Diploma Thesis

Therapeutical and Educational Aspects of Adults Suffering from Primary Adrenal Insufficiency
a Systematic Review

submitted by

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Graz, am 20.11.2017 *Birgit Ratz eh*

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Zusammenfassung

Bei der primären Nebenniereninsuffizienz handelt es sich um eine seltene Erkrankung mit unzureichender Glukokortikoid- und Mineralokortikoidproduktion. Seit der Einführung der Glukokortikoidtherapie im Jahr 1949 wurde diese Erkrankung behandelbar. Allerdings sterben auch heute noch immer Patienten/Innen mit bereits diagnostizierter Nebenniereninsuffizienz an den Folgen einer adrenalen Krise, d.h. einer akuten Verschlechterung des Gesundheitszustandes aufgrund eines Glukokortikoidmangels. Diese akuten Episoden sind leider sehr häufig. Eine/r von 13 Patienten/Innen erlebt innerhalb eines Jahres eine adrenale Krise, wodurch die Morbidität und Mortalität gegenüber der Normalbevölkerung deutlich erhöht ist. Warum aber ist die Todesrate bei einer Krankheit so hoch, deren fatale Folgen durch rechtzeitige Medikation verhindert werden können?

In diesem systematischen Übersichtsartikel werden Therapien, Einflussfaktoren und Methoden zur Therapiesteuerung entsprechend dem heutigen Wissensstand zusammengefasst. Es wird auf die Notwendigkeit einer intensiven Patienten/Innenschulung eingegangen, wobei vor allem Techniken zur Vermeidung der adrenalen Krise vordergründig behandelt werden. Der tatsächliche Wissenstand der Patienten/Innen und dessen Umsetzbarkeit unter physischem Stress werden anhand von Studien genauer erörtert. Diese Studien zeigen die Notwendigkeit von strukturierten Schulungsansätzen, wobei insbesondere auf Aspekte eingegangen wird, auf die bei solchen Schulungen geachtet werden muss. Weiters enthält der Artikel eine Übersicht von verfügbarem Informationsmaterial aus dem Internet, inklusive Schulungsvideos.

Zusammenfassend kann man sagen, dass es sich bei der Nebenniereninsuffizienz um eine behandelbare Krankheit handelt, die aber aufgrund der Unterlassung von Notfallmaßnahmen bedauerlicherweise relativ häufig zum Tod führt. Daher ist es an der Zeit, dass strukturierte Patienten/Innenschulungen eingesetzt werden, um den Patienten/Innen und dessen Angehörigen in einen wiederkehrenden Zyklus, der aus Lehren, Wissensevaluation und Rückmeldung besteht, zu bekommen. Dieser Zyklus scheint nach heutigem Wissensstand die erfolgversprechendste Methodik zu sein, um korrekte Reaktionen bei Patienten/Innen unter physischem Stress hervorzurufen.

Abstract

Primary adrenal insufficiency is a rare, but chronic disease which is characterized by a deficient production of glucocorticoids and mineralocorticoids. Since the discovery of glucocorticoid therapy in 1949, this disease was expected to be manageable. Nevertheless, patients under glucocorticoid therapy are still dying from adrenal crisis, an acute deterioration of the patient's health due to a shortage in glucocorticoids. Unfortunately, these acute episodes are frequent, since one out of 13 patients will experience a crisis within the next twelve months. Thus, morbidity and mortality are unreasonably high. But why is there such a high death-toll in a disease whose fatality can be avoided by appropriate and timely medication?

This systematic review provides insight in the state-of-the-art in treating adrenal insufficiency, i.e. patient medication, influencing factors, recommendations/suggestions for monitoring and adaptation of medication, and proper patient education. Particular emphasis is placed on compulsory knowledge and skills to prevent adrenal crisis, or at least its fatality. Subsequently, statistics are provided from various studies investigating the actual patients' knowledge, and its application under physical stress. These studies highlight the requirement for structured education strategies. Consequently, details are provided about recommended educational aspects which are completed by an overview of online information which include excellently intelligible educational videos.

In summary, primary adrenal insufficiency seems to be a manageable but under-managed event leading to preventable deaths. Sophisticated education strategies have to be implemented to keep the patient and her/his family in a constant teaching-evaluation-feedback cycle to guarantee for adequate patients' actions under physical stress.

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Abbreviations

ACTH	adrenocorticotropic hormone
AI	adrenal insufficiency
AR	Arabic
BP	blood pressure
CAH	congenital adrenal hyperplasia
CBG	cortisol binding globulin
CNS	central nervous system
CRH	corticotropin-releasing hormone
CYP11A1	cytochrome P_{450} 11A1
CYP3A4	cytochrome P_{450} 3A4
DA	Danish
DE	German
DHEA	dehydroepiandrosterone
DHEAS	dehydroepiandrosterone sulfate
EN	English
FR	French
HCP	health care provider
HPA axis	hypothalamic-pituitary-adrenal axis
HRQoL	health-related quality of life
ICD-9	International Classification of Diseases, ninth revision
ICD-10	International Classification of Diseases, tenth revision
IgA	immunoglobulin A
im	intramuscular
iv	intravenous
NADF	National Adrenal Diseases Foundation
NL	Dutch
PDF	Portable Document Format
PPT	Powerpoint
py	patient years
sBP	systolic blood pressure
TNFα	tumor necrosis factor α

