 to T3 is compromised in patients who are hypothyroid, some authorities suggest combined IV T4 and T3 in these patients. However, patients with cardiovascular disease are at greater risk of arrhythmia and infarction.

T3 has a short half-life and must be administered q8h. Because of concerns about abrupt onset and fluctuating concentrations in tissues, experts advise coadministration of T3 with T4***(Brent et al., 2008).***

Corticosteroids:

Corticosteroids have anti-inflammatory properties and cause profound and varied metabolic effects. They modify the body's immune response to diverse stimuli ***(Brent et al., 2008).***

Hydrocortisone (Solu-Cortef, Hydrocortone):

Patients presenting with myxedema coma/crisis may have adrenal insufficiency, and stress doses of IV steroids must be administered along

with initial thyroid replacement until adrenal function has been determined to be normal ***(Brent et al., 2008).***

Follow-up:

Further Inpatient Care*:*

- Closely monitor vital signs, electrolytes, and glucose until the levels are within reference ranges and the patient is alert.
- Substitute oral medications for intravenous ones in patients who are extubated and eating.
- Watch for signs of infection, myocardial ischemia, and congestive heart failure.
- Patients who, before hospitalization, did not take their thyroid medication regularly must be evaluated to determine whether they require assistance in taking their thyroid hormone replacement every day.
- Institute physical therapy to assist in strength training and reconditioning. ***(Wartofsky, 2006).***

Further Outpatient Care:

- Follow-up care is necessary to ensure compliance with thyroid hormone replacement.
- If primary hypothyroidism was diagnosed, assess the TSH level every 6 weeks and adjust the T4 dose. Once a normal TSH level is obtained, it may be monitored yearly. If compliance is an issue, check the patient every 3-6 months.

- In hypothyroidism secondary to pituitary dysfunction, monitor free T4 levels. The TSH level is not an accurate measure of thyroid function.

- Obtain assurance that the precipitants of the initial presentation will not recur. ***(Wartofsky, 2006).***

Prevention:

Patients with a history of thyroid resection or ablation for hyperthyroidism and persons with a history of Hashimoto thyroiditis are at risk for developing hypothyroidism, and the TSH level should be monitored yearly. Such patients should be informed that hypothyroidism could occur in the future. They should understand the symptoms that signal the condition and the need to seek medical attention for appropriate testing.

- Patients who are likely to be noncompliant with medication regimens must have their thyroid function closely monitored.

In cold climates, inadequately heated residences are a significant cause of myxedema coma/crises in patients with undiagnosed or inadequately treated hypothyroidism. ***(Wartofsky, 2006).***

Complications: -

Adrenal crisis is a major complication if patients presenting with myxedema coma/crisis also have adrenal insufficiency and are not treated concomitantly with stress doses of intravenous corticosteroids. Myocardial infarction can cause myxedema coma/crisis but may also be a complication of intravenous treatment with thyroid replacement hormones in patients whose myocardial function is already precarious. ***(Rodriguez et al., 2004)***.

Prognosis:

Observational studies have analyzed the predictors of survival for patients presenting with myxedema coma.

In a study of 11 patients with myxedema coma in which 7 survived, statistically significant factors correlated with mortality included the following:

- Coma on entry
- Lower Glasgow Coma Scale
- High APACHE II score

The following factors were not significantly correlated with survival:

- Age.
- Body temperature.
- Heart rate.
- Free T4, TSH.

In a study of 23 consecutive patients presenting with myxedema coma, 11 of whom survived, statistically significant predictors of mortality included the following :

- Hypotension and bradycardia at presentation.
- Need for mechanical ventilation.
- Hypothermia that is not responsive to treatment.
- Sepsis.

- Lower Glasgow Coma Scale.
- High APACHE II score.
- High Sequential Organ Failure Assessment (SOFA) score. The SOFA score at baseline was most predictive, and a day 3 score of more than 6 was predictive of a poor outcome ***(Dutta et al., 2008).***

ADDISONIAN CRISIS

Introduction:

Adrenal crisis and severe acute adrenocortical insufficiency are often difficult to be diagnosed that may result in severe morbidity and mortality when undiagnosed or ineffectively treated. Although it is thought by experts that more than 50 steroids are produced within the adrenal cortex cortisol and aldosterone are by far the most abundant and physiologically active ***(Hahner et al., 2009)***.

In primary adrenocortical insufficiency, glucocorticoid and mineralocorticoid properties are lost; however, in secondary adrenocortical insufficiency (ie, secondary to disease or suppression of the hypothalamic-pituitary axis), mineralocorticoid function is preserved. Although suppression of the hypothalamic-pituitary axis from chronic exogenous steroid use is the most common cause of secondary adrenal insufficiency, the possibility of hypopituitarism due to hypothalamic-pituitary disease must be considered. With acute hypopituitarism, other hormone deficiencies must be identified and treated in addition to treating adrenal insufficiency with corticosteroids ***(Hahner et al., 2009)*** .

For instance, if a patient with panhypopituitarism due to Sheehan syndrome (postpartum pituitary infarction) is only treated for adrenal crisis, severe cardiovascular compromise from the untreated associated hypothyroidism likely occurs. Death can result if the hypothyroid state is not diagnosed . Every emergency physician should be familiar with adrenocortical insufficiency, which is a potentially life-threatening entity. The initial diagnosis and decision to treat are presumptive and are based on history, physical examination, and, occasionally, laboratory findings.

Delay in treatment while attempting to confirm this diagnosis can result in poor patient outcomes

Epidemiology:

In USA, primary adrenocortical insufficiency is an uncommon disorder with an incidence in Western populations near 50 cases per 1,000,000 persons. With the advent of widespread corticosteroid use, however, secondary adrenocortical insufficiency due to steroid withdrawal is much more common. Approximately 6,000,000 persons in the United States are considered to have undiagnosed adrenal insufficiency, which is clinically significant only during times of physiologic stress. Primary adrenocortical insufficiency has multiple etiologies; however, 80% of cases in the United States are caused by autoimmune adrenal destruction. Glandular infiltration by tuberculosis is the second most frequent etiology***(Hahner et al., 2009)***.

In patients with primary adrenocortical insufficiency due to idiopathic autoimmune lymphocytic infiltration, the presence of other associated endocrine disorders must be entertained. Consider polyglandular autoimmune disorders (PGAs) such as Schmidt syndrome. Schmidt syndrome (PGA type II) includes adrenal insufficiency, autoimmune thyroid disease, and, occasionally, insulin-dependent diabetes mellitus. Adrenal insufficiency usually occurs in these patients when they are older than 20 years. In approximately 40-50% of patients with PGA II, the first manifestation of the syndrome is adrenal insufficiency ***(Hahner et al., 2009).***

PGA type I includes hypoparathyroidism and mucocutaneous candidiasis in conjunction with adrenal insufficiency. The full triad may manifest in approximately 30% of patients with PGA type I.

Mortality/Morbidity

Acute adrenocortical insufficiency is a difficult diagnosis to make. The disorder rarely occurs without concomitant injury or illness. Many of the presenting signs and symptoms are nonspecific. For instance, postoperative fever may presumptively be treated as infection or systemic inflammatory response syndrome when it may be a subtle indicator of adrenal insufficiency Left untreated, a patient with acute adrenal insufficiency has poor prognosis for survival. Therefore, treatment upon clinical suspicion is mandatory. Any delay in management while waiting for diagnostic confirmation cannot be justified ***(Hahner et al., 2009).***

Sex

Although primary adrenocortical insufficiency affects men and women equally, women are affected 2-3 times more often by the idiopathic autoimmune form of adrenal insufficiency ***(Hahner et al., 2009).***

Age

In idiopathic autoimmune adrenal insufficiency, the diagnosis is most often discovered in the third to fifth decades of life; however, it is particularly important to recognize that adrenocortical insufficiency is not limited to any specific age group ***(Hahner et al., 2009).***

Causes :

Exogenous steroid withdrawal, surgery, volume loss, trauma, asthma, hypothermia, alcohol, myocardial infarction, fever, hypoglycemia, pain, psychoses or depression, anesthesia (eg, etomidate). ***(Hahner et al., 2009).***

Etomidate, a parenteral hypnotic agent, is a steroid synthesis inhibitor. Although the use of continuous etomidate infusion in ICU fell from favor due to reports of adrenal crisis, single-dose etomidate for induction of anesthesia is common for the hemodynamically unstable patient or in patients who may not tolerate wide variance in heart rate or blood pressure. A case is presented of acute adrenocortical insufficiency and crisis after a standard induction dose of etomidate. Acute adrenal insufficiency should be suspected in ICU patients who have undergone general anesthesia with etomidate induction and present with hypotension refractory to standard vasopressor ***(J Intensive Care Med, 2007)***.

Pathophysiology:

Adrenal medullae normally secrete 80% epinephrine and 20% norepinephrine. Sympathetic stimulation results in secretion. The adrenal cortex produces cortisol, aldosterone, and androgens. Cortisol is produced from 2 hydroxylations of 17alpha-hydroxyprogesterone. Cortisol, also known as hydrocortisone, is 90-93% protein bound (primarily by corticosteroid-binding globulin) ***(Guyton et al., 2000)***.

