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Endocrine problems in the critically ill 2: endocrine emergencies

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Key points

- Most endocrine emergencies are triggered by a secondary insult, which should be sought and managed appropriately.
- Clinical features may be non-specific, mimicking other disease processes. Maintain a high index of suspicion.
- Derangement of thyroid/adrenal function is common in the critically ill; correction of these derangements in the absence of underlying adrenal or thyroid disease is not required.
- Confirmation of diagnosis should not delay treatment in suspected acute adrenal insufficiency.
- Vitamin D deficiency is associated with increased all-cause mortality, yet there is no current evidence to support its routine replacement in critical illness.

Endocrine emergencies account for approximately 1.3% of UK critical care admissions. Although relatively uncommon, many of these emergencies are potentially life-threatening. Most endocrine crises are triggered by a secondary insult, commonly infection, and clinical features are often vague and potentially attributable to other causes, such as the precipitating illness. Consequently, the underlying endocrine disorder may easily be overlooked. This article will outline the presentation, investigation, and acute management of adult endocrine emergencies. Diabetic emergencies and glycaemic control in critical illness are discussed in the accompanying article, 'Endocrine problems in the critically ill 1: diabetes and glycaemic control'.[1]

The adrenal gland

Phaeochromocytoma and paraganglioma are described elsewhere.[2]

Adrenal insufficiency

Adrenal insufficiency (AI) may be primary, secondary, or relative. In developed countries, up to 90% of primary disease is autoimmune in origin.[3] Secondary causes include infection, adrenal gland haemorrhage or infiltration, and drugs inhibiting steroidogenesis (e.g. ketoconazole, fluconazole, and etomidate).[3]

Primary disease is rare (incidence 4 per million), while secondary hypoadrenalism occurs in around 150–280 per million.[3] The commonest cause of the latter is exogenous glucocorticoid administration, the effects of which may persist for up to a year after discontinuing steroid treatment. Patients taking >5 mg day^{-1} prednisolone (or equivalent) for $\geq$4 weeks are at risk.

Relative AI represents an inadequate cortisol response to stress and is described elsewhere.[4]

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Acute AI

AI often remains unidentified until an acute crisis develops, typically triggered by additional physiological stress (e.g. infection or surgery), following abrupt discontinuation of steroid treatment, or secondary to medications that increase cortisol clearance such as CYP3A4 enzyme inducers (e.g. carbamazepine, St John's Wort) or thyroxine.[3]

Clinical features

Clinical features include refractory hypotension, vomiting, diarrhoea, and anorexia. Skin hyperpigmentation may occur in patients with primary hypoadrenalism, secondary to raised serum adrenocorticotrophic hormone (ACTH).[3] Hypotension is pronounced with primary disease, where both mineralocorticoid and glucocorticoid secretion is reduced. Hyponatraemia, hyperkalaemia, hypoglycaemia, and acidosis are common.

Investigations and management

Recognition needs a high index of suspicion and biochemical diagnosis should not delay treatment. Administering glucocorticoids to treat a suspected crisis will not cause harm. Initial management involves immediate hydrocortisone 100 mg parenterally. This is continued as 200 mg day^{-1} hydrocortisone administered via either continuous infusion or 6 hourly i.v./i.m. injection, based on specialist endocrinology advice.[3]

Cautious fluid resuscitation (typically 2–3 litre isotonic crystalloid) is usually required.[3] Undiagnosed, unstable patients will often have received substantial fluid resuscitation prior to critical care referral, and until appropriate steroid replacement is instituted they will remain refractory to fluid and vasopressors. Such patients should be admitted to critical care where their haemodynamic status can be more intensively managed.

Mineralocorticoid deficiency, as seen in primary disease, does not usually require supplementation initially, as crystalloids provide adequate sodium and volume replacement, and high-dose hydrocortisone has sufficient mineralocorticoid activity. Identification and management of any precipitating illnesses is also crucial.

