

Hypoadrenocorticism

Hypoadrenocorticism, or Addison's disease, is the result of mineralocorticoid and glucocorticoid deficiency. Søren Boysen DVM DACVECC and Jantina McMurray DVM, Faculty of Veterinary Medicine, University of Calgary, Canada, provide an overview of the diagnosis and treatment options

Hypoadrenocorticism is uncommon in dogs and extremely rare in cats. Acute adrenal crises may be life-threatening due to hypovolaemic shock, hypoglycaemia, hyperkalaemia, and bradycardia. Chronic cases have a more gradual onset and may have a history of vomiting, diarrhoea, melaena, weight loss, anorexia and lethargy. Diagnosis relies on adrenocorticotrophic hormone (ACTH) stimulation testing. Overall prognosis is good with appropriate mineralocorticoid and glucocorticoid therapy.

AETIOLOGY AND PATHOGENESIS

ADRENAL ANATOMY AND PHYSIOLOGY

The adrenal glands are located near the craniomedial poles of the kidneys. Each adrenal gland is comprised of a cortex surrounding a medulla. The cortex has three layers (from external to internal) including the zona glomerulosa, zona fasciculata and zona reticularis. The zona glomerulosa secretes mineralocorticoids (aldosterone), the zona fasciculata secretes glucocorticoids (cortisol) and the zona reticularis secretes androgens (androstenedione, dehydroepiandrosterone). The medulla contains chromaffin cells that secrete catecholamines (epinephrine, norepinephrine). Cortisol production in the zona fasciculata is regulated by ACTH secreted by the pituitary gland, and ACTH release is regulated by corticotropin-releasing hormone (CRH) secreted by the hypothalamus. Mineralocorticoid production is regulated by several physiological mechanisms, most importantly angiotensin II (part of the renin-angiotensin-aldosterone system) and increased plasma potassium concentration.

PATHOGENESIS OF HYPOADRENOCORTICISM

There are two general categories of hypoadrenocorticism: primary and secondary. Primary hypoadrenocorticism is more common and is most often the result of an immune-mediated process damaging all three layers of the adrenal cortex.¹ It is reported that up to 90% of the adrenal cortex must be destroyed before clinical signs become evident (Figures 1a and 1b).^{1,2} Primary hypoadrenocorticism is over-represented in certain dog breeds including Nova Scotia Duck Tolling Retrievers, Standard Poodles, Bearded Collies, Portuguese Water Dogs, Great Danes, West Highland White Terriers, Saint Bernards, Wheaton Terriers, Leonbergers and Rottweilers.^{1,3-7} Most patients with primary hypoadrenocorticism (85-90%) will have both glucocorticoid and mineralocorticoid deficiencies and will present with electrolyte abnormalities.^{1,2} Primary hypoadrenocorticism resulting in only glucocorticoid deficiency without electrolyte imbalances is rare.⁶ Secondary hypoadrenocorticism involves dysfunction of the pituitary gland (a lack of ACTH secretion) or the hypothalamus

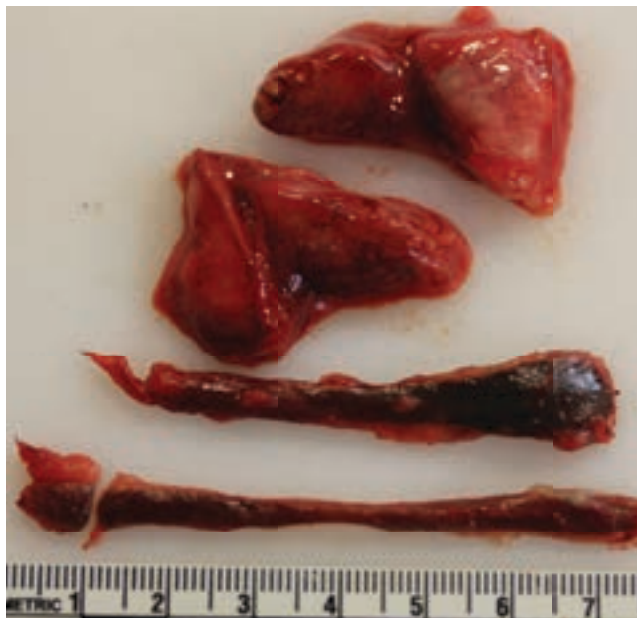


Figure 1a: Normal adrenal glands from a medium-sized dog (top) compared to adrenal glands from a Great Dane with hypoadrenocorticism (bottom).