Physiologic effects of glucocorticoids:

Glucocorticoids are nonspecific cardiac stimulants that activate release of vasoactive substances. In the absence of corticosteroids, stress results in hypotension, shock, and death. Glucocorticoids act as follows to:

- Stimulate gluconeogenesis and decrease cellular glucose use.
- Mobilize amino acids and fatty acids.
- Inhibit the effects of insulin.

- Give rise to ketone bodies in metabolism (ketogenesis).
- Elevate RBC and platelet levels.
- Exhibit anti-inflammatory effects, including the following:
- Maintenance of normal vascular response to vasoconstrictors.
- Opposition to increases in capillary permeability.
- Inhibition of interleukin-2 (IL-2) production by macrophages
- Stimulation of polymorphonuclear neutrophil (PMN) leukocytosis.
- Reduction of adherence of macrophages to endothelium.
- Depletion of circulating eosinophils and lymphocytes.
- Reduction of circulating lymphocytes (primarily T cells) ***(Guyton et al., 2000).***

Physiologic effects of aldosterone:

Aldosterone is produced by multiple hydroxylations of deoxycorticosterone and is normally 60% protein bound. The renin-angiotensin system stimulates aldosterone release. Increased potassium stimulates aldosterone production, and decreased potassium inhibits production. Chronic adrenocorticotropic hormone (ACTH) deficiency may inhibit production The primary actions of aldosterone cause the kidneys, gut, and salivary/sweat glands to affect electrolyte balance. The primary targets are the kidneys; these organs stimulate reabsorption of sodium and secretion of potassium and hydrogen ions. The kidneys' effect on sodium and potassium depend on the intake of these cations (ie,

increased sodium intake = increased potassium secretion). The effects on hydrogen probably can occur independently***(Guyton et al., 2000)***.

Persistent aldosterone excess results in atrial natriuretic factor release and renal hemodynamic changes for compensation. Congestive heart failure (CHF) and cirrhosis with ascites are exceptions that cause progressive sodium retention. Excess aldosterone results in sodium retention, hypokalemia, and alkalosis. Aldosterone deficiency results in sodium loss, hyperkalemia, and acidosis. Hyperkalemia stimulates aldosterone release to improve potassium excretion. Aldosterone is the first-line defense against hyperkalemia ***(Guyton et al., 2000)***.

Primary adrenal insufficiency:

Primary adrenal insufficiency, which can be acute or chronic, may be caused by the anatomic destruction of the gland. This destruction can have various causes, including tuberculosis or fungal infection, other diseases infiltrating the adrenal glands, and hemorrhage. However, the most frequent cause is idiopathic atrophy, which is probably autoimmune in origin***(Guyton et al., 2000)***.

Primary adrenal insufficiency also may be caused by metabolic failure (eg, insufficient hormone production). This failure may be a result of congenital adrenal hyperplasia, enzyme inhibitors (eg, metyrapone), or cytotoxic agents (eg, mitotane) ***(Guyton et al., 2000)***.

Primary adrenocortical insufficiency is rare and occurs at any age. The male-to-female ratio is 1:1 ***(Guyton et al., 2000)***.

Secondary adrenal insufficiency:

Secondary adrenal insufficiency may be caused by hypopituitarism due to hypothalamic-pituitary disease or may result from suppression of the hypothalamic-pituitary axis by exogenous steroids or endogenous steroids (ie, tumor). Secondary adrenocortical insufficiency is relatively common. Extensive therapeutic use of steroids has greatly contributed to increased incidence ***(Guyton et al., 2000)***.

Acute adrenocortical insufficiency:

Adrenal crisis may result from an acute exacerbation of chronic insufficiency, usually caused by sepsis or surgical stress. Acute adrenal insufficiency also can be caused by adrenal hemorrhage (eg, usually septicemia-induced Waterhouse-Friderichsen syndrome (fulminant meningococcemia) and anticoagulation complications. Steroid withdrawal is the most common cause of acute adrenocortical insufficiency and almost exclusively causes glucocorticoid deficiency. ***(Guyton et al., 2000)***

Management of addisonian crisis

Diagnosis:

History:

The following are important elements in the history of patients with adrenal crisis or adrenal insufficiency:

- Weakness (99%).
- Pigmentation of skin (98%).
- Weight loss (97%).

- Abdominal pain (34%)
- Salt craving (22%).
- Diarrhea (20%).
- Constipation (19%).
- Syncope (16%).
- Vitiligo (9%) ***(Marik et al., 2008).***

Physical signs:

Physical findings in patients with adrenal insufficiency are subtle and nonspecific Patients with mineralocorticoid insufficiency may show signs of sodium and volume depletion (eg, orthostatic hypotension, tachycardia).Evidence of hyperpigmentation is observed, particularly in areas exposed to the sun or areas subject to friction or pressure.
(Lelubre and Lheureux 2008).

Laboratory Studies:

The following should be assessed in patients with suspected adrenal crisis or adrenal insufficiency:

- CBC count.
- Electrolyte levels.
- BUN level.
- Creatinine level.
- Cortisol level
- Serum calcium level.
- Thyroid function (possibly performed in ED but unlikely to influence immediate management) ***(Hahner et al., 2009).***

Imaging Studies:

- Chest radiograph.
- CT scan:

A CT scan of the abdomen may show hemorrhage in the adrenals, calcification of the adrenals (seen with tuberculosis), or metastasis.

In cases of secondary adrenal insufficiency, a head CT scan may show destruction of the pituitary (ie, empty sella syndrome) or a pituitary mass lesion ***(Simm et al., 2004).***

Other Tests:

- Adrenocorticotropic hormone (ACTH) stimulation test
- Note: In emergent situations, do not delay treatment of presumed adrenal insufficiency during diagnostic testing. Treatment with dexamethasone allows ACTH stimulation testing without affecting or interfering with the measurement of serum cortisol levels.
- Obtain baseline serum cortisol and ACTH levels.
- Administer 0.25 mg (250 mcg) of cosyntropin (synthetic ACTH) intravenously (IV) or intramuscularly (IM).
- Repeat cortisol levels every 30 minutes (some authors recommend 60 min) and 6 hours after ACTH administration.
- Normal response is indicated when the cortisol level doubles in response to ACTH stimulation.
- In adrenal insufficiency, serum cortisol levels fail to rise after ACTH administration.
- Electrocardiograph (ECG): Elevated peaked T waves may indicate hyperkalemia ***(Simm et al., 2004)***.

Treatment:

Emergency Department Care:

- Maintain airway, breathing, and circulation in patients with adrenal crisis.
- Use coma protocol (ie, glucose, thiamine, naloxone).
- Use aggressive volume replacement therapy (dextrose 5% in normal saline solution [D5NS]).
- Correct electrolyte abnormalities as follows:
- Hypoglycemia (67%).
- Hyponatremia (88%).
- Hyperkalemia (64%).
- Hypercalcemia (6-33%).
- Use dextrose 50% as needed for hypoglycemia.
- Administer hydrocortisone 100 mg intravenously (IV) every 6 hours. During adrenocorticotropic hormone (ACTH) stimulation testing, dexamethasone (4 mg IV) can be used instead of hydrocortisone to avoid interference with testing of cortisol levels.
- Administer fludrocortisone acetate (mineralocorticoid) 0.1 mg every day.
- Always treat the underlying problem that precipitated the crisis.

(Anand Swaminathan ,2015)

Consultations:

- Endocrine consultation following admission is beneficial. If no endocrinologist is available, a general internist can manage the process. Emergency management should be implemented in the ED

prior to consultation when sufficient clinical suspicion for this diagnosis is present.

- ICU admission is necessary for most patients with acute adrenal insufficiency and adrenal crisis ***(Anand Swaminathan ,2015)***.

Medications:

One of the goals in treating adrenal insufficiency is glucocorticoid replacement Electrolyte and metabolic abnormalities, as well as hypovolemia, must also be corrected. In addition, address the event precipitating abrupt decompensation ***(Hahner and Allolio 2009)***.

Steroid Replacement:

Initial Dose

Hydrocortisone 100mg

IV preferred but can be given IM if necessary Stress dose hydrocortisone has mineralocorticoid activity (20mg = 0.1mg Florinef) Continued dosing: Hydrocortisone 25mg Q6h

(Anand Swaminathan ,2015).

Consider **dexamethasone** 4mg IV if no known diagnosis of adrenal insufficiency (does not interfere with ACTH stimulation test likely to be performed by inpatient team Even if residual adrenal fx, hydrocortisone dose the same, IVF requirements may just be lower. Less acute illness may consider 50-100 mg hydrocortisone IM q 6h

Hypoglycemia

Treat severe hypoglycemia with 1-2 gm/kg of D50 Consider infusion of D5NS for continued hypoglycemia Check FS glucose Q1-2 hours to ensure improving hypoglycemia***(Anand Swaminathan ,2015)***.

Hypotension

IVF bolus of 30 cc/kg Consider using D5NS for resuscitation if the patient has concomitant hypoglycemia

Blood/urine cultures, antibiotics if infection suspected

Improvement in BP and clinical picture should occur within 1 hour of 1st dose hydrocortisone

If Na >130 consider change to D5 ½ NS to avoid rapid rise Na If Na <130 and rate of rise slow, continue D5 NS *(Trudi Cloyd, 2015)*

Hyperkalemia

Usually normalized with fluids and steroid replacement Monitor K Q2-3 hours as may fall during initial rehydration ***(Trudi Cloyd, 2015)***.

