

**REVIEW ARTICLE****CLINICAL APPROACH TO ADRENAL INSUFFICIENCY****Atiase Y<sup>1,2</sup>, Ampong C<sup>3</sup>, Donkor-Baah C<sup>2</sup>, Yorke E<sup>1,2</sup>, Akpalu J<sup>1,2</sup>**<sup>1</sup>Department of Medicine and Therapeutics University of Ghana Medical School;<sup>2</sup>Department of Medicine and Therapeutics, Korle bu Teaching hospital;<sup>3</sup>Pentecost Hospital.**Summary**

Adrenal insufficiency refers to inadequate production of glucocorticoids, mineralocorticoids, or both by the adrenal glands. This may result from dysfunction or complete destruction of the adrenal cortex (primary adrenal insufficiency), inadequate adrenocorticotropic hormone production by the pituitary (secondary adrenal insufficiency), or inadequate corticotropin-releasing hormone production by the hypothalamus (tertiary adrenal insufficiency). Diagnosis of adrenal insufficiency requires a high index of suspicion because of its nonspecific signs and symptoms. It is associated with a high morbidity and low quality of life even in

patients on treatment. When it presents as adrenal crisis it has a high mortality. Glucocorticoid replacement is the mainstay of management, and this may be combined with mineralocorticoids in the case of primary adrenal insufficiency.

Health care personnel must be reminded of this condition, to improve rates of early diagnosis and improve outcomes in management. In this review, we also look at the management of adrenal insufficiency in special populations and the potential role of newer long-acting steroids in the management of adrenal insufficiency is briefly discussed.

**Introduction**

Adrenal insufficiency, a disorder characterized by a reduction in adrenal hormone synthesis appears to be increasing in incidence in many parts of the world; in Europe there has been an increase from 117/million in Italy in the nineties<sup>1</sup> to 144/million in 2007 in Norway<sup>2</sup> to 221/million in 2016 in Iceland<sup>3</sup>. There are few studies done on the disease in Africans<sup>4</sup> and when reported the prevalence is low at 3/million in South Africa<sup>5</sup>. It has been suggested that the diagnosis of Addison's disease is relatively more difficult in black Africans as hyperpigmentation a predominant sign is more difficult to identify in the black skin in addition to confounding illness like HIV and Tuberculosis being more prevalent with similar presentation<sup>6</sup>. In Ghana, there is a paucity of data on adrenal insufficiency; in a study on the spectrum of endocrine disorders in central Ghana, adrenal disorders were among the lowest in prevalence with Cushing Syndrome, hyperaldosteronism, adrenal carcinoma and pheochromocytoma reported but no case of adrenal insufficiency being recorded over a 5-year period in the second largest hospital in Ghana<sup>7</sup>. Adrenal Insufficiency may be misdiagnosed or undiagnosed and often may present late in adrenal crisis which is associated with higher mortality<sup>8</sup>.

**Anatomy and Physiology of the Adrenal Gland**

The adrenal glands also known as the suprarenal glands, are paired structures located superior to the

kidneys, weighing about 4-5grams each. The gland is divided into an outer cortex and an inner medulla covered by a thin membrane known as the capsule. The cortex is derived from mesodermal tissue near the gonads on the adrenogenital ridge<sup>9</sup>, secreting steroids as early as the 6th week of life. The adrenal medulla on the other hand is derived from the neural crest, which is of ectodermal origin<sup>9</sup>.

The adrenal gland gets its blood supply from the inferior phrenic artery, the aorta and the renal arteries. Venous drainage of the right adrenal gland is into the inferior vena cava, whereas the left gland drains into the left renal vein. The cortex constitutes 90% of the gland and is made up of 3 zones: the outermost zona glomerulosa, the middle zona fasciculata and the innermost the zona reticularis. Glucocorticoid (cortisol 10-20mg /day) is produced from the zona fasciculata and the adrenal androgens from the zona reticularis; these two hormones together are under the control of Adrenocorticotropic Hormone (ACTH) from the pituitary gland. Mineralocorticoid, is produced in the zona glomerulosa under the influence of the Renin Aldosterone Angiotensin System (RAAS). The inner medulla however is responsible for the production of the "flight or fight hormone" adrenaline and noradrenaline. Adrenocortical insufficiency refers to the deficiency of adrenal hormones i.e. glucocorticoids, mineralocorticoids and sex hormones. It may occur when both adrenal glands are destroyed with resultant deficiency of all adrenal hormones; this is known as primary adrenal insufficiency. Secondary adrenal insufficiency occurs when there is a deficiency of adrenocorticotropic hormone (ACTH) resulting in deficiency of cortisol and adrenal androgens with