TSH	thyroid-stimulating hormone
TR	Turkish

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1 Introduction

1.1 Physiology and pathophysiology of hormones focusing on the hypothalamic-pituitary-adrenal axis

Hormones are messenger substances that transport information signals relevant for the cell function. Endocrine hormones are produced in endocrine glands such as the hypothalamus, thyroid, the ovary and testes or the adrenal medulla and cortex for example. These endocrine hormones are transported in the blood to their target tissues whereas paracrine hormones affect nearby cells only. Peptide hormones and glycoprotein hormones are hydrophilic hormones. They are stored in secretory granules and released by exocytosis when they are required, whereas steroid hormones and calcitriol are lipophilic; they are not stored in endocrine glands, but are synthesized on demand. Steroid hormones are metabolized from cholesterol. When lipophilic hormones are transported in the blood, they are bound to plasma proteins. The corticosteroids for example are bound to corticosteroid binding globulin and albumin. There are different kinds of hormone receptors, those for glycoprotein hormones, peptide hormones and the catecholamines are transmembrane proteins. The transmembrane proteins bind to their specific receptors on the outer cell surface before intracellular second messengers are released which transmit the hormone signal inside the cell. The secretion of hormones is regulated by neural impulses from the central nervous system (CNS). “The hypothalamus is the main neurohormonal control center.” (1) The pituitary hormone secretion is triggered by the hypothalamus. The hypothalamic hormones can stimulate or inhibit the hormone production and secretion in the anterior pituitary. Because of this, they are called releasing hormones (RH, liberins) or release-inhibiting hormones (IH, statins). The hormones secreted from the pituitary stimulate or inhibit the hormone production in glands in the periphery (1).

The two major peripheral components of the stress system are the hypothalamic-hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system. In response to stress, corticotropin-releasing hormone (CRH) and vasopressin are responsible for activating the hypothalamic-pituitary axis. These hormones are the principal regulators of the adrenocorticotropic hormone (ACTH) secretion in the pituitary (2). CRH and ACTH regulate the synthesis and secretion of cortisol. The ACTH

secretion itself is stimulated by CRH and epinephrine and inhibited by cortisol because of a negative feedback circle. “The mineralocorticosteroids aldosterone, corticosterone and 11-desoxycorticosterone are synthesized in the glomerular zone whereas the glucocortiocsteroids cortisol and cortisone are synthesized in the zona fasciculata of the adrenal cortex.” (1) Additionally, the adrenal cortex produces the androgen dehydroepiandrosterone (DHEA) which is a precursor of various sex hormones.

There is a circadian rhythm in the CRH, ACTH and cortisol secretion which has its peak in the morning. Glucocorticoids have numerous effects such as the increase of myocardial contractility and vasoconstriction due to the enhancement of catecholamine effects. These effects are called permissive effects of cortisol. Glucocorticoids also have anti-inflammatory and anti-allergic effects because they stabilize lymphokine synthesis and histamine release. Their renal function is to delay the excretion of water and to maintain a normal glomerular filtration rate (1).

Patients suffering from primary or secondary adrenal insufficiency lack the ability to produce the adrenal hormones, especially cortisol which is produced in the adrenal cortex under the influence of ACTH from the anterior pituitary. In healthy subjects, the production of cortisol by adrenal glands is increased by disease, fever, medication or stress. In patients with insufficient adrenal function, this increase has to be substituted by oral treatment with glucocorticoids (3).

2 Primary adrenal insufficiency

The adrenal cortex secretes the essential steroid hormones cortisol and aldosterone under the control of the pituitary adrenocorticotropic hormone (ACTH) (4). “Primary adrenal insufficiency is defined by the inability of the adrenal cortex to produce sufficient amounts of glucocorticoids and/or mineralocorticoids.” (5) The reason why it is a severe and potentially life-threatening illness is that the affected hormones play a central role in energy, salt and fluid homeostasis. Primary adrenal insufficiency was first described by Thomas Addisson and is therefore called Addisson´s disease as well (5).

Until 1949, all patients with primary adrenal insufficiency died, since no artificial synthesis of glucocorticoids was possible, which are essential for the patient’s survival. There are three different forms of adrenal insufficiencies. The primary adrenal insufficiency has to be distinguished from the secondary form affecting the pituitary and the tertiary form affecting the hypothalamus. The secondary adrenal insufficiency is a result of an illness of the pituitary with reduced ACTH production or, in extremely rare cases, an insufficient reaction of the adrenal glands on ACTH because of ACTH resistance. The tertiary adrenal insufficiency is caused by an insufficient synthesis of CRH and/or ADH by the hypothalamus. As a consequence, ACTH secretion is deficient. While in the central forms (secondary and tertiary), there is only a deficiency in glucocorticoids, in the primary form the production of glucocorticoids, mineralocorticoids such as aldosterone, and androgens is affected (6). In primary adrenal insufficiency, secretion of both cortisol and aldosterone is lost, whereas in the secondary form the aldosterone secretion is not affected because aldosterone secretion is mainly regulated by the renin angiotensin aldosterone system (4).

2.1 Etiology

Compared to the secondary and tertiary form, primary adrenal insufficiency is rare, with a prevalence of 1 in 8000 people (7). Recent publications show that the primary form has an increasing prevalence especially in woman (8). In both the primary and secondary form lower quality of life and higher mortality was reported (9). According to the etiology, there is a difference between developed countries and developing countries. In developed nations, an autoimmune attack directed against the adrenal steroidogenic

enzymes (predominantly 21-hydroxylase) accounts for about 85% of cases (10). In such a case, a destruction of all three parts of the adrenal cortex can be found. Resulting from the destruction of the zonae glomerulosa, fasciculata and reticularis, there is a lack of mineralocorticoids, glucocorticoids and the precursor of androgens and estrogens, the DHEA (11). About 60% of patients with autoimmune Addisson's disease have additional autoimmune illnesses such as thyroid disease or type 1 diabetes (4). In developing countries the infectious adrenalitis occurring with a tuberculosis infection is still the main cause for the primary adrenalin insufficiency (11). Other causes in developing countries are disseminated fungal infections and HIV (4).

Another very common cause of adrenal insufficiency is an exogenous steroid use. Thus, the patient´s medication history is important to consider. The measurement of ACTH distinguishes between primary and secondary adrenal failure (12). Autoimmune Addison disease shows high plasma ACTH levels. In this case, the serum adrenal or steroid 21-hydroxylase antibodies should be measured. If these are negative, a computer tomography scan can show tuberculosis, haemorrhage or malignant disorders for differential diagnosis. In the case of low or normal ACTH, a pituitary magnetic resonance scan and the measurement of anterior pituitary hormones is recommended (4). Secondary and tertiary adrenal insufficiency are often caused by adenoma or traumatic injury (13). Autoimmune adrenalitis can occur isolated (40%) or as part of a polyglandular autoimmune syndrome in 60%. The polyglandular autoimmune syndrome type 2 is the most frequent one; in this case, the primary adrenal insufficiency is associated with autoimmune thyreoiditis, type 1 diabetes, vitiligo, primary gonadal insufficiency or chronical atroph gastritis. The main manifestation of this disease is between 35 and 40 years (11).