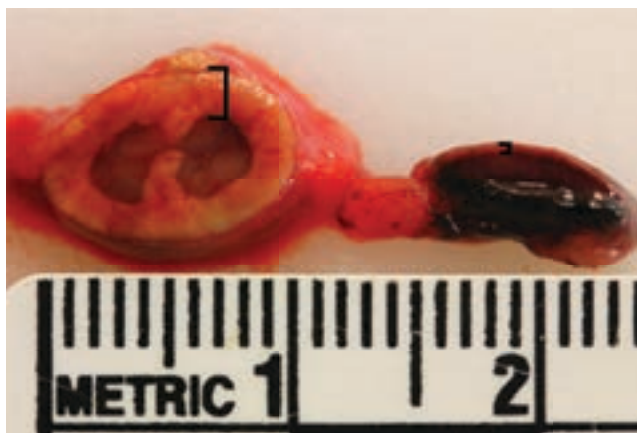


Figure 1b: Cross-section of a normal adrenal gland from a medium-sized dog (left) compared to a cross-section of an adrenal gland from a Great Dane with hypoadrenocorticism (right) showing extensive chronic adrenocortical atrophy (>90%). Brackets indicate the width of the adrenal cortex.

(a lack of CRH secretion), causing atrophy of the zona fasciculata and zona reticularis with a corresponding lack of cortisol production, while the zona glomerulosa is preserved and mineralocorticoid production remains unaffected.^{1,2,8} Treatment is not the same with primary and secondary causes of hypoadrenocorticism so it is important to differentiate the two conditions. Common underlying causes of secondary hypoadrenocorticism include trauma and neoplasia affecting normal pituitary or hypothalamic function.



Figure 2: Left lateral thoracic radiograph of a mixed breed dog with hypoadrenocorticism. Note the marked microcardia and narrowing of the caudal vena cava (CVC), consistent with hypovolaemia.

MINERALOCORTICOID DEFICIENCY

Aldosterone acts primarily on the cells of the distal renal tubules to increase sodium reabsorption; negative ions such as chloride are reabsorbed along with sodium due to electrical potentials, and water is reabsorbed passively as it follows the concentration gradients created by movement of sodium and chloride. In cases of hypoadrenocorticism, aldosterone deficiency causes increased loss of sodium, chloride, and water via the urine. This contributes to dehydration, prerenal azotaemia, unconcentrated urine, hypovolaemia, weakness and shock. Aldosterone also promotes sodium absorption in the gastrointestinal (GI) tract. Aldosterone deficiency impairs the absorption of sodium, chloride and water from the GI tract, contributing to the development of diarrhoea and vomiting, which further contribute to hypovolaemia, hypoperfusion and shock. Aldosterone also promotes the renal excretion of potassium and plays a vital role in maintaining normal plasma potassium concentrations. Aldosterone deficiency can lead to marked hyperkalaemia. Hyperkalaemia can be exacerbated by hypovolaemia and decreased glomerular filtration rate (GFR), which can occur in cases of hypoadrenocorticism. Hyperkalaemia can cause abnormal cardiac conduction (prolonged refractory periods during cardiac action potentials), leading to bradycardia, atrial standstill, decreased cardiac output and, in severe cases, ventricular fibrillation and death.^{9,10} Aldosterone also regulates renal excretion of hydrogen ions, so aldosterone deficiency can lead to mild acidosis. During an adrenal crisis in a patient with hypoadrenocorticism, lactic acidosis and decreased GFR secondary to hypoperfusion can lead to severe acidosis. Acidosis contributes to the movement of potassium out of cells, which further exacerbates hyperkalaemia.

GLUCOCORTICOID DEFICIENCY

Cortisol plays an important role in regulating blood pressure, blood volume and blood glucose concentration.