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sparing of mineralocorticoids. This is because mineralocorticoids are not under the influence of ACTH but rather the renin-aldosterone-angiotensin System (RAAS). This accounts for the differences in presentation and management of primary adrenal insufficiency and secondary adrenal insufficiency.

**Causes Of Adrenal Insufficiency**

The causes of adrenal Insufficiency are many and are summarized in table 1. In developed countries, autoimmune causes account for approximately 85% of cases.

**Clinical Presentation of Adrenal Insufficiency**

Adrenal insufficiency has been described as the great mimicker, with nonspecific symptoms such as anorexia, abdominal pain, weakness, fatigue, lethargy, fever, nausea and vomiting. The clinical presentation of adrenal insufficiency will depend on the extent and rate of loss of adrenal function; whether it is associated with mineralocorticoid deficiency or otherwise<sup>14</sup>.

**Adrenal Crisis or Acute Adrenocortical Insufficiency**

Patients will usually present as an emergency often in shock and sometimes with other nonspecific symptoms

**Table 1: Causes of Adrenal Insufficiency**

Primary Dysfunction of the Adrenal gland disease	Secondary Dysfunction of the Pituitary gland	Tertiary Dysfunction of the hypothalamus
<ul style="list-style-type: none"> <li>• Autoimmune-commonest cause in developed countries (70%) which can occur in isolation or as part of:                             <ul style="list-style-type: none"> <li>○ Autoimmune Polyglandular deficiency</li> </ul> </li> <li>• Infiltration- Amyloid, sarcoid, histiocytosis, lymphoma hemochromatosis</li> <li>• Infection- tuberculosis, fungal, HIV-AIDS, Cytomegalovirus infection</li> <li>• Vascular hemorrhage- anticoagulants, Friedrichson-Waterhouse Syndrome, thrombocytopenia, anticoagulant treatment</li> <li>• Infarction- antiphospholipid syndrome</li> <li>• Malignancy – primary/secondary or lymphoma</li> <li>• Adrenoleucodystrophy</li> <li>• Congenital adrenal hyperplasia</li> <li>• Congenital adrenal hypoplasia</li> <li>• Iatrogenic- bilateral adrenalectomy, Drugs e.g., ketoconazole, phenytoin, rifampicin</li> </ul>	<p><b>Lesions of pituitary gland</b></p> <ul style="list-style-type: none"> <li>• Tumours- pituitary tumours, metastasis, craniopharyngioma</li> <li>• Infection- tuberculosis</li> <li>• Inflammation- sarcoid, histiocytosis X, haemochromatosis</li> <li>• Iatrogenic- surgery, radiotherapy of head and neck</li> <li>• Other – isolated ACTH deficiency,</li> <li>• Trauma</li> </ul> <p><b>Suppression of hypothalamo-pituitary- adrenal axis</b></p> <ul style="list-style-type: none"> <li>• Glucocorticoid administration commonest cause of adrenal insufficiency (5) Cushing’s disease (after pituitary tumour removal)</li> </ul>	<p><b>Lesions of hypothalamus</b></p> <ul style="list-style-type: none"> <li>• Infection- tuberculosis</li> <li>• Inflammation- sarcoid, histiocytosis X, haemochromatosis</li> <li>• Iatrogenic- surgery, radiotherapy of head and neck</li> <li>• Withdrawal of chronic suppressive glucocorticoid therapy</li> <li>• Hypothalamic tumours</li> <li>• Metastases to the hypothalamus</li> <li>• Cranial irradiation</li> <li>• Infiltrative diseases affecting the hypothalamus</li> <li>• Infections (e.g. tuberculosis)</li> <li>• Trauma</li> </ul>