Dexamethasone (decadrone)

Alternative to hydrocortisone to avoid interference with testing of cortisol levels.

Dosing:

Adult

- 4 mg IV; repeat q2-6h if necessary.

Pediatric:

0.03-0.15 mg/kg/d IV divided q6-12h. ***(Trudi Cloyd, 2015)***

Further Inpatient Care:

Inpatient care of adrenal insufficiency should consist of the following:

- Employ supportive measures as necessary.
- Correct electrolyte abnormalities.
- Perform judicious volume resuscitation.
- Continuously monitor and administer glucose.

Once the patient stabilizes, usually by the second day, the corticosteroid dose may be reduced and then tapered. Oral maintenance can usually be achieved by the fourth or fifth day. ***(Trudi Cloyd, 2015)*** .Mineralocorticoid administration is not needed unless a corticosteroid with low mineralocorticoid activity (eg, dexamethasone) is used, or cortisol/corticosteroid administration has been reduced to near maintenance levels. Mineralocorticoid administration is usually not necessary for treatment of secondary adrenocortical insufficiency . Pursue and manage precipitating factors of adrenal crisis or insufficiency. Infectious etiologies commonly precipitate adrenal crisis. Recognition and treatment of causative factors are crucial aspects of managing adrenal hypofunction ***(Simm et al., 2004)***.

Further Outpatient Care:

Maintenance of cortisol levels may be achieved by administering hydrocortisone 15-20 mg orally (PO) every morning and 5-10 mg PO between 4:00-6:00 PM every afternoon. Maintenance mineralocorticoid levels may be achieved by administering 9alpha-fluorocortisol 0.05-0.1 mg every morning. (This treatment is necessary only for primary adrenocortical insufficiency) . Periodically assess blood pressure, body weight, and electrolytes.Advise patients to increase their cortisol dosage during times of physical stress ***(Gilliland, 2003).***

PHEOCHROMOCYTOMA

Introduction:

Pheochromocytoma is a rare catecholamine-secreting tumor derived from chromaffin cells. When such tumors arise outside of the adrenal gland, they are termed extra-adrenal pheochromocytomas, or paragangliomas. Because of excessive catecholamine secretion, pheochromocytomas may precipitate life-threatening hypertension or cardiac arrhythmias. If the diagnosis of a pheochromocytoma is overlooked, the consequences could be disastrous, even fatal; however, if a pheochromocytoma is found, it is potentially curable. The term pheochromocytoma (in Greek, *phios* means dusky, *chroma* means color, and *cytoma* means tumor) refers to the color the tumor cells acquire when stained with chromium salts. Roux performed the first surgical resection of a pheochromocytoma in Lausanne, Switzerland in 1926. Later the same year, Charles Mayo performed the first surgical resection in the United States ***(Waguespack et al., 2010)***.

Recent studies

Parnaby et al., 2010 investigated whether significant differences exist between perioperative hemodynamic changes arising from laparoscopic adrenalectomy (LA) for pheochromocytomas and those stemming from LA for other types of adrenal tumors. The study included 34 patients who underwent LA for pheochromocytomas (total resections = 35) and 104 patients who underwent LA for other tumors (total resections = 106). Severe hypertension was associated with 5 of the 35 pheochromocytoma resections (14.3%), compared with 2 of the 106 nonpheochromocytoma resections (1.9%), and there was a significant

increase in the need for intraoperative hypertensive treatment in the pheochromocytoma patients. However, no instances of transient or persistent systolic blood pressure of greater than 220 mm Hg occurred in either group, and no significant differences in recovery room hemodynamic parameters, the frequency of persistent hypotension, or the occurrence of heart rates greater than 120/min were noted between the 2 groups ***(Parnaby et al., 2010)***.

Epidemiology:

Frequency:

In USA Pheochromocytomas are rare, reportedly occurring in 0.05-0.2% of hypertensive individuals. Patients may be completely asymptomatic. A retrospective study from the Mayo Clinic revealed that in 50% of cases, the diagnosis was made at autopsy Approximately 10% of pheochromocytomas are discovered incidentally. Pheochromocytomas may occur in certain familial syndromes, including multiple endocrine neoplasia (MEN) 2A and 2B, neurofibromatosis, and VON HIPPEL-LINDAU (VHL) disease ***(Lenders et al., 2005)***.

Mortality/Morbidity:

Although pheochromocytomas are rare, making the diagnosis is critical because the malignancy rate is 10%, they may be associated with a familial syndrome (10%), they are 10% recurrent, 10% extraadrenal, 10% bilateral, they may precipitate life-threatening hypertension, and the patient may be cured completely with their removal. Cardiovascular morbidity: Many cardiac manifestations are associated with pheochromocytomas. Hypertension is the most common complication. Cardiac arrhythmias, such as atrial and ventricular fibrillation, may occur because of excessive plasma catecholamine levels. Other complications

include myocarditis, signs and symptoms of myocardial infarction, dilated cardiomyopathy, and pulmonary edema, either of cardiac or noncardiac origin ***(Lenders et al., 2005)***.

Neurologic complications:

Apheochromocytoma-induced hypertensive crisis may precipitate hypertensive encephalopathy, which is characterized by altered mental status, focal neurologic signs and symptoms, or seizures. Other neurologic complications include stroke due to cerebral infarction or an embolic event secondary to a mural thrombus from a dilated cardiomyopathy. Intracerebral hemorrhage also may occur because of uncontrolled hypertension ***(Lenders et al., 2005)***.

Race

Pheochromocytomas occur in people of all races, although they are diagnosed less frequently in blacks***(Lenders et al., 2005)***.

Sex

Pheochromocytomas occur with equal frequency in males and females***(Lenders et al., 2005)***.

Age

Pheochromocytomas may occur in persons of any age. The peak incidence, however, is between the third and the fifth decades of life. Approximately 10% occur in children. In children, 50% of pheochromocytomas are solitary intra-adrenal, 25% are present bilaterally, and 25% are extra-adrenal ***(Lenders et al., 2005)***.

Pathophysiology:

The clinical manifestations of a pheochromocytoma result from excessive catecholamine secretion by the tumor. Catecholamines typically secreted, either intermittently or continuously, include norepinephrine and epinephrine; rarely, dopamine is secreted. The biological effects of catecholamines are well known. Stimulation of alpha-adrenergic receptors results in elevated blood pressure, increased cardiac contractility, glycogenolysis, gluconeogenesis, and intestinal relaxation. Stimulation of beta-adrenergic receptors results in an increase in heart rate and contractility Catecholamine secretion in pheochromocytomas is not regulated in the same manner as in healthy adrenal tissue. Unlike the healthy adrenal medulla, pheochromocytomas are not innervated, and catecholamine release is not precipitated by neural stimulation. The trigger for catecholamine release is unclear, but multiple mechanisms have been postulated, including direct pressure, medications, and changes in tumor blood flow***(Boulkina et al., 2007).***

Relative catecholamine levels also differ in pheochromocytomas. Most pheochromocytomas secrete norepinephrine predominantly, whereas secretions from the normal adrenal medulla are composed of roughly 85% epinephrine. Familial pheochromocytomas are an exception because they secrete large amounts of epinephrine. Thus, the clinical manifestations of a familial pheochromocytoma differ from those of a sporadic pheochromocytoma ***(Karger and Basel 2014).***

Management of pheochromocytoma

Diagnosis:

History:

The classic history of a patient with a pheochromocytoma includes spells characterized by headaches, palpitations, and diaphoresis in association with severe hypertension. These 4 characteristics together are strongly suggestive of a pheochromocytoma. In the absence of these 3 symptoms and hypertension, the diagnosis may be excluded. The spells may vary in occurrence from monthly to several times per day, and the duration may vary from seconds to hours. Typically, they worsen with time, occurring more frequently and becoming more severe as the tumor grows. Symptoms include headache, diaphoresis, palpitations, tremors, nausea, weakness, anxiety, epigastric pain, flank pain, constipation, weight loss ***(Elenkova et al., 2010)***.

Pheochromocytomas are known to occur in certain familial syndromes. These include MEN 2A and 2B, neurofibromatosis (von Recklinghausen disease), and VHL disease. The MEN 2A and 2B syndromes, which are autosomally inherited, have been traced to germline mutations in the *ret* proto-oncogene. The *ret* proto-oncogene, located on chromosome 10, encodes a tyrosine kinase receptor involved in the regulation of cell growth and differentiation. Pheochromocytomas occur bilaterally in the MEN syndromes in as many as 70% of cases Pheochromocytomas may produce calcitonin, opioid peptides, somatostatin, corticotropin, and vasoactive intestinal peptide. Corticotropin hypersecretion has caused Cushing syndrome, and vasoactive intestinal peptide overproduction causes watery diarrhea ***(Elenkova et al., 2010)***.

Physical signs:

The clinical signs associated with pheochromocytomas include hypertension, postural hypotension, retinopathy, fever, pallor, tremor, café au lait spots, and neurofibromas.