Cortisol stimulates the release of vasoactive substances, sensitises blood vessels to the effects of catecholamines, and decreases blood vessel permeability.¹¹ In the absence of cortisol, intravascular volume decreases and blood pressure decreases, contributing to hypovolaemia, hypotension and shock.¹¹ Cortisol also contributes to blood glucose regulation by stimulating gluconeogenesis and exerting anti-insulin effect that inhibits glucose uptake and metabolism in peripheral tissues. In the absence of cortisol, hypoglycaemia can develop and, in rare cases, may be severe enough to cause ataxia, tremors or seizures.¹¹ Cortisol deficiency may also contribute to GI ileus, further exacerbating diarrhoea and vomiting.¹²

CLINICAL SIGNS

The history in patients with hypoadrenocorticism can be non-specific and may include signs that wax and wane over time. Dogs often have a history of primary GI signs that may have previously responded to fluids and/or glucocorticoid therapy. Vomiting, diarrhoea, and melaena are the most common clinical signs reported in dogs with hypoadrenocorticism.⁶ Other clinical signs include lethargy, weight loss, anorexia, dehydration, polyuria/polydipsia, as well as ataxia, tremors or seizures. In an acute adrenal crisis, bradycardia and signs of shock (collapse, pale mucous membranes, hypothermia, weak pulses, abnormal respiratory pattern) are often present. Patients presenting in shock with concurrent bradycardia should prompt consideration of diseases leading to hyperkalaemia, including hypoadrenocorticism. Shock is more likely in dogs with both glucocorticoid and mineralocorticoid deficiency (most cases of primary hypoadrenocorticism), while clinical signs tend to be milder in dogs with only glucocorticoid deficiency and normal electrolytes (cases of secondary hypoadrenocorticism or rare cases of primary hypoadrenocorticism).⁶ Hypoadrenocorticism is extremely rare in cats, with only a few cases reported in the literature. Clinical findings in cats are similar to those in dogs, with lethargy, anorexia, and weight loss being the most common signs reported by owners and depression, dehydration, weakness, and hypothermia being the most common physical exam findings.

DIAGNOSIS

EMERGENCY DATABASE

When patients present in shock, an emergency minimum database should be collected including blood pressure measurement, basic biochemistry (urea, creatinine, lactate, electrolytes, total solids, glucose), packed cell volume, acid-base status and electrocardiogram (ECG). Patients in an acute adrenal crisis will often show pre-renal azotaemia, hyperlactataemia, hyponatraemia, hyperkalaemia, hypoglycaemia and acidosis on emergency bloodwork.¹³ ECG may reflect hyperkalaemia including sinus bradycardia, flattened or absent P-waves (atrial standstill), prolonged PR intervals (first-degree atrioventricular block), prolonged QRS intervals, and tall spiked T-waves.^{9,10} Imaging is often performed as part of the initial diagnostic work-up for patients with GI signs or undifferentiated shock.

Abdominal ultrasound may reveal bilateral adrenal atrophy (in cases of primary hypoadrenocorticism); however, the finding of normal-sized adrenal glands on ultrasound should not preclude a diagnosis of hypoadrenocorticism.¹³ Radiographs are often unremarkable or may show evidence of hypovolaemia in cases of adrenal crisis (Figure 2).

COMPLETE BLOOD COUNT

Most dogs and cats with hypoadrenocorticism will have variable leukocyte counts. However, the absence of a stress leukogram (neutrophilia, lymphopenia, monocytosis and eosinopenia), particularly the presence of lymphocytosis, in a sick patient should prompt consideration of hypoadrenocorticism.^{1,6,7,13,14} Patients with gastrointestinal haemorrhage (melaena) may have anaemia.⁷

SERUM CHEMISTRY PANEL

The most common abnormalities on the serum chemistry profile in patients with hypoadrenocorticism are hyperkalaemia, hyponatraemia and azotaemia.^{1,7,13} A sodium:potassium ratio <27 should raise suspicion of hypoadrenocorticism and a sodium:potassium ratio <24 is extremely suggestive of hypoadrenocorticism.^{13,14} However, it is important to remember that some patients with hypoadrenocorticism (especially cases of glucocorticoid deficiency without concurrent mineralocorticoid deficiency) may have a sodium:potassium ratio >27 and other conditions (such as gastrointestinal disease, *Trichuris vulpus* infection, third space fluid losses, congestive heart failure, and diabetes mellitus) can also result in sodium:potassium ratios <27. ACTH stimulation testing should be strongly considered in cases with ratios <30 if another cause is not evident and clinical signs are supportive of hypoadrenocorticism.¹³ Azotaemia is most likely prerenal in origin due to hypovolaemia and hypoperfusion. Patients with hypoadrenocorticism often have renal medullary washout secondary to hyponatraemia, which results in low urine specific gravity (USG) with concurrent azotaemia. Therefore, USG does not reliably distinguish prerenal from renal azotaemia in these patients. Other common abnormalities associated with hypoadrenocorticism include hypocholesterolaemia, hypoproteinaemia/hypoalbuminaemia, hypercalcaemia and hypoglycaemia.