2.2 Symptoms

The clinical presentation of Addison's disease is very unspecific and as a consequence, diagnosis is often delayed. There are often wrong diagnoses like anorexia nervosa or other causes for the weight loss like cancer or gastro abdominal problems (11). As the symptoms of adrenal insufficiency are unspecific, a high level of clinical suspicion is required for correct diagnosis (4). "Common features of adrenal insufficiency are weight

loss, anorexia, nausea, vomiting, lethargy and fatigue." (4) Other symptoms are dehydration, hypotension with orthostatic dysregulation, articular and muscle pain and hypoglycaemia. A very specific sign is hyperpigmentation, not only on sun-exposed parts of the skin but also on the inner sides of the hands, on the mammilla and the mucosa. Hyperpigmentation can only be found in 50-55% of patients. The cause of this hyperpigmentation is enhanced secretion of ACTH and pro-opiomelanocortin peptides (5).

The lack of mineralocorticoids can manifest in salt craving (14). Because of the androgen deficiency, loss of libido, dry skin and the loss of secondary hair-growth can be found in women (11). In blood tests, hyponatraemia, hyperkalaemia and changes in blood count (anemia, eosinophilia and lymphocytosis) as well as hypoglycaemia are indicators for adrenal insufficiency.

2.3 Diagnosis

"Doctors are poor at recognizing adrenal insufficiency, with two thirds of patients presenting to medical professionals three or more times with symptoms of adrenal failure before the correct diagnosis is made" (4). Cortisol secretion has a circadian rhythm and as a consequence, the timing of sampling affects the result. It is also a "stress hormone" which makes the cortisol secretion also dependent on the health state of the patient (4). "Generally a random serum cortisol of over 400 nmol/l at any time of the day makes adrenal insufficiency highly unlikely, while a morning serum cortisol of less than 100 nmol/l strongly suggests adrenal failure." (4) The patient's current or prior steroid usage, pregnancy or oral estrogen therapy can result in deceivingly high cortisol concentrations and so these aspects always have to be considered when interpreting the results (11). Bornstein *et al.* (5) recommend a short corticotropin test (250µg) as the "gold standard" diagnostic tool to establish the diagnosis. If this test is not possible in the first instance, an initial measurement of morning plasma ACTH and cortisol level should be undertaken. In order to find the cause, there should also be a validated assay of autoantibodies against 21-hydroxylase. In autoantibody negative individuals other causes should be excluded (5).

In case of suspected adrenal crisis, treatment shall be prioritized, and diagnosis is secondary (please refer to chapter "Therapeutic intervention") (15).

3 Results

This diploma thesis aims to systematically review the therapeutical and educational aspects of primary adrenal insufficiency. This thesis is based on a systematic review in PubMed/Medline performed until November 10th 2017 using the search terms “adrenal insufficiency” and “education” in combination. Reference list of retrieved articles and personal reference lists were used to expand the literature. Even though medication is quite standardized nowadays, this disease can easily develop into life-threatening adrenal crisis, even in treated patients (16;17). This hazardous event occurs typically in the absence of trained endocrinologists and other health professionals are usually not so familiar with the required emergency actions due to the rare nature of this disease (18). Accordingly, patients have to be trained to recognize onsets of adrenal crisis and to act correspondingly in emergency situations until they are subject to qualified medical care.

In order to provide profound insights in the challenges of treating adrenal insufficiencies appropriately and demonstrating the necessity of proper patient education, this review provides an overview about patient medication, influencing factors, and recommendations/suggestions for monitoring and adaptation of medication. Particular emphasis is placed on situations inducing adrenal crisis. Subsequently, the current educational status of patients is reviewed. Finally, this document provides an overview of currently recommended educational concepts and available educational material such as videos.

3.1 Therapeutical treatment

Patients suffering from primary adrenal insufficiency require substitution for the following three substance groups (11): (i) glucocorticoids; (ii) mineralocorticoids; (iii) dehydroepiandrosterone (DHEA) for women, because in contrast to men, women produce androgens predominantly in the adrenal glands (11). In the following subchapters, each substance group will be evaluated individually.

In 2016, two guidelines for the diagnosis and treatment of adrenal insufficiency were written and almost simultaneously published. These efforts demonstrate the need for a standardized treatment of this disease. The first guideline was developed as a combined effort of the European Society of Endocrinology and the American Association for Clinical

Chemistry (5), in the following referred to as European/American guideline. This guideline focuses on primary adrenal insufficiency which is the topic of this diploma thesis. The second clinical practice guideline was published by the Japan Endocrine Society (19), and includes secondary and tertiary adrenal insufficiency too. Both guidelines propose similar treatment and actions for emergency cases. The presented work in this chapter primarily relies on recommendations and suggestions from these guidelines. Interestingly, the European/American guideline used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system (20) to provide means for the significance of their statements. In this system, the individual statements are classified in strong recommendations, which are indicated by "we recommend", and weak recommendations indicated by "we suggest". Furthermore, the quality of the underlying evidence is ranked from "high quality", over "moderate quality" and "low quality", to "very low-quality". Surprisingly, up to now, still many of the given recommendations/suggestions rely on low quality or very low-quality evidence, or ungraded best practice statements (21), indicating the need for further studies in that area (5). A detailed description on the grading of each recommendation are beyond the scope of this thesis whose primary focus lies on the educational aspects, nonetheless, very low-quality suggestions are indicated.