Clinical signs:

- Hypertension (paroxysmal in 50% of cases).
- Postural hypotension (from volume contraction).
- Hypertensive retinopathy.
- Weight loss.
- Pallor.
- Fever.
- Tremor.
- Neurofibromas.
- Café au lait spots: These are patches of cutaneous pigmentation that vary from 1-10 mm and occur any place on the body. Characteristic locations include the axillae and intertriginous areas (groin). The name refers to the color of the lesions, which varies from light to dark brown.
- Tachyarrhythmias.
- Pulmonary edema.
- Cardiomyopathy.
- Ileus ***(Elenkova et al., 2010)***.

Causes:

signs		Symptoms	
Hypertension	++++	**Headaches**	++++
Sustained hypertension	++	**Palpitations**	++++
Paroxysmal hypertension	++	**Anxiety nervousness**	+++
Postural hypertension	+	**Tremulousness**	++
Tachycardia or reflex bradycardia	+++	**Weakness fatigue**	++
Excessive sweating	++++	**Nausea vomiting**	+
Pallor	++	**Pain in chest abdomen**	+
Flushing	+	**Dizziness or faintness**	+
Weight loss	+	**Paresthesias**	+
Fasting hyperglycemia	++	**Constipation (rarely diarrhea)**	+
Decreased gastrointestinal motility	+	**Visual disturbances**	+
Increased respiratory rate	+		

Table (2) : symptoms and signs in patients with pheochromocytoma

Precipitants of a hypertensive crisis are anesthesia induction, opiates, dopamine antagonists, cold medications, Radiographic contrast media, drugs that inhibit catecholamine reuptake, such as tricyclic antidepressants and cocaine, childbirth ***(Gergics et al., 2009).***

Laboratory Studies:

The choice of diagnostic test should be based on the clinical suspicion of a pheochromocytoma. Plasma metanephrine testing has the highest sensitivity (99%) for detecting a pheochromocytoma, but it has a lower specificity (89%). In comparison, a 24-hour urinary collection for catecholamines and metanephrines has a sensitivity of 90% and a specificity of 98% ***(de Jong et al., 2009)***.

- High-risk patients, including those who have a genetic syndrome that predisposes them to pheochromocytoma (eg, MEN 2A or 2B, VHL disease or neurofibromatosis, a prior history of a pheochromocytoma, a family history of a pheochromocytoma), should be screened with plasma metanephrine testing. In these scenarios, a higher-sensitivity test that lacks specificity is justified.

- A fractionated plasma free metanephrine level may be measured in a standard venipuncture sample taken from a seated, ambulatory patient.

- Patients at lower risk for a pheochromocytoma, including those with flushing spells, poorly controlled hypertension, should be screened with a 24-hour urine collection for catecholamines and metanephrines. This test has a high specificity and acceptable sensitivity.

- Perform a 24-hour urine collection for creatinine, total catecholamines, vanillylmandelic acid, and metanephrines.

- Provocative testing, although used in the past, rarely is needed. Agents used in the past to provoke a catecholamine surge include histamine, tyramine, glucagon, and metoclopramide. Suppression tests using phentolamine and clonidine can also be used for diagnostic purposes ***(de Jong et al., 2009)***.

Chromogranin A is an acidic monomeric protein that is stored with and secreted with catecholamines. Plasma levels of chromogranin A reportedly are 83% sensitive and 96% specific for identifying a pheochromocytoma. Chromogranin A levels are sometimes used to detect recurrent pheochromocytomas ***(Kudva et al., 2003)***.

test	SEN	SPEC
$U_{catechols}$	83%	88%
$U_{total\ metanephrines}$	76%	94%
$U_{catechols+metaneph}$	90%	98%
U_{VMA}	63%	94%
Plasma catecholamines	85%	80%
Plasma metanephrines	99%	89%

Table (3): sensitivity and specificity of lab tests in pheochromocytoma

Imaging Studies:

Over 90% of pheochromocytomas are located within the adrenal glands, and 98% are within the abdomen. Extra-adrenal pheochromocytomas develop in the paraganglionchromaffin tissue of the sympathetic nervous system. They may occur anywhere from the base of the brain to the urinary bladder. Common locations for extra-adrenal pheochromocytomas include the organ of Zuckerkandl (close to origin of the inferior mesenteric artery), bladder wall, heart, mediastinum, and carotid and glomusjugulare bodies
(de Jong et al., 2009).

Imaging studies should be performed only after biochemical studies have confirmed the diagnosis of pheochromocytoma ***(Baid et al., 2009)***.

Magnetic resonance imaging (MRI) This is preferred over computed tomography (CT) scanning. MRI has a reported sensitivity of up to 100% in detecting adrenal pheochromocytomas, does not require contrast, and does not

expose the patient to ionizing radiation. MRI is also superior to CT scanning for detecting extra-adrenal pheochromocytomas. In approximately 70% of cases, pheochromocytomas appear hyperintense on T2-weighted images because of their high water content ***(Baid et al., 2009)***.

Abdominal CT scanning has an accuracy of 85-95% for detecting adrenal masses with a spatial resolution of 1 cm or greater CT scanning is less accurate for lesions smaller than 1 cm. Differentiating an adenoma from a pheochromocytoma is more difficult using CT scanning. Although it has been thought that the use of intravenous contrast poses a risk of inducing hypertensive crisis in patients with pheochromocytomas, a controlled, prospective study in patients receiving low-osmolar CT contrast and a retrospective review in patients who received nonionic contrast concluded that this use of contrast is safe, even in patients not receiving alpha or beta blockers***(Bessell-Browne and O'Malley 2007).***

Scanning with iodine-131–labeled metaiodobenzylguanidine:

Ascan with iodine-131 (^{131} I)–labeled metaiodobenzylguanidine (MIBG) is reserved for cases in which a pheochromocytoma is confirmed biochemically but CT scanning or MRI does not show a tumor. The molecular structure of iodine-123 (^{123} I) MIBG resembles norepinephrine and concentrates within adrenal or extra-adrenal pheochromocytomas. This isotope has a short half-life and is expensive. It frequently is used in cases of familial pheochromocytoma syndromes, recurrent pheochromocytoma, or malignant pheochromocytoma ***(de Jong et al., 2009)***.

Positron emission tomography (PET) scanning:

This has been used as an imaging modality and has shown promising results. PET with 18F-fluorodeoxyglucose, which is

selectively concentrated as part of the abnormal metabolism of many neoplasms, has been demonstrated to detect occult pheochromocytomas. Pheochromocytomas usually show increased uptake on PET scanning, as do adrenal metastases. The most impressive results to date have been with 6-[18F] fluorodopamine PET scanning and carbon-11 hydroxyephedrine PET scanning. Results of these studies suggest that PET scanning performed with both of these radioisotopes is extremely useful in the detection and localization of pheochromocytomas. Further study results with these agents are eagerly awaited ***(Trampal et al., 2004)***.

MR spectroscopy:

Initial studies have suggested that MR spectroscopy can be used to distinguish pheochromocytomas from other adrenal masses ***(Faria et al., 2007 and Kim et al., 2009)***. Specifically, a resonance signature of 6.8 ppm appears to be unique to pheochromocytomas; the signature apparently is attributable to the catecholamines and catecholamine metabolites present in pheochromocytomas ***(Kim et al., 2009)***.

Other Tests:

Once the diagnosis of pheochromocytoma is made, perform additional studies to rule out a familial syndrome, such as MEN 2A or 2B:

- Obtain a serum intact parathyroid hormone level and a simultaneous serum calcium level to rule out primary hyperparathyroidism (part of MEN 2A).
- Perform screening for mutations in the *ret* proto-oncogene in any patient with a familial syndrome or to distinguish a sporadic

pheochromocytoma from a familial pheochromocytoma ***(Kim et al., 2009)***.

Patients with seizures, unexplained shock, weight loss, cardiomyopathy, neurofibromatosis, and/or orthostatic hypotension should be screened for pheochromocytomas.

Treatment:

Preoperative preparation:

The chronic elevation of catecholamines and rapid fluctuations in circulating catecholamine levels produce a number of significant cardiovascular changes which require attention preoperatively. Most obviously there are abrupt marked changes in arterial pressure often accompanied by a tachycardia. These changes can be extreme with systolic pressures in excess of 200 mm Hg and diastolic pressures over 100 mm Hg. In patients with co-existing heart disease these pressures, particularly in association with a heart rate in excess of 100 beats per minute, impose a considerable workload on the heart and can lead to myocardial ischaemia (as a result of the high intraventricular pressures and shortening of diastole, during which the myocardium is perfused). In contrast, postural hypotension can also occur during periods when there is no catecholamine release. This is in part due to the relative hypovolaemia which results from prolonged alpha-adrenergic stimulation. That is, chronic peripheral vascular vasoconstriction adjusts the 'normal' intravascular volume to a lower value. In addition, chronic stimulation of the alpha-adrenergic receptors will lead to a change in receptor density and responsiveness which blunts the normal homeostatic response to postural change. Preoperative preparation is therefore aimed at controlling the surges and drops in arterial pressure and restoring blood

volume to normal. It is useful for the anaesthetist to be involved at an early stage in the preoperative preparation ***(George et al., 2010)***.