In developing countries, Tuberculosis (TB), cases<sup>10</sup>, disseminated fungal infection and Human Immunodeficiency Virus (HIV) remain significant causes<sup>11,12</sup>. Autoimmune adrenalitis (Addison’s disease) is the most common cause of primary adrenal insufficiency and is associated with increased levels of 21-hydroxylase antibodies. It may occur in isolation or as part of an autoimmune polyglandular syndrome. Withdrawal of glucocorticoids after long-term administration is the most common cause of central (secondary/tertiary) adrenal insufficiency.

described. It is important to note that both primary and secondary adrenal insufficiency can present acutely in crisis<sup>15</sup>. This acute presentation may occur or be precipitated by 1. Acute destruction of the adrenal glands e.g. bilateral adrenal hemorrhage or infarction 2. Patients with chronic primary adrenal insufficiency, with an acute illness or stress precipitating the crisis, 3. Sudden withdrawal of glucocorticoids in patients on long term glucocorticoid therapy for a chronic condition, 4. Inadequate treatment (e.g., underdosing, malabsorption) in patients known to have adrenal insufficiency.

### **Chronic Adrenal Insufficiency**

The presentation of chronic adrenal insufficiency is less dramatic, it is insidious and often with non-specific symptoms like anorexia, weight loss, fatigue, weakness, abdominal pain, nausea, vomiting, joint and/ muscle pain. Psychiatric disorders like depression, mania and psychosis have all been reported<sup>16,17</sup>. Additionally, women may present with decreased axillary and pubic hair associated with low libido as females derive androgens responsible for axillary hair and libido mainly from adrenal androgens. In addition to these non-specific signs, skin hyperpigmentation of the buccal mucosa, gums, palmar creases, nail beds, scars (forming after the onset of adrenal insufficiency), sun exposed and friction exposed areas present in chronic PAH due to increased levels of proopiomelanocortin (POMC) a prohormone that cleaves into biologically active ACTH and melanocyte stimulating Hormone (MSH)<sup>18,19</sup>. High levels of MSH results in increased melanin synthesis, which results in hyperpigmentation. Additionally, postural hypotension and salt craving due to mineralocorticoid deficiency occurs. Laboratory investigations may show hyponatremia, hyperkalemia, elevated urea, anaemia (normocytic, normochromic), elevated ESR, eosinophilia, mild hypercalcaemia and hypoglycaemia.

### **Diagnosis of Adrenal Insufficiency**

Adrenal insufficiency can be diagnosed if it can be shown that the functional capacity of the adrenal cortex to synthesize cortisol is impaired. Screening is by serum cortisol levels; random morning cortisol concentrations lower than 80 nmol/L (3 µg/dL) are strongly predictive of adrenal insufficiency<sup>20</sup> however, ACTH stimulation test must always be done to confirm the diagnosis although tests should never delay treatment with lifesaving steroids in patients suspected to have adrenal crisis. In individuals on chronic glucocorticoid therapy, in order to avoid detecting exogenous cortisol in the test assay, it is important to withhold hydrocortisone and prednisolone for 12 hours and 24 hours respectively<sup>21</sup> before the test.

Confirmation is done using the adrenocorticotrophin stimulating hormone (ACTH) stimulating test also known as cosyntropin or Synacthen test<sup>22</sup>. It assesses cortisol levels at baseline, 30mins and 60mins after parenteral administration of 250micrograms of adrenocorticotrophic hormone. Although time 60mins seems to have a better response than time 30mins, there has not been well documented advantages of one time over the other and the exact cut-offs have been set at 500-550nmol/L(18-20 µg/dL) after stimulation with Synacthen depending on the assay being used<sup>23</sup>. If a corticotropin stimulation test is not available, a morning cortisol <140 nmol/L (5 µg/dL) in combination with an elevated ACTH as an initial test is suggestive of adrenal insufficiency until confirmatory testing with corticotropin stimulation is available<sup>30</sup>.