3.1.1 Therapeutical treatment of the "normal case"

Glucocorticoid replacement is the most critical medication, because deteriorations in glucocorticoid supply may have immediate aggravating effects (22) and this substitution therapy has the highest impact on the quality of life (23). For glucocorticoid therapy, hydrocortisone, cortisone acetate, prednisolone, prednisone, or dexamethasone can be used. While hydrocortisone or cortisone acetate are the preferred replacements, dexamethasone shall be used only if no other alternatives are available, since it possesses a relatively high risk of inducing Cushingoid symptoms (24). Emphasis has to be placed on the glucocorticoid administration regimen to mimic the circadian rhythm of glucocorticoid release, which is highest in the morning, shows lower levels in the evening and reaches its lowest value after midnight (25).

For hydrocortisone and cortisone acetate, 15-25 mg/d (in Japan, 10-20 mg/d (19)) and 20-35 md/d are recommended, respectively (5). These oral replacement doses are

based on the finding of mean cortisol production rates of 5–8 mg/m^2/d depending on body composition and age (26;27). Due to the short plasma half-life of 90 min for hydrocortisone (28), a multiple dosing regimen is recommended for this drug. In the literature, two-dose, three-dose and four-dose administration regimens are proposed. What they have in common is that the highest dose should be given in the morning, preferably before breakfast (29). The twice-daily dose should be administered in a 2:1 ratio between the morning and early afternoon dose (30). Thrice-daily dose was independently proposed by two studies (31;32), whereupon the Japanese guidelines (19) suggest 3:2:1 ratio between the morning, afternoon and evening dose, respectively. According to two studies (33;34), the cortisol curves were more similar to the endogenous one, however, similar (30) or worse (35) health-related quality of life (HRQoL) scores were reported for the three compared to the two dose administration. Similarly, Ekman *et al.* (36) suggested to ingest hydrocortisone four times a day. In summary, there is too little evidence present to recommend a certain hydrocortisone administration regimen, but patients may preferably adhere to less frequent strategies (37). Recently, so-called modified-release hydrocortisones which mimic the circadian cortisol secretion cycle better are released on the market or under development. Plenadren® is a dual-release hydrocortisone which showed improved metabolic outcomes and improved quality of life scores (38;39). The drug Chronocort® is a hydrocortisone showing a delayed absorption (40).

Prednisolone is prescribed in a dose of 3-5 mg/d to patients that do not recover in terms of HRQoL (5). In contrast to hydrocortisone, prednisolone is a longer acting steroid (28). Correspondingly, prednisolone is administered only once or twice a day. While prednisolone seems to avert metabolic inconveniences (41), there are no studies available comparing the safety of hydrocortisone and prednisolone. In addition, the lower mineralocorticoid effects of prednisolone must be considered (14).

Patients suffering from primary adrenal insufficiency require replacement of mineralocorticoids in addition to glucocorticoid replacement. For this purpose, 9α-fludrocortisone is provided in a daily dose of 0.05-0.2 mg. Fludrocortisone is administered daily in the morning, since aldosterone's circadian rhythm is similar to the one of cortisol (42).

The European/American guideline (5) suggests DHEA replacement in women with low libido, depressive symptoms and/or abnormal fatigue, however, the suggestion is based on low quality evidence. DHEA replacement may be considered as a single dose of 25-50 mg. Effects of the replacement are observed typically after several months. Principally, DHEA replacement may have quite positive effects (43-45), but generally, these effects are most of the times moderate and individually different (46).

3.1.2 Interfering drugs and food, and comorbidities

For the determination of the correct dose for the replacement therapy, besides weight and age, concomitant drugs and food must be considered. Particular attention has to be paid to drugs affecting cytochrome P_{450} 3A4 (CYP3A4), the central enzyme for cortisol metabolism (11), and drugs affecting the effectiveness of the cortisol binding globulin (CBG). The following drugs and food have an increasing effect on hydrocortisone, and require as such a dose reduction: aprepitant, cimetidine, diltiazem, fluoxetine, itraconazole, ritonavir (other anti-retroviral drugs and serotonin reuptake inhibitors), and licorice and grapefruit (47). In contrast, the following drugs decrease the effect of hydrocortisone, and require as such an increased hydrocortisone dose: carbamazepine, ethosuximide, exanitad, mitotane, phenobarbital, phenytoin, pioglitazone, primidone, rifampizin, valporic acid, and to a small extend St John's wort. Drugs enhancing the effect of hydrocortisone typically show inhibiting effects on CYP3A4 activity (48-53). Drugs suppressing the effect of hydrocortisone induce drug-metabolizing enzymes (54;55), are anti-epileptic agents enhance the effect of CBG (56;57), or are growth hormones inducing inhibitory effects on 11β-hydroxy dehydrogenase type (58;59), which convert cortisone to cortisol. For mineralocorticoid replacement, phenytoin increases fludrocortisone metabolism, thus, requiring a higher administered dose (60).

Comorbidities are very prevalent in patients suffering from primary adrenal insufficiency. The two most frequent comorbidities are thyroid disease and type 1 diabetes, which develop in about 50% of the patients either individually or even in combination (61). Particular care has to be taken for the concomitant presence of hypothyroidism, which is more frequent in female than in male patients. In such a case, the glucocorticoid replacement has to be adjusted before initiating the thyroid treatment, since the thyroid hormone further enhances the metabolization of hydrocortisone.

Consequently, thyroid treatment will aggravate the patient's burden, and may even cause adrenal crisis in the worst case (62). Another potential trigger for adrenal crisis is concomitant diabetes insipidus (63), which is concealed before glucocorticoid replacement therapy (64). Further frequent complications are hyperlipidemia, arterial hypertension, anxiety, depression (65;66), retained follicular function (67), vitamin B12 deficiency caused by autoimmune gastritis (68), and celiac disease (69;70).

3.1.3 Pregnancy

Glucocorticoid and mineralocorticoid replacement have to be adjusted during pregnancy. Women suffering from primary adrenal insufficiency have a little lower chance to become pregnant and a slightly increased risk for spontaneous abortion and premature delivery (71;72). Nevertheless, most gravidities are reported without further complications.