Preoperative drug therapy:

The initial therapy is the use of alpha-adrenergic blockade, usually phenoxybenzamine but other alpha blockers such as doxazosin or prazosin have also been used. This controls surges in arterial pressure and restores the blood volume by blocking the chronic vasoconstriction. Following alpha-adrenergic blockade it may be necessary to introduce beta-adrenergic blockade (e.g., atenolol) to control reflex tachycardia. Labetolol has a theoretical advantage in producing some alpha blockade as well but this is insufficient on its own. Virtually, every class of antihypertensive drugs has been used in the control of hypertension in patients with phaeochromocytoma but, other than alpha blockade, there are no particular indications based on mechanism of action. Due to the relative rarity of this disease, there is an overall lack of randomized studies comparing the different pharmacological approaches ***(George et al., 2010)***.

Alpha-adrenergic block:

Phenoxybenzamine is the 'traditional' agent used preoperatively in phaeochromocytoma patients and it is still the most widely used. It is a long-acting agent which produces blockade of both α1- and α2-adrenergicreceptors and thus acts both pre- and post-synaptically.It is usually started at a dose of 10 mg twice daily,but it may require a total daily dose of up to 100 mg.It has a relatively slow onset and the dose should be adjusted only every 2–3 days to allow for this. ***(Kocak et al., 2002)***.

Various guidelines have been proposed as the target for preoperative alpha blockade. These include: maintenance of normotension at rest; pressures less than 160/90 mmHg for 24 hours; the presence of orthostatic hypotension;and a systolic arterial pressure > 90 mm Hg on standing. These effects usually take at least seven days to be established and thus treatment for two weeks before the operation is generally recommended. Phenoxybenzamine is associated with several side effects, including tachycardia, miosis, gastrointestinal upsets and postural hypotension ***(Kocak et al., 2002)***.

Doxazosin and prazosin are quinazoline derivatives which have selective post-junctional α1 inhibitory activity. They therefore produce a fall in arterial pressure with less of an increase in heart rate than is seen with phenoxybenzamine. Doxazosin is given in a dose of 2–16 mg per day in a once daily dose, and prazosin over a similar range up to a maximum of 20 mg per day in divided doses. Both drugs will produce postural hypotension at higher doses. Both have been used successfully in the preoperative preparation of patients with phaeochromocytoma ***(Kocak et al., 2002).***

Several studies have compared the use of phenoxybenzamine, doxazosin and prazosin in the preparation of patients with phaeochromocytoma The rarity of the disease means that these studies are of relatively small numbers. However, the preoperative haemodynamic stability achieved is comparable withall the agents. The argument is put forward that thelonger duration of action of phenoxybenzamine may lead to greater postoperative haemodynamic instability,but this is not a consistent finding ***(Prys-Roberts and Farndon 2002).***

Urapidil is a short-acting, post-junctional, competitive α1-antagonist which also has a central 5-HT(serotonin) agonist action. It can be given orally or by intravenous infusion. This drug has been available in some European and Asian countries for several years but not in the UK or the USA However, it is apotentially interesting drug for wider use in the managementof phaeochromocytoma. Several studies from France have described its use in the acute management of phaeochromocytoma, with an infusion of 10–15mg / hfor 3 days preoperatively providing reasonable haemodynamic stability A recent study has evaluatedthe use of an even higher dosage regimen ***(Tauzin-Fin et al., 2004)***.

Beta-adrenergic blockade may be required following establishment of alpha blockade. Alpha blockade, particularly with phenoxybenzamine (α1 and α2), can produce significant tachycardia and even tachyarrhythmias. However, it is important that beta blockade is not started before alpha blockade as this will result in severe hypertension – alpha-mediated peripheral vasoconstriction without the modulation of the beta-mediated vasodilation in other vessel beds***(Gosse et al., 2009)***.

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Atenolol 25–50 mg daily is appropriate and this has largely replaced the use of propranolol. There is potentially some attraction in the use of labetolol in these patients as it has both alpha and beta adrenergic blocking effects. However, the beta effect outweighs that of the alpha effect by a consider able margin and, while it may be a useful alternative for controlling tachycardia following alpha blockade, it should not be used as the first line treatment for the reasons stated above ***(Gosse et al., 2009)***.

Calcium channel blockers have been used in the preoperative preparation. They exert their effect by inhibiting calcium transport in vascular smooth muscle. The most widely used agent is nicardipine, which has the advantage that it can be used orally preoperatively and by infusion peroperatively. Orthostatic hypotension is much less of a problem than with the use of alpha-adrenergic blockade. Preoperative control similar to that achieved with adrenergic blockade has been claimed Calcium channel blockers have also been used as an additional agent when adrenergic blockade (alpha and beta) has not produced adequate control of arterial pressure ***(Pacak et al., 2007)***.

Metyrosine an alternative, or additional, method of reducing the effect of circulating catecholamines is to interfere with their synthesis. Metyrosine is a competitive inhibitor of tyrosine hydroxylase, a key enzyme in catecholamine synthesis. It acts to deplete the catecholamine stores in the body and thus to minimise surges in arterial pressure. The dose is 1–2 g per day in divided doses. It is not widely used as a sole agent but is given in some centres as additional therapy in patients who still have poor control despite adrenergic blocking drugs. Unfortunately, it has quite marked systemic side effects as it can cross the blood brain

barrier, particularly at higher doses, and these include sedation, depression, anxiety and diarrhea ***(Pacak et al., 2007)***.

In summary, alpha-adrenergic blockade is the mainstay of preoperative control in patients with phaeochromocytoma. Phenoxybenzamine is still the mostwidely used agent for this in the UK. Beta-adrenergic blockade is often added to control the heart rate after alpha blockade is established. Alternatively, calcium channel blockade can be used successfully. As noted earlier, there is a need for randomised controlled studies comparing these treatment options ***(Tiberio et al., 2008)***.

Perioperative management:

It is important that the team involved in the management of a patient (physician, surgeon and anaesthetist) communicate well and are all involved in preparing the patient for surgery. In most countries, phaeochromocytoma are referred to specialist centres for management and this is to be commended. It is obviously more appropriate that these relatively rare cases are dealt with by a team that manage 10–20 per year rather than a team that see only 1 case every 5–10 years. For an anaesthetist managing a phaeochromocytoma patient for the first time it is sensible to use techniques and drugs that they are familiar with as this reduces the variables involved.

Surgical management:

The advent of laparoscopic surgery has changed the surgical approach to resection of phaeochromocytoma ***(Tiberio et al., 2008)***. The majority of tumours are now resected laparoscopically but large, bilateral or malignant tumours may require laparotomy. The majority of

phaeochromocytoma can be removed laparoscopically using a retroperitoneal approach with the patient in a lateral position with some break on the operating table. Larger or bilateral tumours may require a supine transperitoneal approach. The same positioning options are required for open surgery. When laparoscopic resection was first introduced 15 years ago the upper-size limit of resectable tumour was set at 6 cm. However, with increasing experience tumours up to 15 cm in diameter have been removed laparoscopically ***(Tiberio et al., 2008)***.

Anaesthetic management:

Premedication:

The patient's medication, including antihypertensive therapy, should be continued through to the operation. However, if phenoxybenzamine is being used, the last dose should be given the day before surgery. As stressful situations can be a trigger to catecholamine release, it is appropriate to prescribe an anxiolytic (benzodiazepine) preoperatively***(Tiberio et al., 2008)***.

Monitoring:

The physiological changes and stress involved in induction of anaesthesia can trigger catecholamine release. It is therefore essential that good cardiovascular monitoring (ECG, oximetry and invasive arterial pressure) is in place before induction. Central venous access for monitoring and for administration of vasoactive drugs is required. In patients with compromised cardiovascular function, either secondary to the phaeochromocytoma or from any other cause, it may be of value to include a method of measuring cardiac output as the operation can entail marked changes in intravascular volume, sympathetic activity and venous

return. It is essential to check arterial gases and blood glucose at regular intervals throughout surgery***(Tiberio et al., 2008)***.

Induction of anaesthesia and tracheal intubation can trigger severe hypertension in patients with phaeochromocytoma. It is essential that induction is carried out in a smooth unhurried manner to minimise the risk of stimuli such as hypotension or the pressor response to intubation. A technique using propofol and a shortacting opioid such as remifentanil is appropriate. Drugs which have the potential to produce histamine release should be avoided ***(George et al., 2010)***.

Following muscle relaxation with a non-depolarising agent, adequate time should be allowed for the block to develop before attempting tracheal intubation to prevent a pressor response. The use of suxamethonium is best avoided as both the potential for histamine release and the effect of muscle fasciculation can trigger massive catecholamine release from the phaeochromocytoma. If a rapid sequence induction is essential, e.g., severe reflux, high dose rocuronium is the best option. Due to its sympathomimetic effects, ketamine is not appropriate in these patients ***(George et al., 2010)***.

Maintenance:

It is usual to use a balanced technique to maintain anaesthesia with an inhalational agent and shortacting opioids. The vasodilatory effects of isoflurane and sevoflurane may be of some benefit and both have been used successfully in these patients. Similarly, all of the short-acting opioids have been used, including remifentanil ***(George et al., 2010)***.

The role of epidural anaesthesia in patients with phaeochromocytoma is less clear. With the majority of surgical

procedures now being laparoscopic there is less need for extensive intra and postoperative analgesia. The arguments for the use of an epidural perioperatively are: provision of good intra and postoperative analgesia (especially in open procedures); the vasodilatory effect requires correction with a fluid load which can minimize the likelihood of hypotension after the tumour is resected;and that the lower arterial pressure from vasodilatation helps to minimise surges in pressure during tumour handling. The arguments against are: placement of the epidural catheter (positioning of the patient, direct pressure and accompanying stress) may trigger a catecholamine surge; hypotension from vasodilatation may also do this; it introduces another (?unnecessary) variable to the patient's haemodynamic status; and that after laparoscopic surgery extensive analgesia is not required. A reasonable synthesis of these arguments may be that the use of an epidural should be considered for open surgical procedures with limited use before resection of the tumour but then used to provide good postoperative analgesia ***(George et al., 2010)***.