RESTING OR BASAL SERUM CORTISOL LEVELS

Measurement of resting cortisol level is rapid and inexpensive. Resting cortisol >2ug/dL makes hypoadrenocorticism extremely unlikely (only 1% of dogs with hypoadrenocorticism have resting cortisol >2ug/dL). However, resting cortisol <2ug/dL is not definitive for hypoadrenocorticism (patients with various non-adrenal diseases may have resting cortisol <2ug/dL) so an ACTH stimulation test should be performed to confirm the diagnosis of hypoadrenocorticism in patients with resting cortisol <2ug/dL.^{15,16}

ACTH STIMULATION TESTING

ACTH stimulation testing is the definitive test for

hypoadrenocorticism. A serum cortisol concentration ≤ 2 ug/dL pre- and one hour post-ACTH administration in dogs (30 minutes post-ACTH administration for cats) is considered diagnostic of hypoadrenocorticism in the absence of exposure to exogenous corticosteroids or mitotane.⁶ Protocols for ACTH administration vary between product manufacturers and it is important to read manufacturer directions. Liquid formulations and sterile powders requiring reconstitution with sterile saline have been used with equivocal results.¹⁷⁻¹⁹ Concerns have been raised over the reliability of ACTH gel preparations leading several authors to recommend avoiding their use.^{17,20} Current recommendations are to administer ACTH at 5ug/kg intravenously (IV) (up to a maximum dose of 250ug) in dogs and to administer a single dose of 125ug ACTH IV in cats.¹⁸⁻²⁰ With the exception of dexamethasone, exogenous glucocorticoids can falsely elevate cortisol assays so administration of these medications should be avoided until after ACTH stimulation testing is performed. It has been suggested to wait 24 hours before performing an ACTH stimulation test if short-acting glucocorticoids have been administered, or longer if glucocorticoids have been used chronically.²⁰ In an acute adrenal crisis, dexamethasone should be used if emergency glucocorticoid therapy is required prior to ACTH stimulation testing.

DIFFERENTIATING PRIMARY VERSUS SECONDARY HYPOADRENOCORTICISM

Results of ACTH stimulation testing can confirm a diagnosis of hypoadrenocorticism but cannot differentiate between primary and secondary causes. The presence of electrolyte imbalances is strongly suggestive of primary hypoadrenocorticism. In patients with normal electrolytes at the time of diagnosis, it is important to monitor electrolytes over time as many primary cases will eventually develop electrolyte abnormalities while secondary cases are unlikely to develop electrolyte imbalances. Endogenous plasma ACTH concentrations must be evaluated to distinguish primary from secondary hypoadrenocorticism (plasma ACTH concentration is high in primary hypoadrenocorticism because decreased cortisol production causes a loss of feedback inhibition on the pituitary, while plasma ACTH concentration is low in secondary hypoadrenocorticism due to decreased release of ACTH from the pituitary gland). Consultation with the local laboratory is recommended regarding the best way to collect and handle sampling for endogenous plasma ACTH concentration.

TREATMENT

Shock can be life-threatening in patients with hypoadrenocorticism that present in an acute adrenal crisis. Initial therapy should focus on correcting hypoperfusion through restoring intravascular volume, correcting arrhythmias, correcting electrolyte imbalances, correcting hypoglycaemia, and administering short-acting glucocorticoids. Once the patient is stable, the diagnosis of hypoadrenocorticism can be confirmed and primary versus secondary causes can be investigated.



Figure 3: A dog in shock with acute adrenal crisis. Emergency fluid resuscitation has been initiated while emergency diagnostic tests are being performed (emergency blood work taken at the time of IV catheter placement, Doppler blood pressure, and pulse oximetry). An ECG should be assessed and an intravenous injection of dexamethasone at 0.25mg/kg is indicated in this patient as part of the emergency therapy while awaiting an ACTH stimulation test.