A random serum cortisol taken at presentation is extremely useful as >500 nmol l^{-1} excludes AI, whereas any lesser value in the acutely unwell patient is inappropriately low and cortisol <100 nmol l^{-1} confirms AI. The short Synacthen test is helpful in patients (once stabilized) with intermediate levels: cortisol ≥ 500 nmol l^{-1} (before or 30 min post-administration of 250 μg tetracosactrin) is considered appropriate.[3]

High-dose hydrocortisone is continued throughout the acute crisis and then tapered to an oral maintenance regimen, with fludrocortisone added in cases of primary disease.

The thyroid gland

Non-thyroidal illness syndrome

During critical illness, disruption to the hypothalamic–pituitary–thyroid axis occurs in the form of non-thyroidal illness syndrome (NTIS). This describes the combination of low triiodothyronine (T_3) with low/normal thyroid-stimulating hormone (TSH) levels; plasma thyroxine (T_4) may also be reduced in more severe illness.[5] The degree of dysfunction seen correlates with underlying disease severity. Arem and Deppe[6] studied 49 critical care patients and found that low-admission T_4 levels, particularly in combination with raised serum cortisol, were predictive of mortality.

The mechanisms underlying NTIS are poorly understood, and there is currently no evidence to support thyroid hormone replacement in critically ill patients. Similarly, routine thyroid function testing should not be performed without a clear clinical indication.

Distinguishing NTIS from primary thyroid disease can be difficult in critical care—TSH is the most useful investigation with normal levels excluding primary disease.[5] Patients with known hypothyroidism should continue their usual thyroxine replacement. For those not absorbing enterally, i.v. T_3 should be administered: 10 μg is equivalent to 50 μg enteral levothyroxine.

Thyroid storm

Thyroid storm is rare, but mortality rates can approach 75% with death predominantly resulting from cardiac complications.[7,8]

Clinical features

Patients typically report chronic, evolving thyrotoxic symptoms (commonly secondary to Graves' disease), with a secondary insult driving the progression to thyroid storm.[7] Infection precedes most cases and other triggers include trauma, surgery, pregnancy, myocardial infarction (MI), gastrointestinal bleeding, and diabetic ketoacidosis. Clinical features reflect a hypermetabolic state, including pyrexia (often $>38.5\,^{\circ}C$), tachycardia, gastrointestinal disturbance, altered consciousness, and arrhythmias. Among the elderly patients, non-specific findings such as cardiac failure and reduced consciousness may predominate, in a so-called 'apathetic thyroid storm'.[7]

Investigations and management

Free T_4 and T_3 levels will be elevated, and TSH suppressed via negative feedback. Blood results cannot discriminate thyrotoxicosis from thyroid storm, as this is a clinical diagnosis. Hypercalcaemia, hyperglycaemia, and elevated hepatic transaminases may be seen. Women of childbearing age should be screened for pregnancy.

Treatment aims are:

- management of any precipitating illness,
- inhibition of thyroid hormone synthesis and release,
- to reduce conversion of T_4 to T_3,
- to inhibit the peripheral effects of thyroid hormone, and
- supportive critical care.

Propylthiouracil inhibits hormone synthesis and prevents T_4 to T_3 conversion and so is usually the first-line therapy. It can be administered enterally or per rectum, with a 600 mg loading dose, followed by 200–250 mg 4–6 hourly. Inhibition of thyroid hormone synthesis can alternatively be achieved with carbimazole (20–30 mg enterally t.d.s.) or i.v. methimazole (20 mg 4–6 hourly) where enteral intake is impossible.[7]

Corticosteroids (hydrocortisone 100 mg 6 hourly i.v. or equivalent) are routinely given, as they also inhibit peripheral conversion of T_4.[7] Other agents include Lugol's iodine, which inhibits the release of stored hormone and cholestyramine, to bind thyroid hormone within the gut and reduce enterohepatic recirculation.[7]

Beta-blockers are recommended to minimize peripheral clinical effects, e.g. propranolol 80–120 mg enterally 6 hourly, or i.v. equivalent, is appropriate. Where beta-blockade is contraindicated enteral or i.v. diltiazem can be used.[7] In thyroid storm, cardiac failure is often secondary to a persistent high output state. Therefore, although beta-blockers should always be administered cautiously, the observed reduction in heart rate may confer

clinical improvement in this group. Cardiac output monitoring can be useful to aid drug titration, especially where i.v. preparations are being given.