A plasma ACTH level must be done to differentiate primary from secondary adrenal insufficiency. Primary adrenal insufficiency will have high ACTH levels usually greater than 100 pg/mL (22 pmol/L)<sup>22</sup> in addition to high renin and low aldosterone. In secondary adrenal insufficiency, plasma ACTH will be low or inappropriately normal<sup>22</sup>. It must however be noted that sometimes, in early secondary adrenal insufficiency, when the adrenals are not yet atrophied from hypo stimulation, ACTH stimulation may yield a response from the adrenal and give the impression that the hypothalamic –pituitary-adrenal axis is normal.

### **Management Of Adrenal Insufficiency**

Whatever the cause of adrenal insufficiency, glucocorticoids must be replaced to preserve life.

#### **Glucocorticoid Replacement**

Patients with adrenal insufficiency may need glucocorticoid replacement for life<sup>24</sup> depending on the cause. However, the frequency, as well as total daily dose remain challenging due to the individual variability of daily cortisol levels, daily stress levels as well as daily activity of the patient. A known fact remains that irrespective of cause most patients on glucocorticoid replacement still show reduced Quality of life(QoL) irrespective of cause<sup>25</sup>. Mode of replacement is dependent on the clinical presentation i.e. whether acute, previously undiagnosed, previously diagnosed or chronic<sup>26</sup>.

#### **1. Acute**

In acute primary adrenal insufficiency (Adrenal crisis) regardless of the cause, cortisol must be replaced along with mineralocorticoid. Within the first 12-24hours, Intravenous saline (0.9%) and dextrose are necessary to correct hypotension and hypoglycemia respectively if they exist.

##### **a. Previously diagnosed**

In patients who are previously known to have adrenal insufficiency, Intravenous (IV) hydrocortisone 100mg bolus should be given, followed by IV 50mg 8 hourly until vital signs are stable, and patient tolerates oral medications when oral steroids are initiated in stress or maintenance doses as needed. Prednisolone can be used if hydrocortisone is unavailable or dexamethasone if hydrocortisone or prednisolone are unavailable but should be the last resort. Acutely, mineralocorticoid replacement may not be needed even in primary adrenal insufficiency, as sodium is given by saline infusion. Additionally, the high dose of hydrocortisone given in the acute setting has adequate mineralocorticoid activity (Table 2).

##### **a. Previously undiagnosed**

In patients who present with classic symptoms of adrenal insufficiency but in whom diagnosis is not confirmed biochemically, dexamethasone is preferred

(IV 4mg) until samples are taken for biochemical confirmation. Under no circumstance must glucocorticoid of any type be withheld awaiting confirmation in a patient suspected to have adrenal crisis. Dexamethasone is preferred because it does not interfere with cortisol assays<sup>27</sup>.

## 2. Chronic

In chronic adrenal insufficiency, short acting hydrocortisone (15-25mg) or cortisone (20-35mg)(see table 2) is recommended in 2 or 3 divided doses with decreasing doses as the day progresses<sup>28</sup> to mimic what

pressure and electrolyte measurements as well as plasma rennin activity (PRA). Plasma rennin activity is kept within the upper normal range for adequate control.

## Androgen Replacement

Dehydroepiandrosterone (DHEA) is not routinely replaced even in primary adrenal insufficiency. In men there is sufficient androgen supply from the testes. In women who get all their androgen from the adrenals however, androgen replacement may be required in primary adrenal insufficiency.

**Table 2: Glucocorticoid equivalencies**

Glucocorticoids	Equivalent dose (mg)	Glucocorticoid potency	HPA Suppression	Mineralo-corticoid potency	Plasma half-life (min)	Biologic half-life (h)
<b>Short-acting</b>						
Hydrocortisone	20.0	1.0	1.0	1.0	90	8-12
Cortisone	25.0	0.8		0.8	80-118	8-12
<b>Intermediate-acting</b>						
Prednisone	5.0	4.0	4.0	0.3	60	18-36
Prednisolone	5.0	5.0		0.3	115-200	18-36
Triamcinolone	4.0	5.0	4.0	0	30	18-36
Methylprednisolone	4.0	5.0	4.0	0	180	18-36
<b>Long acting</b>						
Dexamethasone	0.75	30	17	0	200	36-54
Betamethasone	0.6	25-40		0	300	36-54
<b>Mineralocorticoids</b>						
Fludrocortisone	2.0	10	12.0	250	200	18-36