FLUID THERAPY

Early aggressive fluid therapy in patients with hypovolaemic shock helps to restore tissue perfusion, helps to correct hyperkalaemia, helps to correct acid-base imbalances, and improves renal perfusion (Figure 3). Isotonic crystalloids are a reasonable initial fluid choice in patients with hypoadrenocorticism. Any commercially available balanced isotonic crystalloid solution can be used; however, isotonic crystalloids that are lower in sodium (eg. lactated Ringer's solution or Plasma-Lyte 148) may be preferable to normal saline in the management of dogs that are markedly hyponatraemic, due to the risk of central pontine myelinolysis when hyponatraemia is corrected too quickly.²¹⁻²³ It has been suggested that the rate of increase in plasma sodium concentration should not exceed 0.5mEq/L/h. Electrolytes should be monitored frequently and fluid therapy adjusted in accordance with the rate of change in electrolytes. In addition to isotonic crystalloids, patients with gastrointestinal haemorrhage (15% of dogs

with hypoadrenocorticism)⁷ may require a blood transfusion, depending on the hematocrit and response to fluid therapy.

HYPERKALAEMIA

Fluid resuscitation is vital for correction of hyperkalaemia via dilution of serum potassium concentration, increased renal excretion of potassium through increased glomerular filtration rate and correction of acidosis. Most hyperkalaemic patients with hypoadrenocorticism will respond well to fluid therapy alone and do not require additional therapy to address the hyperkalaemia. However, in patients with compromised cardiac output and relevant ECG changes consistent with hyperkalaemia (described above), additional therapy for hyperkalaemia is warranted. Calcium gluconate can be used to stabilise cardiac function while other therapies are initiated to decrease serum potassium concentration. Calcium gluconate (10% solution given IV at a dose of 0.5-1.0ml/kg to effect over 5-10 minutes) antagonises the cardiotoxic effects of hyperkalaemia with a rapid onset of action and a duration of 30-60 minutes. An ECG should be monitored closely during administration of calcium gluconate, and the infusion should be discontinued if the heart rate decreases or if other significant ECG findings develop (such as arrhythmias or ST segment elevation). Once the ECG changes resolve, the calcium gluconate infusion can be restarted at a slower rate.²⁴ In addition to fluid therapy, a dextrose bolus (0.5-1.0ml/kg 50% dextrose diluted to <25% with isotonic crystalloids) can be used to decrease serum potassium concentration. IV dextrose increases endogenous insulin secretion from the pancreas and shifts potassium intracellularly, decreasing serum potassium concentrations up to 0.5-1mEq/L within an hour with effects lasting up to six hours.^{9,10} Dextrose can be administered in combination with insulin (0.5-1.0ml/kg 50% dextrose diluted to <25% with isotonic crystalloids) for a more pronounced and rapid decrease in serum potassium concentration. Insulin should only be given with an accompanying IV dextrose bolus and an IV CRI of dextrose (add 50% dextrose to IV fluids to make a 2.5-5% solution) for at least six hours to prevent iatrogenic hypoglycaemia. Ideally, the serum glucose concentration should be measured hourly for at least six hours following IV insulin administration.

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GLUCOCORTICOIDS

Patients presenting in an acute adrenal crisis should have rapid-acting glucocorticoids administered as soon as possible concurrent with initiation of fluid resuscitation. Dexamethasone (0.2-0.25mg/kg IV q12-24 hours) can be given intravenously, is rapid acting, and does not interfere with ACTH stimulation testing. Other glucocorticoids (prednisone, prednisolone, hydrocortisone) interfere with ACTH stimulation testing and should therefore be avoided until after a diagnosis is confirmed. Mineralocorticoid therapy is not required until electrolytes have been corrected and the animal is stable following initial therapy. Administration of mineralocorticoids early in the course of treatment may contribute to more rapid increases in sodium concentrations and predispose the patient to central pontine myelinolysis.

CHRONIC MANAGEMENT

Patients diagnosed with hypoadrenocorticism and electrolyte imbalances require glucocorticoid and mineralocorticoid therapy for life. Patients with primary hypoadrenocorticism and normal electrolytes require glucocorticoid therapy and close electrolyte monitoring as they will likely develop electrolyte imbalances and eventually require mineralocorticoid therapy.¹³ Patients with secondary hypoadrenocorticism require lifelong glucocorticoid therapy but are very unlikely to need mineralocorticoid therapy. Long-term mineralocorticoid supplementation in dogs can be provided by oral administration of fludrocortisone (0.02mg/kg PO q24 hours or 0.01mg/kg PO q12 hours with a daily increase of 0.05-0.1mg increments (not mg/kg) until serum electrolyte concentrations are stable). Fludrocortisone does have some glucocorticoid activity but some dogs may still need additional prednisone supplementation, particularly in stressful situations.¹⁰ Alternatively, mineralocorticoid supplementation can be provided to dogs with an injection of deoxycorticosterone pivalate (DOCP; 2mg/kg SQ or IM

q25 days).²⁵ DOCP does not possess any glucocorticoid activity so prednisone (0.22mg/kg PO SID) is often required concurrently.