Physiologically, the cortisol and blood ACTH levels rise continuously during normal pregnancy in healthy women (73;74). According to Suri *et al.* (75), basal cortisol levels at peak times in the morning are 9.3±2.2, 14.5±4.3, and 16.6±4.2 µg/dL, in the first-, second- and third trimester, respectively. These changes are primarily caused by the antagonistic effects of progesterone on glucocorticoid efficiency and alterations in the CBG level (73;76). Correspondingly, glucocorticoid dose has to be increased during pregnancy, particularly in order to prevent adrenal crisis (63). A replacement strategy of 12-15 mg/m^2 hydrocortisone is recommended based on clinical experience (77), but there is only little evidence for the exact dose. Particularly in the last trimester, the dose should be elevated by 5-10 mg each day in comparison to the normal dose (74). During pregnancy, hydrocortisone, cortisone acetate, prednisolone, or prednisone shall be used (78;79), and dexamethasone must be avoided since the fetal permeability is reported to be 100% (80), although a study showed that no abnormalities in the central nervous system arose in children exposed to high dexamethasone levels *in utero* (81). However, high doses of glucocorticoids increase the risk of oral clefts three to four times (82).

Furthermore, it has been reported that aldosterone levels rise during normal pregnancy as well (75), and elevated progesterone levels might negatively impact the mineralocorticoid effects due to anti-mineralocorticoid actions. Thus, adjustments of fludrocortisone dosage must be considered too (83), particularly in late gestation (84).

Pregnant women must be examined for signs of glucocorticoid over- and undersubstitution (see chapter “Management and monitoring”) at least once in each trimester (5). Furthermore, in the active phase of labor, the glucocorticoid dosage should be increased to the one of major surgical stress (see chapter “Dose adaptations in stress conditions”). At onset of active labor, 100 mg hydrocortisone shall be administered iv by a bolus injection. Subsequently, further 200 mg shall be continuously infused over a period of 24 hours (14;74). Post-delivery, glucocorticoid dosage shall be adjusted back to normal levels.

3.1.4 Management and monitoring

Therapeutical management of primary adrenal crisis is guided by two major aspects:

- Prevention of adrenal crisis
- The patient’s health-related quality of life (HRQoL)

The former aspect is reviewed in detail in the chapters “Dose adaptations in stress conditions” and “Adrenal crisis”. Of note, in the view of a potential onset of an adrenal crisis, emphasis has to be placed on the prevention of a critical shortage in glucocorticoids rather than the side-effects of a temporary over-dosage (5). For the latter aspect, there are several things that have to be considered with the ultimate goal to reduce the risk of premature death and restore normal life as much as possible, which is indicated by well-being, professional activity, normal sexual function and stable weight.

The most important issue is to ascertain that patients adhere to the treatment prescribed. Recently, a study reported on patients disrespecting the prescribed glucocorticoid dosage due to concerns regarding weight gain and osteoporosis (85). Such disrespect may have fatal consequences, e.g., premature mortality caused by cardiovascular, malignant and infectious diseases (86). Hence, patients have to be well-instructed about their disease and the potential consequences of their misbehavior. Owing to the indispensable necessity for patients’ cooperation, this important point was accentuated in a separate chapter (see chapter “Patient education”). Besides problems arising from educational aspects, patients suffering from primary adrenal insufficiency experience typically impairment of their quality of life (66;87). In addition to the comorbidities described in chapter “Interfering drugs and food, and comorbidities”, such

patients suffer from metabolic and affective disorders (65;66;88), which substantially reduce their subjective perception on their quality of life. Epidemiologically, these patients experience in comparison to the healthy population (9):

- Significantly reduced work capacity
- Doubled absence times
- Four times increased hospital admissions

A major reason for this impairment seems to be the unphysiological replacement of glucocorticoids (9). Therefore, and for the increased risk of cardiovascular disease, physicians must meticulously attempt to find the optimal dosage. One study reported on reduced physical function, heart symptoms and stomach symptoms in patients where the hydrocortisone dosage exceeded 30 mg/d (89). Another study reported that a twice daily dose of hydrocortisone is better suited in respect to quality of life than a thrice daily dose (30).

Glucocorticoid replacement therapy must be regularly monitored. According to guidelines (5), patients (adults and children) with primary adrenal insufficiency must be seen by professional with endocrine expertise at least annually, infants at least every three to four months. The assessment for optimal treatment, under- or over-dosage should be primarily based on clinical judgment. Primary complication for a persistent under-dosage is adrenal crisis. Clinical symptoms indicating under-dosage are (4;90):

- Anorexia
- Breathlessness
- Fatigue/lethargy
- Headache
- Hyperpigmentation
- Increase of pigmentation
- Nausea
- Retching or vomiting
- Weight loss

Persistent over-replacement of glucocorticoids may entail metabolic disorders, leading to cardiovascular complications, and subsequently, to a higher mortality rate (86;91). Clinical signals for overtreatment are (4;5):

- Double chin

- Glucose intolerance
- Hypertension
- Hyperglycaemia
- Moon face
- Insomnia
- Osteoporosis
- Peripheral edema
- Thin skin
- Weight gain

In view of the expected consequences, the requirement for an adequate glucocorticoid substitution therapy is apparent. In order to support the physician in optimizing the dosage, the following ten questions were suggested by Napier *et al.* (92) (questions were literally taken from (4)):

- "Are you clock-watching for one particular dose?"
- "Do you often miss a dose because you haven't noticed the time?"
- "How are your general energy levels/get up and go?"
- "Do you have low spots during the day?"
- "Are you napping during the day?"
- "What time is bedtime?"
- "Do you sleep okay?"
- "How do you feel first thing in the morning?"
- "Changes in weight?"
- "Changes in pigmentation?"

Additional questions should address daily habits, family relations, mental concentration, professional duties, self-esteem, working patterns and overt glucocorticoid excess (5). Furthermore, postural blood pressure monitoring should be taken in account for the clinical assessment. Compliance to the administration regimen and extra doses should be registered, as well as instances of adrenal crisis. In the case of supposed malabsorption, monitoring is indicated of salivary or serum cortisol day curves (5). In contrast to the clinical evaluation, the European/American guideline advises against the dosage adjustment based on hormonal monitoring of glucocorticoid replacement, since it usually leads to overdosing. Apart from the patients who require life-long glucocorticoid

replacement, for patients not requiring replacement any longer after a long period of time (e.g. patients with glucocorticoid treatment due to autoimmune diseases), the dose has to be tapered to prevent adrenal crisis. The reason is that glucocorticoid replacement suppresses the endogenous HPA axis irrespective of the administration type (nasal (93) and transbronchial (94) applications are affected too).