Intraoperative problems:

There are two major problems that will be encountered intraoperatively: hypertension during resection, and hypotension following devascularisation of the tumour. While preoperative preparation may minimize the incidence of the latter, the former is a consistent problem in phaeochromocytoma surgery ***(Weismann et al., 2006)***.

Hypertension:

Severe hypertension can abruptly occur at several stages of the procedure including induction, retroperitoneal insufflation and tumour

handling. The rise in arterial is abrupt and severe with systolic pressures in excess of 200 mm Hg and diastolic pressures over 100 mm Hg being not uncommon ***(Atallah et al., 2001)***. This may be accompanied by a tachycardia, particularly if the patient has not been given beta-adrenergic blockers preoperatively. Tumour handling or manipulation is the most consistent stimulus and can produce life-threatening rises in arterial pressure, which can precipitate myocardial infarction, cardiac failure, pulmonary oedema and cerebrovascular effects. However, this can occur in some patients before surgery during placement of lines, tracheal intubation, movement and positioning of the patient (e.g., into the lateral position for surgery), or insufflation with carbon dioxide. It is essential, therefore, that the anaesthetist has a strategy to deal with these complications well before inducing anaesthesia and has an antihypertensive agent available immediately for infusion (preferably using a central line) ***(Atallah et al., 2001)***.

Many drugs have been used successfully including: sodium nitroprusside, phentolamine, esmolol, nicardipine, magnesium sulphate and urapidil .Again, using an agent that the anaesthetist is familiar with is probably more important than themechanism of action. It is important to remember that the action of these agents may be altered by the antihypertensivedrugs given preoperatively ***(Atallah et al., 2001)***.

Sodium nitroprusside (SNP) is an inorganic ferrous salt which is a potent vaso- and venodilator, producing its action through release of nitric oxide (NO). In contact with blood it rapidly decomposes to produce NO. As NO is a potent but short-acting dilator, SNP must be given by continuous infusion. Its potential advantages are a rapid onset and offset, and its potency. Disadvantages include severe hypotension with a compensatory e.g., adrenergic blockers attenuating the compensatory

mechanisms), toxicity from the iron metabolites which produce thiocyanate and tachyphylaxis. It is given in a dose of 0.5–1.5 μg / kg / min, max. 8 μg kg / min ***(Atallah et al., 2001)***.

Phentolamine is a competitive α1 and α2 antagonist which has been widely used to control hypertensive episodes in phaeochromocytoma patients. It has a relatively rapid onset and a duration of action of around one hour. It is given by infusion. It is potentially of use in the alarming situation of dealing with a previously undiagnosed phaeochromocytoma in an anaesthetized patient undergoing surgery. The infusion should be started cautiously as severe hypotension can occur. ***(Baid et al., 2009).***

Esmolol is a short-acting (nine minute half-life) cardioselective beta-adrenergic blocker which has been used, often in combination with one of the other drugs described here, to control intraoperative hypertension and tachycardia. Its short action is of benefit following removal of the tumour as prolonged beta-adrenergic blockade is a disadvantage at that stage ***(Baid et al., 2009).***

Nicardipine: Magnesium sulphate has a number of antiadrenergic effects which are mediated mainly through its actions on calcium channels. Calcium is required for the release of catecholamines from the adrenal medulla and magnesium appears to block its action. Magnesium has effects on L-type calcium channels in membranes and the sarcoplasmic reticulum. It also has vasodilatory and antiarrhythmic effects and a small, dose-dependent myocardial depressant effect***(Baid et al., 2009).***

Magnesium sulphate has been used successfully to control arterial pressure intraoperatively in phaeochromocytoma patients In patients pretreated with phenoxybenzamine or prazosin, ***(James, 1989)***.

The onset of hypertensive episodes is abrupt and is triggered by events such as induction of anaesthesia, movement of the patient, insufflation and, in particular, handling of the tumour. These episodes are accompanied by surges of catecholamines which may achieve very high concentrations. For example, during one study peak norepinephrine (noradrenaline) concentrations of 200–300 ng ml-1 (normal < 510 pg ml-1) and epinephrine (adrenaline) concentrations of 150–200 ng ml-1 (normal < 170 pg ml-1) were measured during insufflation and tumour handling As catecholamines have a short duration of action the episodes are self-limiting, if the stimulus is removed. Thus all procedures must be done in a controlled manner; for example, insufflation should be done gradually and unnecessary manipulation of the tumour avoided. The surgeon must be prepared to stop operating for several minutes to allow severe arterial pressure/heart rate increases to be brought back under control ***(Tauzin et al., 2004)***.

Hypotension:

Following ligation of the tumour's venous drainage, there is an abrupt removal of sympathetic activity. This can result in severe and refractory hypotension, particularly if the patient has had incomplete alpha blockade preoperatively. Some patients may require a vasoconstrictor/inotropic infusion (e.g., norepinephrine) for some hours postoperatively. One of the arguments for the use of alpha-adrenergic blockade for a sufficiently long period preoperatively is to allow restoration of intravascular volume, which can help to minimise the immediate hypotensive effect of withdrawal of catecholamines. Treatment of the hypotension should include intraoperative volume loading and minimising the infusion of antihypertensive drugs As mentioned briefly above, there are good reasons not to use long-acting

hypotensive drugs to control arterial pressure during the earlier part of surgery. Similarly, it is advisable to avoid the use of long acting alpha- and beta-adrenergic blockade immediately pre and perioperatively; for example, the last dose of phenoxybenzamine is given the day before surgery. It is said that with good preoperative alpha blockade using phenoxybenzamine (with beta blockade if required) and intraoperative fluid replacement, the need for postoperative inotropes is rare ***(George et al., 2010)***.

Postoperative care:

In addition to routine postoperative care, it is appropriate to have the patient in a high dependency unit (HDU). Intra-arterial pressure monitoring should be continued to detect any episodes of hyper- orhypotension. Likewise, central venous pressure monitoring should be used to direct fluid and (if required) inotrope therapy. Blood glucose should be monitored as insulin levels may rise following removal of the suppressioncaused by the catecholamines. Postoperative analgesia can be provided with opioids or, if the procedure was an open one, with epidural analgesia ***(George et al., 2010)***.

SUMMARY

Only recently have endocrine disorders in critically ill patients been given detailed consideration.

Diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar state (HHS) are the major hyperglycaemic crises associated with diabetes mellitus. They are frequently considered as separate conditions but as will be shown in the following discussions they really represent two ends of a spectrum of hyperglycaemic and metabolic derangement, and not infrequently exist in combination. As many as 30–33% of all hyperglycaemic crisis admissions can be expected to have a mixed DKA/HHS metabolic picture.

Diabetic ketoacidosis (DKA) is an acute, major, life-threatening complication of diabetes. DKA mainly occurs in patients with type 1 diabetes, but it is not uncommon in some patients with type 2 diabetes. DKA is defined clinically as an acute state of severe uncontrolled diabetes that requires emergency treatment with insulin and intravenous fluids. Biochemically, DKA is defined as an increase in the serum concentration of ketones greater than 5 mEq/L, a blood glucose level of greater than 300 mg/dL (although it is usually much higher) and metabolic acidosis.

Thyroid storm is a clinical manifestation of an extreme hyperthyroid state that results in significant morbidity or disability or even death. Previously, thyroid storm was a common complication of toxic goiter surgery during intraoperative and postoperative stages. Preoperative control of the thyrotoxic state and use of radioiodine ablation has greatly reduced this phenomenon. Today, thyroid storm more commonly is seen

in a thyrotoxic patient with intercurrent illness or surgical emergency. Early recognition and prompt intervention are necessary to prevail in management of this phenomenon.

myxedema coma, an uncommon but life-threatening form of untreated hypothyroidism with physiological decompensation.The condition occurs in patients with long-standing, untreated hypothyroidism and is usually precipitated by a secondary insult, such as climate-induced hypothermia, infection, or another systemic condition, or drug therapy. Patients with myxedema coma have changes in their mental status, including lethargy, stupor, delirium, or coma. A more appropriate term for myxedema coma is myxedema crisis; we often use the term myxedema coma/crisis.

Adrenal crisis and severe acute adrnocortical insufficiency are often elusive diagnoses that may result in severe morbidity and mortality when undiagnosed or ineffectively treated.

In primary adrenocortical insufficiency, glucocorticoid and mineralocorticoid properties are lost; however, in secondary adrenocortical insufficiency (ie, secondary to disease or suppression of the hypothalamic-pituitary axis), mineralocorticoid function is preserved.

Every emergency physician should be familiar with adrenocortical insufficiency, which is a potentially life-threatening entity. The initial diagnosis and decision to treat are presumptive and are based on history, physical examination, and, occasionally, laboratory findings. Delay in treatment while attempting to confirm this diagnosis can result in poor patient outcomes.