Supportive measures include cautious fluid resuscitation and thermoregulation. The latter can be achieved by external cooling devices alongside pharmacological agents such as paracetamol and chlorpromazine.[7] Salicylates should be avoided as they may displace thyroid hormone from thyroid-binding globulin.

In refractory disease, more drastic interventions include peritoneal dialysis, plasma exchange, or thyroidectomy. The latter can be lifesaving and is ideally timed around 10 days after presentation, once circulating thyroid hormone levels have fallen. Plasma exchange has been used both in thyroid storm and to optimize thyrotoxic patients before surgery, although the evidence for this is limited. It can only remove the free fraction of hormone, so must be repeated on several occasions and used alongside pharmacological therapies. Specialist advice should always be sought.

Thyrotoxic periodic paralysis

This rare condition occurs only in thyrotoxic patients, classically Asian and Hispanic males. The biochemical hallmarks are elevated T_3/T_4 and hypokalaemia. Symptoms involve attacks of muscle weakness or paralysis that can last several days. Rarely, dyspnoea and bulbar symptoms develop, necessitating critical care support.

Therapy involves management of the thyrotoxicosis, as described, and correction of hypokalaemia to prevent arrhythmias. The hypokalaemia is secondary to rapid movement of extracellular potassium into the intracellular space and will correct naturally as the thyrotoxicosis is treated. Careful monitoring during therapy is therefore required to prevent overshoot hyperkalaemia.[9]

Myxoedema coma

Myxoedema coma is a rare, potentially life-threatening manifestation of decompensated hypothyroidism and has a 20–60% mortality.[10]

Clinical features

The condition classically affects females over 60 years.[11] Primary hypothyroidism is usually the underlying cause although 5–25% of patients have secondary disease.[10] Numerous precipitating factors have been identified, including infection, MI, cardiac failure, stroke, and several drugs (e.g. lithium, amiodarone, sedatives, and anaesthetic agents). Discontinuation of thyroid medication may also be a trigger.[10]

Myxoedema coma is characterized by altered consciousness plus manifestations of severe hypothyroidism—hypothermia, dry skin, hair loss, sluggish tendon reflexes, oedema, and macroglossia. The term 'coma' can be misleading, as the patient may present with milder manifestations of impaired consciousness. Respiratory failure is common because of an attenuated response to hypoxia and hypercarbia.[10] This can be augmented by associated infection, pleural effusions, and the effects of obesity on respiratory mechanics.

Investigations and management

Serum TSH will typically be significantly elevated and free T_4 markedly reduced. Other abnormalities include hyponatraemia, elevated creatinine phosphokinase, elevated lactate dehydrogenase, hypoglycaemia, and anaemia.[10] An acquired von Willebrand's disease may occur, possibly due to reduced factor synthesis secondary to thyroid insufficiency.[10]

Electrocardiograph abnormalities are common, ranging from sinus bradycardia and left ventricular hypertrophy, to bundle branch block and, rarely, torsade de pointes.[10,11] Chest radiography may demonstrate features of cardiac failure or infection.

Key treatment goals are:

- thyroid hormone replacement,
- management of precipitating factors, and
- supportive care.