happens physiologically i.e. higher doses of glucocorticoids are secreted in the morning and with progressive reduction as the day progresses. Prednisolone 3-5mg/day may also be used but dexamethasone with a long half-life (table 2) should not be encouraged, as the risk of Cushing's syndrome may be greater. Table 2 describes the glucocorticoid equivalences and their pharmacokinetics and dynamics; understanding this is important for appropriate steroid replacement therapy which will be discussed shortly.

## Mineralocorticoids Replacement

Mineralocorticoid replacement is indicated only in Primary Adrenal insufficiency. Fludrocortisone at an initiation dose of 50-100 micrograms daily is recommended without salt restriction<sup>26</sup>. Patients with mineralocorticoid deficiency experience weakness, hypotension, salt craving and electrolyte imbalance such as hyponatremia and hyperkalemia. Mineralocorticoid deficiency is confirmed with significantly decreased aldosterone level and a highly elevated plasma rennin activity. Monitoring of mineralocorticoid replacement is carried out using clinical parameters such as the patient's well-being, physical examination, blood

Particularly if after optimum replacement of glucocorticoids and mineralocorticoids the patients still complains of low energy levels accompanied by low libido or depression<sup>26,29</sup>. DHEA is given for 6 months and if there is no improvement it is stopped<sup>30</sup>.

## Monitoring

Monitoring is essential in patients being managed for adrenal insufficiency. Glucocorticoids can be monitored clinically using general well-being, weakness, body weight and Cushingoid features. Mineralocorticoids replacement is monitored using salt craving, oedema and blood pressure measurement where hypotension or hypertension may indicate inadequate or over replacement of mineralocorticoids respectively<sup>26</sup>. Additionally, electrolytes and rennin may be used to monitor with rennin levels expected to be in the normal upper range. Androgen levels are monitored with early morning DHEAS and the sample must be taken before the replacement dose is taken.

## Patient Education

As for most chronic disorders, education of the patient is important, the patient must understand the rational of

treatment and the risks of non-adherence and noncompliance. One important aspect of education that is essential is what to do in the event of sickness or stress known as the sick day rules. Sick day rules are important in managing patients with adrenal insufficiency because patients with adrenal insufficiency have no physiological increase in cortisol during stress, therefore, the patient must increase dose of glucocorticoid during acute illness, stress, prolonged physical exercise and during surgery<sup>31</sup> noting that steroid dose is dependent on the type of surgery<sup>32</sup> as shown in table 3.

**Table 3: Steroid cover for patients with adrenal insufficiency requiring surgery**

Preoperative preparation	Post operative preparation
IV/IM 100mg hydrocortisone just before induction of anaesthesia with IV infusion hydrocortisone 200mg in 24 hrs. Or IV/IM hydrocortisone 100mg every 6 hours till out of ITU , then double dose for 48hours+ then taper to regular dose  1. major surgery with long recovery time e.g. open heart surgery, major bowel surgery 2. major surgery with rapid recovery e.g. Caesarean section, joint replacement	Continuous IV infusion 200mg hydrocortisone or IM/IV 100mg hydrocortisone every 6 hours until able to eat Double oral dose for 48hours for major surgery then  a. Taper dose to regular dose in major e.g. open heart surgery, bowel surgery b. Return to normal dose in major surgery with rapid recovery.
Overnight admission, with IV fluids, Then IV/IM 50mg hydrocortisone during purgative stage. Then IV/IM 100mg hydrocortisone just before Invasive procedures requiring laxatives e.g. colonoscopy before the procedure	Double dose oral medication for 24 hours then return to normal 1. Minor surgery e.g. cataract 2. Invasive bowel procedures with or without laxatives e.g. endoscopy, colonoscopy 3. Dental procedures
IM/IV 100mg hydrocortisone just before anesthesia or commencement of procedure if anesthesia is not required e.g. in major dental surgery or gastroscopy	Normal dose unless hypo adrenal symptoms occur when an extra dose should be given in minor procedures e.g. skin biopsy, removal of skin moles, minor dental procedures like dental filling

**Note**

- a. IV bolus hydrocortisone should be given over 10 mins
- b. If there are post operative complications, return to normal may be delayed
- c. IVI is preferred to bolus
- d. If nil per os, IV Fluids must be given adequately
- e. Post procedure monitoring of clinical signs and electrolytes may be necessary.