Cats are generally treated with DOCP (12.5mg/kg SQ q3-4 weeks) and daily oral prednisone (0.22mg/kg q24 hours). If cat owners are having difficulty with oral medications then methylprednisolone acetate (Depo-Medrol; 10mg/cat SQ q3-4 weeks) has been suggested by some authors to replace oral prednisone therapy.¹⁰

COMPLICATIONS

Major complications in patients with hypoadrenocorticism are rare, although central pontine myelinolysis and acute renal failure have been reported in cases with combined glucocorticoid and mineralocorticoid deficiency.²⁰⁻²² Central pontine myelinolysis involves damage to the myelin sheath surrounding neurons in the brainstem, which can cause untreatable and irreversible neurological signs that may develop several days to weeks after an adrenal crisis. Rapid correction of severe chronic hyponatraemia (increase in plasma sodium concentration >0.5mEq/L/h) increases the risk of central pontine myelinolysis. Acute renal failure can be a result of renal ischaemia secondary to hypoperfusion. Aggressive fluid therapy to improve perfusion and close monitoring of renal parameters is recommended to help prevent acute renal failure and to help differentiate renal failure from prerenal azotaemia.

PROGNOSIS

Prognosis for patients with hypoadrenocorticism is good-to-excellent if they survive the acute adrenal crisis without major complications.

Most dogs with hypoadrenocorticism can have a normal quality of life and a normal life expectancy.²⁰

However, owners must be informed that treatment will be lifelong and that an increase in glucocorticoid dosage is often necessary during periods of stress (eg. travel, surgery, etc).

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READER QUESTIONS AND ANSWERS

1. WHAT IS THE MOST COMMON CAUSE OF HYPOADRENOCORTICISM IN DOGS?

- A: Pituitary tumour
- B: Bilateral adrenal gland tumours
- C: Immune-mediated destruction of the adrenal cortex
- D: Age-related degeneration of the zona glomerulosa
- E: Congenital adrenal gland hypoplasia

2. COMMON CLINICAL SIGNS OF HYPOADRENOCORTICISM INCLUDE:

- A: Tachycardia, seizures, ataxia
- B: Vomiting, diarrhoea, melaena
- C: Dyspnoea, weight loss, anorexia
- D: Lethargy, waxing and waning lameness
- E: Abdominal distension, polyuria, polydipsia

3. THE MOST COMMON ABNORMALITIES ON SERUM CHEMISTRY PROFILE REPORTED IN PATIENTS WITH HYPOADRENOCORTICISM INCLUDE:

- A: Hypercalcaemia, hyperglycaemia, azotaemia
- B: Hyponatraemia, hyperkalaemia, hypocholesterolaemia

- C: Hyponatraemia, hypokalaemia, hypoglycaemia
- D: Hyponatraemia, hyperkalaemia, azotaemia
- E: Hypocalcaemia, hypoalbuminaemia, hypochloroemia

4. WHICH DIAGNOSTIC TEST CAN BE USED TO DEFINITELY DIAGNOSE HYPOADRENOCORTICISM?

- A: Resting serum cortisol level
- B: Serum chemistry profile with sodium:potassium ratio <27
- C: Endogenous plasma ACTH concentration
- D: ACTH stimulation test
- E: Abdominal ultrasound

5. INITIAL THERAPY DURING AN ACUTE ADRENAL CRISIS SHOULD INCLUDE:

- A: Intravenous fluids, dexamethasone, dextrose
- B: Intravenous fluids, fludrocortisone, insulin
- C: Subcutaneous fluids, prednisone, sodium bicarbonate
- D: Blood transfusion, dexamethasone, potassium chloride
- E: Calcium gluconate, dextrose, DOCP

ANSWERS: 1: C, 2: B, 3: B, 4: D, 5: A