Numerous thyroid replacement regimens are described, using either T_4, T_3, or both. No clear consensus exists as to which regimen is best, so expert help is likely to be required. A typical 'high-dose' thyroxine regimen involves a bolus of levothyroxine 300–500 μg p.o./n.g., followed by 50–100 μg daily.[10] I.V. T_3 is advocated by some because of its more rapid onset and because of a concern that conversion of T_4 to T_3 may be impaired in myxoedema. However, this preparation is not readily available and can cause cardiac effects with rapid administration, potentially increasing mortality.[10] However, T_3 replacement may be necessary if the enteral route is unavailable.

Supportive care may include mechanical ventilation and correction of fluid and electrolyte disturbances, particularly hyponatraemia. Rapid warming may precipitate circulatory collapse, so the use of passive warming systems, such as space blankets, is advocated. Most patients have a degree of adrenal impairment, thus early institution of regular hydrocortisone is recommended.[10]

The pituitary gland

A detailed discussion regarding the management of patients undergoing pituitary surgery is beyond the scope of this article. However, two potentially life-threatening manifestations of pituitary disease are worthy of discussion—pituitary apoplexy and diabetes insipidus (DI).

Pituitary apoplexy

Pituitary apoplexy usually results from haemorrhage or infarction into an existing pituitary adenoma, although cases in non-adenomatous lesions and normal pituitary glands have been reported. It occurs in 0.6–10% of cases of surgically treated adenoma.

Clinical features

Pituitary apoplexy typically occurs in the fifth to sixth decades of life with 25% of patients having a prior history of endocrine dysfunction.[12] Multiple triggers exist, the commonest being hypertension. Others include major surgery (particularly involving cardiac bypass), anticoagulants, trauma, dynamic pituitary function testing, and various drugs (e.g. oestrogens, bromocriptine, and aspirin).[13]

Diagnosis can be problematic, as the clinical features can mimic subarachnoid haemorrhage (SAH), meningitis, or cavernous sinus thrombosis. Headache is seen in up to 80% of cases and is classically acute, retro-orbital, and severe.[13] The presence of visual field defects, reduced visual acuity, and oculomotor nerve palsies help differentiate it from other causes. Symptoms usually develop over hours or days, though occasionally an insidious onset is seen.

Investigations and management

Anterior pituitary hormone dysfunction is present in approximately 80% at diagnosis,[13] so blood samples should be obtained for serum cortisol, prolactin, follicle-stimulating hormone, luteinizing hormone, oestradiol/testosterone, free T_4, insulin-like growth factor, and ACTH. These investigations should ideally precede hydrocortisone administration or any other hormone replacement therapy.[13] Magnetic resonance imaging identifies over 90% of cases. Computerized tomography (CT) is diagnostic in 21–28%, although a pituitary mass is visible in over 80%.[13] Any patient presenting with features of SAH, in whom a pituitary fossa mass is suggested on CT, should be treated as possible pituitary apoplexy.

Immediate management is supportive: cardiovascular collapse secondary to ACTH deficiency is classically the feature warranting most urgent attention. Hydrocortisone replacement should be commenced empirically if the patient is haemodynamically unstable, has altered consciousness, or visual abnormalities.[12] In the absence of these, a 9 a.m. cortisol level can be taken, and steroid replacement commenced if levels are $<500\,nmol\,l^{-1}$, per the regimen for acute adrenal insufficiency.[13] Note that initial serum cortisol values may be preserved at the onset of apoplexy, so have a low threshold for treatment with hydrocortisone if any haemodynamic compromise develops.

Other pituitary hormone deficiencies will often be found, and replacement should be commenced based on expert advice. It is important to initiate glucocorticoid replacement before T_4 in hypothyroid patients; failure to do so can worsen cardiovascular collapse.

Following stabilization, early neurosurgical opinion should be sought for consideration of surgical decompression and tumour resection.

Diabetes insipidus

DI is a syndrome characterized by the production of large volumes of dilute urine. Diagnosis and management can be challenging and requires specialist input. When encountering patients with known DI in the clinical setting, it is essential that any desmopressin treatment is not stopped and early endocrinology involvement sought.