Mineralocorticoid monitoring has many parallels to glucocorticoid monitoring. Similarly, annual examination is recommended. Thus, appropriateness of both glucocorticoid and mineralocorticoid levels are evaluated typically simultaneously. Assessment is here primarily based on clinical judgment as well (5). Of note, higher dose of fludrocortisone has to be prescribed in cases where other glucocorticoids than hydrocortisone are used, since higher doses of hydrocortisone can serve as mineralocorticoid replacement (40 mg hydrocortisone are equivalent to 0.1 mg fludrocortisone (5)). Typical symptoms for insufficient mineralocorticoid substitution are fainting, orthostatic hypotension, nocturia, peripheral edema and salt craving (4;11). Patients shall be instructed to eat salt and sodium-rich food (such as seafood), and that they should ignore healthy eating recommendations to reduce salt intake (4). Additionally, blood electrolytes such as sodium and potassium are recommended for the adjustment, and should be measured on a regular basis (4). Furthermore, plasma renin levels or plasma renin activity, whose levels should be at the upper normal range or slightly elevated, are helpful measures for the adequacy of the fludrocortisone substitution (95;96). Indication for a dosage reduction of fludrocortisone is sustained hypertension. In such cases, not only the fludrocortisone dose but also the glucocorticoid dose might require adjustment. When hypertension persists after adjustment, angiotensin II receptor blockers or angiotensin converting enzyme blockers shall be prescribed (97). The usage of diuretics is not advised and aldosterone receptor blockers are contraindicated (5).

Additionally, it is suggested that the mandatory annual examination encompasses further diagnostics to detect the frequently occurring comorbidities. These checks should comprise thyroid disease, diabetes mellitus, premature ovarian failure, celiac disease and autoimmune gastritis causing vitamin B12 deficiency (5). Correspondingly, TSH, free T_4, and HbA1c shall be determined. For detection of premature ovarian insufficiency, testing for CYP11A1 autoantibodies may be performed (98). Furthermore, a complete blood

count is suggested. If there are symptoms for vitamin B12 deficiency, the following additional tests should be performed according to (5): determination of the holotranscobalamin, homocysteine, methylmalonic acid, and/or autoantibodies against parietal cells and intrinsic factor. For celiac disease, sporadic testing for transglutaminase 2 autoantibodies and total IgA is suggested (5).

DHEA substitution effects cannot be sufficiently evaluated before several months of treatment, thus, a revision of the DHEA dose is recommended after 6 months of treatment (5). Clinical assessment of DHEA treatment efficiency comprises of evaluation of symptoms induced by androgens, such as gain in lipid content in skin, acne, hirsutism, and alopecia (11). Laboratory tests include DHEA sulfate (DHEAS), androstenedione, and free androgen index (11), whereupon DHEAS levels should be monitored before daily intake of DHEA dose. A discontinuation of DHEA medication is suggested, when there are no sustained beneficial effects within the first six months of treatment. However, there are no studies present describing long-term effects of DHEA replacement.

3.1.5 Dose adaptations in stress conditions

In healthy individuals, 5-8 mg/m^2 (20-30 mg) cortisol are secreted daily (26), however, in stress situations, this value may increase to 300 mg each day (99). While mild stress situations increase cortisol production to values between two and three times of the normal conditions, severe stress situations require replacements where oral administration is not feasible any longer (19). Moreover, increased glucocorticoid consumption is considered to be necessary in stress situation to avoid overreaction of defense mechanisms, resulting in toxicity (100). Hence, the cortisol replacement strategy has to be adopted correspondingly (101), otherwise an adrenal crisis might be precipitated. Stress situations that have to be considered for patients suffering from primary adrenal insufficiency include:

- Infectious diseases
- Gastrointestinal disturbances
- Trauma, such as operations, accidents, or other injuries
- Psychological stress
- Prolonged and strenuous athletic activity

- Hot climate

This chapter reviews the recommended dose adaptations, which are immediately necessary in most of the presented cases to prevent adrenal crisis, which in turn might be lethal.

There are many events triggering stress and subsequently more glucocorticoids are consumed, where infections are among the most common ones (63). In the case of sickness, 2-3 times the usual hydrocortisone dose is recommended (19). The recommendations in literature are not completely consistent, e.g., a doubling of the dose is suggested in cases where the patient's temperature exceeds 37.5-38 °C (5;12). Temperatures exceeding 38.5-39 °C warrant already for thrice daily glucocorticoid dose (5). In both cases, this elevated glucocorticoid dose should be administered until recovery, typically 2-3 days, and appropriate hydration shall be ensured by electrolyte-containing fluids as tolerated.

Patients and their families have to be particular cautious in the case of gastrointestinal disturbances, since more than 60% of emergencies caused by adrenal crisis are due to this kind of disorder (22;63). As soon as patients develop diarrhea, a doubling of the dose is imperative (4). In the case of vomiting, the patient must take the doubled hydrocortisone dose immediately after vomiting took place (4). When the patient vomits repeatedly within 30 minutes after taking this dose, early parenteral hydrocortisone (iv, im, or sc) supply of 100 mg hydrocortisone is indicated (5), where subcutaneous self-injection seems to be favored by the patients (102) and sufficiently timely for emergencies (103). Nonetheless, even after successful injection, the patient must visit her/his physician. For gastroenteritis, anyway, the following algorithm for hydrocortisone replacement is recommended (11): 100 mg iv bolus injection; followed by 200 mg continuously over 24 hour infused or 50 mg every six hours, until the patient is able to receive medication orally.