**Steroid Alert**

Patients must also be given a steroid alert card/bracelet informing health care personnel of their condition and their regular dose of glucocorticoids<sup>31</sup>. It is therefore important that doctors look out for these alert cards/bracelets in any patient brought in an unconscious state.

**Dosing Regimen**

Irrespective of the type of steroid used, subjective health status is reduced when steroids are given to patients with adrenal insufficiency<sup>25,33</sup>. Higher doses of hydrocortisone (>30mg) have a more impaired QoL than those on a lower dose although a complaint of impaired QoL may lead to increment in dose with an obvious selection bias<sup>33</sup>.

Conventionally, hydrocortisone is given thrice daily<sup>30</sup>, hydrocortisone is short acting and although this frequent dosing attempts to give a full steroid cover; this regimen is far from physiological with gaps between doses where adrenal insufficiency may occur<sup>28</sup>. It may also be given twice usually given to non-compliant patients who find the thrice-daily regimen difficult to keep up. Surprisingly; thrice daily dosing was not superior to twice daily dosing<sup>34</sup> although periods of adrenal insufficiency may be longer<sup>35</sup>.

**Adrenal Insufficiency In Special Populations**

It has been suggested that in special populations, doses and timing of medications may need to be changed<sup>36</sup> as discussed below:

**Shift workers**

In shift workers, it is recommended that steroid replacement should be such that the larger doses are taken on waking up which may be in the night and the second dose 6-8 hours after that<sup>37</sup>.

**Hypertension**

Although patients with adrenal insufficiency can develop essential hypertension, it is important to make sure that the developing hypertension is not from fludrocortisone which may need to be reduced. Addition of antihypertensives as required is necessary using calcium antagonists and alpha blockers. Angiotensin Converting Enzyme Inhibitors and Angiotensin I Receptor Blockers may not be effective due to the disruption of rennin angiotensin aldosterone system.

**Thyroid dysfunction**

Patients with hyperthyroidism have high cortisol metabolism and may require higher doses of steroids until they are euthyroid. Patients with adrenal insufficiency may develop new onset hyperthyroidism which can precipitate an adrenal crisis. Adrenal insufficiency may coexist with hypothyroidism; in these patients, levothyroxine should not be started until cortisol has been replaced to prevent precipitation of an adrenal crisis.

### **Pregnancy**

Patients with adrenal insufficiency may have problems associated with pregnancy including reduced fertility, increased risk of miscarriage, preterm births, low birth weight infants and increased Caesarean section rates<sup>38,39</sup>. Adrenal insufficiency may actually present for the first time in pregnancy and mimic hyperemesis gravidarum<sup>40</sup>, as it may do with most of the symptoms of pregnancy like fatigue, nausea and vomiting. Low cortisol and high ACTH are the expected in Primary adrenal insufficiency in adrenal crisis however, in pregnancy, cortisol may be normal due to the contribution of placental fetal steroids<sup>41</sup>, rise in corticosteroid-binding globulin concentrations and increased cortisol half-life due to decreases in hepatic clearance of the bound hormone<sup>42, 41</sup>.

However, there may be lack of cortisol increase in response to ACTH stimulation<sup>43</sup> therefore, higher total cortisol cut-offs may be needed to confirm a diagnosis of adrenal insufficiency. The recommended diagnostic cut-offs are 700 nmol/L (25 µg/dL) for the first trimester, 800 nmol/L (29 µg/dL) for the second trimester, and 900 nmol/L (32 µg/dL) for the third trimester vrs 700 nmol/L [26 µg/dL] post-partum<sup>44</sup>. Most patients can safely go through pregnancy on their pre pregnancy dose of glucocorticoids although a few will require higher doses in the third trimester<sup>45</sup>. Hydrocortisone is preferred over prednisolone and dexamethasone is not recommended<sup>26</sup>.