Three forms of DI exist (Table 1), and accurate identification is important for effective management.[14,15] Note that DI requires distinction from primary polydipsia where excess fluid consumption results in polyuria, but without physiological abnormality: hypotonic serum with low/low-normal sodium is typically seen.

Clinical features

Dehydration and hypernatraemia are common if the patient cannot access water or if there is an abnormality of thirst. Ideally diagnosis should be made when the patient has a normal oral intake and is not taking medication that can interfere with the results. A urine volume of $>3\,l\,day^{-1}$, and urine osmolality $<300\,mOsm\,kg^{-1}$ alongside a serum osmolality $>300\,mOsm\,kg^{-1}$ and the absence of glycosuria (to exclude diabetes mellitus) is usually diagnostic. However, diagnosis can be difficult in sedated critical care patients receiving i.v. fluids.[14,15]

Investigations and management

Effective management depends on accurate determination of the type of DI. In general terms, pituitary and nephrogenic DI can be distinguished by the urine osmolarity response to 1 μg i.v. desmopressin (DDAVP). However, a mixed picture is possible, and more complex investigations, such as water deprivation testing, may be indicated.

Patients who are hyperosmolar and cannot replace their urine losses with enteral water will require 5% dextrose i.v. as this is hypo-osmolar to the patient's serum. To avoid hyperglycaemia, volume overload and rapid correction of hypernatraemia, fluid replacement should not exceed 500–750 ml h^{-1} and requires careful monitoring. Table 1 summarizes the aetiology and management of the specific types of DI. In all cases, the

Table 1 Aetiology and treatment options for DI[15]

Aetiology of DI	Aetiology	Treatment
Pituitary DI: *Inadequate production and secretion of antidiuretic hormone (ADH)*	• Trauma • Neoplasm—primary/metastatic • Infection (e.g. meningitis, encephalitis) • Inflammation (e.g. systemic lupus erythromatosis) • Vascular (e.g. Sheehan's syndrome, hypoxic encephalopathy) • Toxin (e.g. snake venom) • Genetic	• Desmopressin 1 μg s.c./i.v. 1–2 times daily (also available as intranasal, oral or sublingual preparations)
Nephrogenic DI: *Renal insensitivity to ADH*	• Drugs (e.g. lithium, demeclocycline, vaptans, aminoglycosides, amphotericin B, rifampicin) • Metabolic (e.g. hypokalaemia, hypercalcaemia) • Vascular (e.g. sickle cell disease, acute tubular necrosis) • Obstructive uropathy • Amyloidosis • Polycystic kidney disease • Bartter syndrome • Granulomatous disease (e.g. sarcoidosis) • Genetic	• Combined therapy with chlorothiazide and amiloride (standard doses) • Indomethacin • High-dose desmopressin
Gestational DI: *Degradation of ADH by* vasopressinase (produced in placenta, third trimester)	• Placental vasopressinase	• Desmopressin

underlying aetiology should be sought and managed appropriately.[14,15]

The parathyroid gland

Acute hypercalcaemia

Hypercalcaemia occurs in up to 32% of critical care patients. The causes are numerous (Table 2), although 90% are because of primary hyperparathyroidism or malignancy.[16]

Clinical features

Features are non-specific, usually appearing once serum calcium exceeds 3 mmol l^{-1}.[16] Fatigue, muscle weakness, thirst, polyuria, vomiting, bone pain, abdominal pain, constipation, and nephrolithiasis may occur. Neurological features develop as the hypercalcaemia worsens, and anxiety or depression can progress to hallucinations and coma. Serum calcium >3.5 mmol l^{-1} is associated with cardiac arrhythmias, and urgent correction is warranted in these cases, including critical care admission if required for close monitoring.[16]

Investigations and management

Serum parathyroid hormone (PTH) will be elevated in primary and tertiary hyperparathyroidism, while low/normal levels in hypercalcaemia suggest malignancy or a rarer cause.[16] PTH samples should be obtained prior to bisphosphonate treatment, as the falling calcium will trigger a rise in PTH and lead to misinterpretation. Further investigations to investigate underlying causes (e.g. myeloma screen) should also be undertaken as appropriate.