Glucocorticoid replacement dose in surgery depends on the severity or degree of invasiveness, and need to be adjusted in cases of trauma, such as operations, accidents, or other injuries. However, glucocorticoid requirements are subject to interindividual variations (104;105). Nevertheless, the authors of the two guidelines have published dose recommendations depending on the severity of the surgery. While the European/American guideline propose the two categories "minor to moderate surgical

stress" and "major surgery with general anesthesia, trauma, delivery, or disease that requires intensive care", the Japanese guideline follows the suggestions of Hahner *et al.* (106) and distinguishes the former group in "minor surgery" and "mild to moderate surgery". For the "mild surgery", 30-50 mg hydrocortisone each day are recommended. For the "minor/mild surgical stress", both guidelines agree on 25-75 mg each day. For a "major surgery", the Japanese guideline proposes 150 mg/day, and the European/American one 200 mg/d. For the latter one, the same algorithm is proposed as for delivery and gastroenteritis, i.e., 100 mg hydrocortisone iv bolus injection; followed by 200 mg continuously infused over 24 hours or 50 mg every six hours. The high dosage for "major surgery" is not physiological anymore, but is recommended to cover unexpected complications. All of these proposed doses should be administered for a few days, and tapered afterwards. Furthermore, fluids shall be administered iv containing 5% dextrose and 0.2 or 0.45 NaCl. For very minor surgeries, such as visits at the dentist, twice the normal dose is recommended before the surgery and on the next day (11).

Furthermore, hydrocortisone doses should be increased 5-10 mg each day for prolonged and strenuous athletic activity, and psychological stress (11;63). As prolonged athletic activities are considered sports such as jogging for longer times or hiking tours taking several hours. As psychological stress reckon events such as stress at exams or bereavement.

There are hardly any stress conditions where mineralocorticoid dose has to be adjusted. The first reason for this is that high dose of glucocorticoids has mineralocorticoid replacement effects, as such a glucocorticoid dose over 50 mg/d covers the mineralocorticoid dose already (5). The second reason is that undersupply of mineralocorticoids exhibit their effects after several days, thus, there is normally no stress adaptation required. However, caution has to be taken when prednisolone or dexamethasone is applied for glucocorticoid replacement, since prednisolone exhibits lower and dexamethasone no mineralocorticoid activity (5). Hot climate is the primary situation where the dose of fludrocortisone shall be increased 50-100% and/or increased salt-intake is recommended (5). In such situations, patients must pay attention to salt craving or orthostatic hypotension, and adapt the dosage accordingly.

In summary, there are many situations in daily life of patients suffering from primary adrenal insufficiency which require immediate dose adjustments. These situations

typically take place in the absence of professionals with endocrine expertise. Thus, patients must be able to judge the severity of the situation and act accordingly. Therefore, appropriate education regarding the correct emergency actions is imperative for this disease (see chapter “Patient education”) to prevent the life-threatening event of an adrenal crisis (see chapter “Adrenal crisis”).

3.2 Adrenal crisis

Adrenal crisis or acute Addison’s disease is in fact a cortisol shortage as a result of an increased need (5;17). This life-threatening medical emergency causes preventable deaths, if it is not recognized in time and appropriate interventive steps are undertaken (15). Moreover, the frequency of these acute episodes is quite high, since one out of 13 patients will experience a crisis within the next twelve months (63). The primary clinical representation of an adrenal crisis is hypotension and volume depletion (5), however, the pathophysiology leading to this fatal event is not completely clear up to now.

The hypotension is caused by an impaired responsiveness of the adrenergic receptors to catecholamines in the absence of glucocorticoids (100;107), and volume depletion seems to be caused by a deficient sodium and fluid preservation in the absence of mineralocorticoids (12;108), but the fundamental mechanisms are only partially understood. Sapolsky *et al.* (100) classified the glucocorticoid influence on stress response in permissive, suppressive, stimulatory, and preparative actions, and the absence of the permissive actions of the glucocorticoids seems to cause the impaired responsiveness. Patients suffering from adrenal insufficiency are assumed to have a reduced permissive action, but the increased suppressive action is missing in an stressful event, which is induced by increased glucocorticoid secretion (17); and this suppressive action prohibits the overreaction of the immune system (109), which is be mediated by inflammation promoting cytokines (100), among them tumor necrosis factor α (TNFα). Koniaris and coworkers (110) showed that TNF receptor Ia and Ib knockout mice and mice treated with anti-TNF serum were even after adrenalectomy resistant to the lethal effects of lipopolysaccharides. Consequently, the lack of suppressive effects on TNFα seems to be a key factor in the development of adrenal crisis. According to Allolio (17), adrenal crisis

may be associated with increased TNFα release, enhanced TNFα sensitivity and TNFα-induced glucocorticoid resistance. This theory holds true for other diseases, since e.g. surgeries may increase TNFα secretion (111) and emotional stress may induce glucocorticoid resistance (112). Nevertheless, further studies on physiological factors for the development of adrenal crisis are apparently required (113).

3.2.1 Triggers for adrenal crisis

Adrenal crises can be attributed to precipitating events in more than 90% of the cases (22;63;114;115). Triggers for adrenal crisis and their preventive dose adaptations are summarized in the chapter "Dose adaptations in stress conditions". Among them, gastroenteritis is undoubtedly the predominant precipitator for an adrenal crisis. Due to vomiting and diarrhea, the appropriate absorption of orally administered glucocorticoids is not guaranteed any longer (15) – an often underestimated event causing preventable deaths (17;115). Thus, it is recommended to administer glucocorticoids parenteral anyway (11;17). This particular precipitator is followed by infectious diseases other than gastrointestinal illnesses (17;63;113;115). As described in the previous paragraph, the uncontrolled release of cytokines seems to be the trigger for the fatal consequences resulting in uncontrolled inflammation, disturbed cardiac function and shock (116;117). Less frequent triggers are physical stress/pain, such as surgery and injuries, and psychological stress (22;115) (an excellent overview of the frequency of precipitating factors for adrenal crisis can be seen in Table 3 of (15)). An often underestimated trigger for adrenal crisis is cessation of glucocorticoid replacement (17;19), therefore tapering is absolutely essential.