Pheochromocytoma is a rare catecholamine-secreting tumorderived from chromaffin cells. When such tumors arise outside of the adrenal gland, they are termed extra-adrenal pheochromocytomas, or paragangliomas. Because of excessive catecholamine secretion, pheochromocytomas may precipitate life-threatening hypertension or cardiac arrhythmias. If the diagnosis of a pheochromocytoma is overlooked, the consequences could be disastrous, even fatal; however, if a pheochromocytoma is found, it is potentially curable.

References

A

American Association for Clinical Chemistry, 2016: Myxedema coma: a well-known but unfamiliar medical emergency. Fluid management in Myxedema Updated: December 17, 2015

Anand Swaminathan , (2015): Addisonian Crisis, Adrenal Gland, Adrenal Insufficiency , December 9, 2015

Atallah F, Bastide-Heulin T, Soulie M, et al., (2001): Haemodynamic changes during retroperitoneoscopic adrenalectomy for phaeochromocytoma. *Br J Anaesth*; **86**: 731–3.

B

Baid SK, Lai EW, Wesley RA, et al. (2009): Brief communication: radiographic contrast infusion and catecholamine release in patients with pheochromocytoma. *Ann Intern Med*. Jan 6;150(1):27-32.

Barbara Young and John Heath W (2000): Wheater's Functional Histology, a text and colour atlas**,** 4th edition ,*CHURCHILL LIVINGSTONE*; p. 320, Figure 17.12.

Barkovich AJ (2000): Pediatric Neuroimaging. 3rd ed. Philadelphia: Lippincott Williams & Wilkins: 281 –354.

Baskin HJ, Cobin RH, Duick DS, et al., (2002): American Association of Clinical Endocrinologists. "Medical Guidelines For Clinical Practice For The Evaluation And Treatment Of Hyperthyroidism And Hypothyroidism". *Endocrine Practice* 2002; 8 (6): 457–69.

Bessell-Browne R and O'Malley ME (2007): CT of pheochromocytoma and paraganglioma: risk of adverse events with i.v. administration of nonionic contrast material. *AJR Am J Roentgenol*. Apr;188(4):970-4.

Bianco AC, Salvatore D, Gereben B, et al., (2002): "Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases". *Endocr Rev*; 23 (1): 38–89.

Boulkina LS, Newton CA, Drake AJ 3rd and Tanenberg RJ. (2007): Acute myocardial infarction attributable to adrenergic crises in a patient with pheochromocytoma and neurofibromatosis 1. *Endocr Pract*. May-Jun;13(3):269-73.

Bowden SA, Duck MM and Hoffman RP (2008)*:* Young children (<5 yr) and adolescents (>12 yr) with type 1 diabetes mellitus have low rate of partial remission: diabetic ketoacidosis is an important risk factor. *Pediatr Diabetes*. Jun 2008;9(3 Pt 1):197-201.

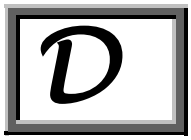
Bradley P, Tobias JD 19. Ten S, New M and Maclaren N (2001): Clinical review 130: Addison's disease . *J Clin Endocrinol Metab*, 2001;86:2909-22.

Brent GA, Larsen PR, Davies TF (2008): Hypothyroidism thyroiditis. In: Kronenberg HM, Melmed S, Polonsky KS, et al, eds. Williams Textbook of Endocrinology.11th ed. Philadelphia, Pa: Saunders /Elsevier;15:345-52.

C

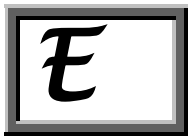
Cabrera O, Berman DM, Kenyon NS, et al., (2006): "The unique cytoarchitecture of human pancreatic islets has implications for islet cell function". Proceedings of the National Academy of Sciences of the USA; 103 (7): 2334–9.

Christine, Saraceni, et al., 2013: Diabetic Ketoacidosis: A Review and Update: March 2013, Volume 1, Issue 1, pp 10–17

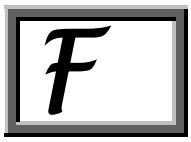


de Jong WH, Eisenhofer G, Post WJ, et al., (2009): Dietary influences on plasma and urinary metanephrines: implications for diagnosis of catecholamine-producing tumors. *J Clin Endocrinol Metab*. Jun 30.12:100-6.

Dutta P, Bhansali A, Masoodi SR, et al., (2008): Predictors of outcome in myxoedema coma: a study from a tertiary care centre. Crit Care.;12(1):R1.



Elenkova A, Matrozova J, Zacharieva S, et al., (2010): Adiponectin - A possible factor in the pathogenesis of carbohydrate metabolism disturbances in patients with pheochromocytoma. *Cytokine*. Apr 10.



Faria JF, Goldman SM, Szejnfeld J, et al., (2007): Adrenal masses: characterization with in vivo proton MR spectroscopy--initial experience. *Radiology*. Dec;245(3):788-97.

Fliers E and Wiersinga WM (2003): Myxedema coma. *Rev Endocr Metab Disord*. May;4(2):137-41.

G

George M, Hall, Jennifer M, Hunter and Mark S, Cooper (2010): pheochromocytroma, preoperative Preparation and perioperative Management. campridge *university;* **5**:48-53.

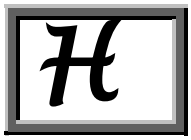
Gergics P, Patocs A, Toth M, et al., (2009: Germline VHL gene mutations in Hungarian families with von Hippel-Lindau disease and patients with apparently sporadic unilateral phaeochromocytomas. *Eur J Endocrinol*. Jul 2.10:170-8.

Gilliland PF (2003): Endocrine emergencies. Adrenal crisis, myxedema coma, and thyroid storm. Postgrad Med. Nov 2003;74(5):215-20, 225-7.

Glaser NS, Marcin JP, Wootton-Gorges SL, et al., (2008): Correlation of clinical and biochemical findings with diabetic ketoacidosis-related cerebral edema in children using magnetic resonance diffusion-weighted imaging. *J Pediatr*. Jun 25; 15:150-7.

Gosse P, Tauzin-Fin P, Sesay MB, Sautereau A, Ballanger P (2009): Preparation for surgery of phaeochromocytoma by blockade of alpha-adrenergic receptors with urapidil: what dose? *J Hum Hypertens*; 23(9): 605–9.

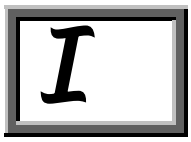
Guyton AC, et al., (2000): The adrenocortical hormones. In: Textbook of Medical Physiology. 7th ed. WB Saunders:909-19.



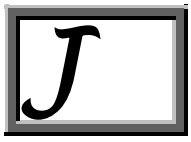
Hahner S and Allolio B (2009): Therapeutic management of adrenal insufficiency. Best Pract Res Clin Endocrinol Metab. Apr;23(2):167-79.

Hahner S, Loeffler M, Bleicken B, et al., (2009): Epidemiology of adrenal crisis in chronic adrenal insufficiency - the need for new prevention strategies. Eur J Endocrinol. Dec 2.13:245-7.

Hill RN, Crisp TM, Hurley PM, et al., (1998): "Risk assessment of thyroid follicular cell tumors". *Environ. Health Perspect*.1998; 106 (8): 447–57.



Ingbar SH (2000): Management of emergencies. IX. Thyrotoxic storm. N Engl J Med. Jun 10; 274(22):1252-4.



James MFM (1989): Use of magnesium sulphate in the anaesthetic management of phaeochromocytoma: a review of 17 anaesthetics. Br J Anaesth; **62**: 616–23.

James W, Findling and Hershel R (2006): Cushing's syndrome: Important issues in diagnosis and management. J Clin Endocrinol Metab. 91; 3746-53

Jansen J, Friesema ECH, Milici C, et al., (2005): Thyroid hormone transporters in health and disease. *Thyroid*:15;757-68.

K

Kaushik Pandit et al., 2011: Myxedema Coma: A New Look into an Old Crisis. Institute of Post-Graduate Medical Education & Research, Calcutta 700020, India Received 1 March 2011; Accepted 12 May 2011

Kester MH, Martinez de Mena R, Obregon MJ, et al., (2004): "Iodothyronine levels in the human developing brain: major regulatory roles of iodothyronine deiodinases in different areas". *J Clin Endocrinol Metab*; 89 (7): 3117–28.

Kim S, Salibi N, Hardie AD, et al., (2009): Characterization of adrenal pheochromocytoma using respiratory-triggered proton MR spectroscopy: initial experience. *AJR Am* J Roentgenol. Feb;192(2):450-4.

Kocak S, Aydintug S and Canakci N (2002): Alpha blockade in preoperative preparation of patients with pheochromocytomas. *Int Surg* 2002; **87**: 191–4.

Kudva YC, Sawka AM and Young WF Jr (2003): Clinical review 164: The laboratory diagnosis of adrenal pheochromocytoma: the Mayo Clinic experience. *J Clin Endocrinol Metab*. Oct;88(10):4533-9.

Kwaku MP and Burman KD (2007): Myxedema coma. *J Intensive Care Med*. Jul-Aug 2007;22(4):224-31.

L

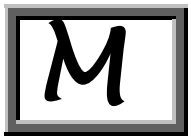
Lawrence JM, Contreras R, Chen W, et al., (2008): "Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus

among a racially/ethnically diverse population of pregnant women, 1999–2005". *Diabetes Care*; 31 (5): 899–904.