During labour and delivery, the recommended dose of hydrocortisone is as for major surgery (see table 2) i.e. 100mg at the time of active labour (cervical dilation of 4cm or contraction every 5minutes or more for 1 hour or both) after which intravenous infusion of 200mg hydrocortisone is given over 24hours or 50 mg of intravenous hydrocortisone every 6 hours until delivery<sup>26</sup>.

Assessing mineralocorticoid sufficiency clinically in pregnancy will be challenging because oedema and postural hypotension often used may be present in normal pregnancies. Blood and urine potassium and sodium can be monitored, but rennin levels may not be useful as concentrations increase in pregnancy. Increased progesterone levels with anti-mineralocorticoid effects may sometimes necessitate adjustment of fludrocortisone doses<sup>46</sup>. In pregnancy, dose adjustments are needed often to compensate for the anti-mineralocorticoid activity of progesterone<sup>47</sup>.

### **Surgery**

Glucocorticoid replacement for surgical procedures is summarized in Table 3.

### **Delayed Preparations**

Currently, most patients with adrenal insufficiency are treated with immediate release hydrocortisone, which is given as multiple doses (2 or 3 doses) in a day because of its short half-life and also in a bid to mimic the normal circadian pattern. This strategy however fails to achieve

this goal<sup>4</sup> The normal circadian rhythm is crucial for infection control, stress management and normal metabolism<sup>48</sup>. Abdominal obesity, glucose intolerance, coronary artery disease and altered sleep patterns have been linked to high levels of cortisol in the evening<sup>26</sup> which may occur with the current cortisol replacement strategies.

Considering the inadequacies of multiple dosing with immediate release hydrocortisone, it must be mentioned that recent modified release once daily forms with an outer shell of rapid release and an inner core of slow release has been shown to mimic the circadian rhythm with improved quality of life and metabolic effects of adrenal insufficiency<sup>49</sup>. Indeed, in randomized controlled studies, the conventional multiple daily doses of hydrocortisone seemed to have more disadvantages, mainly by causing a pro inflammatory state associated with a weakened immune system. The more physiological once daily dosing reduced body weight, improved the immune system quality of life<sup>50</sup>, but that has been questioned suggesting that the multiple doses used higher, immune suppressive doses compared to the lower once daily dosing<sup>51</sup>.

The once daily modified-release prednisone originally licensed for rheumatoid arthritis has shown promise in patients with adrenal insufficiency ; it is taken at 10pm and commences effect around 3am mimicking the physiological early morning cortisol rise<sup>52</sup>. Importantly, delayed release glucocorticoids forms may improve adherence because of single dosing compared to multiple dosing<sup>53</sup> with possible improved cost implications<sup>54</sup>. It is unlikely that any preparation will completely mimic the physiological pattern especially, the increase in cortisol that occurs during stress, however the success of a pilot study with the use of hydrocortisone pumps, which were acceptable to patients, is most encouraging<sup>55</sup>.

These pumps which resulted in normalization of ACTH and near normal circadian variation gives hope for the future<sup>56</sup>. In the future, multiple daily dosing is likely to give way to single daily-dosing or pump therapy with better outcomes and better Quality of life; perhaps even increase dose during stress. Importantly, delayed forms may improve adherence because of single dosing<sup>53</sup> with possible improved cost implications<sup>54</sup>. However, more studies are needed before this becomes routine. In conclusion, a functional adrenal gland is essential for life, adrenal insufficiency can be life threatening and all physicians in all specialties must be able to identify, investigate, educate, and manage patients appropriately to preserve life.

### **Authors' Contributions**

**Atiase Y**- involved in conceptualizing, drafting and finalizing the manuscript; **Among C**- involved in drafting and finalizing manuscript; **Donkor-Baah C**-involved in drafting and finalizing the manuscript; **Yorke E**- involved in drafting and finalizing the

manuscript; **Akpalu J-** involved in drafting and finalizing the manuscript.

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