Initial management involves fluid replacement as dehydration can be profound. Typically, 4–6 litre of crystalloid will be required for 24 h. Saline 0.9% is preferred, as saliuresis encourages urinary calcium excretion.[16] Following rehydration, i.v. bisphosphonate treatment will usually restore calcium levels to the normal range for 2–4 days, and maintain normocalcaemia for several weeks—levels require close monitoring. The Society for Endocrinology recommends 4 mg zolendronic acid i.v., given for 15 min (slower if renal impairment).[16] Some patients fail to respond to bisphosphonate. Expert opinion regarding further treatments (e.g. denosumab or glucocorticoids) should be sought. Haemodialysis or urgent parathyroidectomy are occasionally required in refractory cases, where the patient remains severely hypercalcaemic.[16]

Table 2 Causes of hypercalcaemia[16]

Parathyroid hormone related	• Primary hyperparathyroidism: Sporadic, familial or associated with multiple endocrine neoplasia (MEN) • Tertiary hyperparathyroidism: Associated with chronic renal failure and vitamin D deficiency
Malignancy	• Solid tumours secreting parathyroid hormone-related protein (PTHrP), such as squamous cell lung cancer, renal cell carcinoma • Osteolysis: myeloma, bony metastases (e.g. breast)
Vitamin D related	• Toxicity • Granulomatous disease (extra-renal calcitriol production): TB, sarcoidosis, berylliosis • Lymphoma
Endocrine disorders	• Adrenal insufficiency • Thyrotoxicosis • Acromegaly • Phaeochromocytoma (thought to produce PTHrP)
Drugs	• Thiazide diuretics • Lithium • Calcium salts (milk–alkali syndrome) • Vitamin A toxicity • Total parenteral nutrition
Genetic	• Familial hypocalciuric hypercalcaemia
Other	• Prolonged immobilization • Rhabdomyolysis

Vitamin D in critical illness

Vitamin D deficiency is common, but rarely recognized. It affects around 40–60% of adults in Europe and is associated with increased all-cause mortality, cardiovascular disease, and cancer.[17] Contributing factors for deficiency include inadequate dietary intake, lack of sun exposure, dark skin pigmentation, chronic renal disease, and advancing age.[17]

In addition to its role in bone metabolism and calcium homeostasis, vitamin D is thought to have other important actions including immune modulation, regulation of cell proliferation, and angiogenesis.[17] 1,25-Hydroxyvitamin D, the active metabolite, enhances the production of cathelicidins, peptides with a key role in the innate immune response to Gram-negative and Gram-positive bacteria, and some viral and fungal infections.[18] Furthermore, vitamin D may down-regulate the action of certain pro-inflammatory cytokines while also up-regulating the action of several anti-inflammatory cytokines.

Several trials have investigated the effects of vitamin D supplementation in critical care.[18–20] To date, these have been small studies reviewing different methods of replacement to achieve adequate serum concentrations and identifying potential adverse effects (e.g. hypercalcaemia and hypercalciuria). They have not established whether active management of deficiency influences outcomes. Enteral and parenteral feeds used within critical care all contain vitamin D, thus some supplementation will be inevitable in this setting. Whether additional supplementation and monitoring of levels should be undertaken remains to be seen.

Conclusion

Endocrine emergencies are a relatively uncommon finding in critical care patients, but many carry a significant mortality. Patients often display non-specific features that may mimic other diseases. Some may present in extremis, with no prior history of endocrine disease. Timely, specific, and supportive management is essential and a high index of suspicion should always be maintained.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at http://www.oxforde-learning.com/journals/ by subscribers to *BJA Education*.

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