Lelubre C and Lheureux PE (2008): Epigastric pain as presentation of an addisonian crisis in a patient with Schmidt syndrome. Am J Emerg Med. Feb;26(2):251.e3-4.

Lenders JWM, Eisenhofer G, Mannelli M et al., (2005): Phaeochromocytoma. *Lancet* 2005; **366**: 665–75.

Lin SF, Lin JD and Huang YY (2005): Diabetic ketoacidosis: comparisons of patient characteristics, clinical presentations and outcomes today and 20 years ago. *Chang Gung Med J*. Jan ;28(1):24-30.



Madhusmita et al, (2016): MD, MPH; Chief Editor: Stephen Kemp, MD, PhDO verview Presentation DDx Workup Treatment Medication Updated: Jun 20, 2016

Marik PE, Pastores SM, Annane D, et al., (2008): Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med. Jun; 36(6):1937-49.

Martin D (2009): Disseminated intravascular coagulation precipitated by thyroid storm. South Med J. Feb; 102(2):193-5.

Martin SL, Hoffman WH, Marcus DM, et al., (2005): Retinal vascular integrity following correction of diabetic ketoacidosis in children and adolescents. *J Diabetes Complications*. Jul-Aug 2005;19(4):233-7.

Medvei and Victor Cornelius (1993): The history of clinical endocrinology. Carnforth, Lancs, U.K: Parthenon Pub. Group; pp. 23–34.

Michael et al., (2013): Diabetic Ketoacidosis: A Review and Update: March 2013, Volume 1, Issue 1, pp 10–17

Migneco A, Ojetti V and Testa A (2005): Management of thyrotoxic crisis. Eur Rev Med Pharmacol Sci. Jan-Feb; 9(1):69-74.

Molitch M (2000): Neuroendocrinology and pituitary disease. In: Atlas of Clinical Endocrinology, vol 4. Philadelphia: Current Medicine,13(4):191-2.

Moller N, Foss AC, Gravholt CH, et al., (2005): Myocardial injury with biomarker elevation in diabetic ketoacidosis. *J Diabetes Complications*. Nov-Dec; 19(6):361-3.

Morgan GE, Maged SM and Michail JM (2006): 4th edition 2006. hyper thyroidism36: 806-8.

N

Nakamura S, Nishmyama T and Hanaoka K (2005): [Perioperative thyroid storm in a patient with undiscovered hyperthyroidism] .*Masui*. Apr; 54(4):418-9.

P

***Pacak K (2007*)**: Preoperative management of the pheochromocytoma patient. *J Clin Endocrinol Metab*; **92**: 4069–79.

Parnaby CN, Serpell MG, Connell JM, et al., (2010): Perioperative haemodynamic changes in patients undergoing laparoscopic

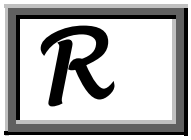
adrenalectomy for phaeochromocytomas and other adrenal tumours. *Surgeon*. Feb;8(1):9-14.

Patrick L (2008): "Iodine: deficiency and therapeutic considerations" *Altern Med Rev*.: 13 (2): 116–27.

Potenza M, Via MA and Yanagisawa RT (2009): Excess thyroid hormone and carbohydrate metabolism. *Endocr Pract*. May Jun; 15(3):254-62.

Prys-Roberts C, Farndon JR (2002): Efficacy and safety of doxazosin for perioperative management of patients with pheochromocytoma. *World J Surg*; **26**:1037–42.

Pugliese G, Zanuso S, Alessi E, et al., (2009): Self glucose monitoring and physical exercise in diabetes. *Diabetes Metab Res Rev*. Sep 2009;25 Suppl 1:S11-7.



Raiz Misgar, et al., 2011: Myxedema Coma: A New Look into an Old Crisis. Institute of Post-Graduate Medical Education & Research, Calcutta 700020, India Received 1 March 2011; Accepted 12 May 2011

Rehman SU, Cope DW, Senseney AD, et al., (2005): Thyroid disorders in elderly patients. *South Med J*. May; 98(5):543-9.

Rimar D, Kruzel-Davila E, Dori G, et al., (2007): Hyperammonemic coma--barking up the wrong tree. *J Gen Intern Med*. Apr;22(4):549-52.

Rodríguez I, Fluiters E, Pérez-Méndez LF, et al., (2004): Factors associated with mortality of patients with myxoedema coma . *J Endocrinol*. Feb; 180(2):347-50.

Rosenberg IN (2006): Thyroid storm. N Engl J Med. Nov 5; 283 (19):1052-3.

Rother KI. (2007): "Diabetes treatment—bridging the divide". *The New* England Journal of Medicine; 356 (15): 1499–501.

Rozansky DJ (2006): The role of aldosterone in renal sodium transport. *Semin Nephrol*; 26:173-181.

S

Scholz GH, Hagemann E, Arkenau C, et al., (2003): Is there a place for thyroidectomy in older patients with thyrotoxic storm and cardiorespiratory failure?. Thyroid. Oct; 13(10):933-40.

Sheu CC, Cheng MH, Tsai JR, et al., (2007): Myxedema coma: a well-known but unfamiliar medical emergency. *Thyroid*. Apr;17(4):371-2.

Simm PJ, McDonnell CM and Zacharin MR (2004): Primary adrenal insufficiency in childhood and adolescence: advances in diagnosis and management. J Paediatr Child Health. Nov;40(11):596-9.

Strawn JR, Keck PE Jr and Caroff SN (2007)*:* Neuroleptic malignant syndrome. *Am J Psychiatry*. Jun; 164(6):870-6.

Sujoy Ghosh et al., 2011:Myxedema Coma: A New Look into an Old Crisis. Institute of Post-Graduate Medical Education & Research, Calcutta 700020, India Received 1 March 2011; Accepted 12 May 2011

T

Taguchi T, Iwasaki Y, Asaba K, et al., (2007): Myxedema coma and cardiac ischemia in relation to thyroid hormone replacement therapy in a 38-year-old Japanese woman. *Clin Ther*. Dec;29(12):2710-4.

Tauzin-Fin P, Sesay M, Gosse P, Ballanger P (2004): Effects of perioperative a1 block on haemodynamic control during laparoscopic surgery for phaeochromocytoma. *Br J Anaesth*; **92**: 512–17.

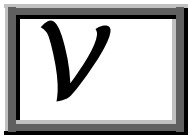
Tiberio GAM, Baiocchi GL, Arru Luca, et al., (2008): Prospective randomized comparison of laparoscopic versus open adrenalectomy for sporadic pheochromocytoma. *Surg Endosc*; **22**: 1435–9.

Tietgens ST and Leinung MC (2006): Thyroid storm. *Med Clin North Am*. Jan; 79(1):169-84.

Timothy E Corden et al ,2014:ABOUT DIABETIC KETOACIDOSIS ON MEDSCAPE MD, MBBS, FRCP(Edin), FRCP, FRCPCH; Apr 25, 2014

Trampal C, Engler H, Juhlin C, et al., (2004): Pheochromocytomas: detection with 11C hydroxyephedrine PET. *Radiology*.;230:423-42.

Trudi Cloyd, 2015: Addisonian Crisis, Adrenal Gland, Adrenal Insufficiency,December 9, 2015



Vivek Mathew et al., 2011 : Myxedema Coma: A New Look into an Old Crisis. Institute of Post-Graduate Medical Education & Research, Calcutta 700020, India Received 1 March 2011; Accepted 12 May 2011

W

Waguespack SG, Rich T, Grubbs E, et al., (2010): A Current Review of the Etiology, Diagnosis, and Treatment of Pediatric Pheochromocytoma and Paraganglioma. J Clin Endocrinol Metab. Mar 9.;50:99-102.

Wall CR (2000): Myxedema coma: diagnosis and treatment. *Am Fam Physician*. Dec 1; 62(11):2485-90.

Wartofsky L. (2006): Myxedema coma. Endocrinol Metab Clin North Am. Dec;35(4):687-98, vii-viii.

Weber C, Kocher S, Neeser K, et al., (2009): Prevention of diabetic ketoacidosis and self-monitoring of ketone bodies: an overview. *Curr Med Res Opin*. May 2009;25(5):1197-207.

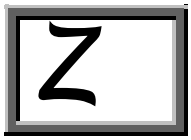
Weismann D, Fassnacht M, Weinberger F, et al., (2006): Intraoperative haemodynamic stability in patients with phaeochromocytoma – minimally invasive versus conventional open surgery. *Clin Endocrinol (Oxf)*; **65**: 1365–2265.

William et al ,2014:ABOUT DIABETIC KETOACIDOSIS ON MEDSCAPE MD, MBBS, FRCP(Edin), FRCP, FRCPCH; Apr 25, 2014

Williams PL et al., (1995): Thyroid Gland. In: Gray's anatomy. New York, NY: Churchill Livingstone:1891-6.

Y

Yalçin B and Ozan H (2006): "Detailed investigation of the relationship between the inferior laryngeal nerve including laryngeal branches and ligament of Berry". *Journal of the American College of Surgeons*; 202 (2):2916.



Zargar AH, Wani AI, Masoodi SR, et al., (2009): Causes of mortality in diabetes mellitus: data from a tertiary teaching hospital in India. *Postgrad Med J*. May; 85 (1003): 227-32.