3.2.2 Definition

While many publications agree on the clinical symptoms of an adrenal crisis, there is no generally agreed definition (17). As such it is reported that even though the ICD-10 lists the diagnosis of an adrenal crisis, a detailed instruction of the symptoms that define an adrenal crisis is missing (113). As a consequence, the prevalence of this ICD-10 code is rather an individual interpretation of the respective practitioner. This situation seems to be due to the lack of a particular feature characteristic for this disease, and the

unspecificity of the other symptoms, which are present in various other diseases as well (see chapter “Symptoms”). Obviously, a detailed definition of a disease is the prerequisite to report correct values of prevalence and incidence, and to derive valid data regarding precipitating factors and risks for a disease. Consequently, there are several attempts to give a more accurate definition for adrenal crisis (5;15;17;113;115;118). Interestingly, most of them appeared in 2016 and 2017 reflecting the current scientific interest in this topic.

The simplest definition of Puar *et al.* described adrenal crisis as (15):

> “An acute deterioration in a patient with adrenal insufficiency”

They further specify the presence of hypotension or hypovolemic shock, and name other symptoms attributed to this disease. However, these symptoms may occur for other diseases too, making this definition fairly unspecific.

According to Smans *et al.*, an adrenal crisis is defined as follows (118):

> “An acute impairment of general health requiring hospital admission and administration of intravenous saline and glucocorticoids in patients with AI.”

In contrast to the former definition, here, the need for administration of glucocorticoids is mentioned.

A similar definition was proposed in the European/American guidelines for primary adrenal insufficiency (5):

> “Adrenal crisis is a medical emergency with hypotension, marked acute abdominal symptoms, and marked laboratory abnormalities, requiring immediate treatment.”

However, the addressed electrolyte abnormalities are now supposed to be present less often than previously assumed, thus, precluding correct instances of adrenal crisis (17).

For the purpose of a prospective study, Allolio and coworkers defined adrenal crisis based on the symptoms (115). This definition was further fine-tuned in a review by Allolio to (17):

"Definition (A): Major impairment of general health with at least two of the following signs/symptoms: hypotension (sBP< 100 mmHg), nausea/vomiting, severe fatigue, fever, somnolence, hyponatraemia (<132 mmol/l) or hyperkalaemia, hypoglycaemia. (B): Parenteral glucocorticoid (hydrocortisone) administration followed by clinical improvement"

In contrast to the definition of Bornstein *et al.*, they realized in the study that deteriorations in sodium and potassium levels contributed to the detection of adrenal crisis only to a very minor extend. Accordingly, they regarded electrolyte abnormalities not to be mandatory any longer. Moreover, they suggested retrospectively, that a positive effect has to be observed subsequent to glucocorticoid treatment to differentiate to other diseases exhibiting similar symptoms, e.g., intestinal perforation.

In a recent review, Rushworth and colleagues proposed an even more accurate definition to differentiate between true adrenal crises and milder forms, i.e. adrenal insufficiency, where even quite detailed instructions were provided (113):

"An acute deterioration in health that is associated with absolute (systolic BP < 100 mmHg) or relative (systolic BP < 20 mmHg lower than the patients usual BP) hypotension, the features of which resolve following parenteral glucocorticoid administration (demonstrated by a marked resolution of hypotension within 1 h and improvement of clinical symptoms over 2 h)"

Apart from the definition, the following additional details were given:

"Frequent concomitant features include acute abdominal symptoms, delirium/obtundation; hyponatraemia/hyperkalaemia/hypoglycaemia and pyrexia. Consideration of the effects of incidental illness as causes of the major features, in particular shock, improves the specificity of diagnosis"

In summary, there are several endeavors to find an appropriate definition for adrenal crisis. The major aim is to provide physicians means to minimize false positives (milder forms or milder forms of adrenal insufficiency considered as adrenal crises) and false

negatives (true adrenal crises considered to be another disease). Nonetheless, there exists currently no commonly accepted definition. Thus, currently available study data reporting findings (e.g. prevalence and incidence) regarding adrenal crisis must be attentively surveyed for potential biases.

3.2.3 Frequency of adrenal crisis

Incidence of adrenal crisis is quite high, and as such an important factor for the increased mortality and morbidity (115) accompanying adrenal insufficiency. The high variability in the reported figures can be certainly accredited to the non-existence of a universally accepted definition of whether a patient's symptoms constitute an adrenal crisis, or they are exclusive (see previous chapter). Nonetheless, the elevated mortality rate is evident (61;86;119), which is particularly regrettable since this fatality is deemed to be avertable by immediate diagnosis and subsequent appropriate emergency actions (15;17).

A patient suffering from adrenal insufficiency has a risk of about 50% to experience an adrenal crisis once in life (22), where patients who survived already are at higher risk for further episodes (22;115). The estimated incidence for patients suffering from adrenal insufficiency is quite high. The reported values range from 4-8.3 instances per 100 patient years (py) (22;63;115;118;120-122). For primary adrenal insufficiency, in these studies, the reported frequency of events is even more increased to a range of 5-9.3 incidences/100py. This higher risk in the primary form seems to be attributable to the absence of mineralocorticoids and the subsequent risk of hypovolemia (63;114;115).

In a Swedish study (86), the mortality risk of patients suffering from primary adrenal insufficiency was investigated. They reported no deaths based on adrenal crisis but a high mortality based on adrenal insufficiency. This might be due to the fact that many assignments were still based on ICD-9 code which does not allow differentiation between primary adrenal insufficiency and adrenal crisis. The study reported on a more than twofold increased in mortality rate in patients suffering from primary adrenal insufficiency. Similarly, a Norwegian study reported on a death rate of 15% for patients suffering from primary adrenal insufficiency, which constituted the most common cause of death followed by infection (10%) (61). Interestingly, this study sees a particularly higher chance of mortality for younger patients.

Up to now, the largest study was conducted by the UK Addision's disease Self Help Group comprising patients from four Commenwealth countries, i.e. Australia, Canada, New Zealand and UK (22). This study reported on 8.3 incidences/100py based on a postal survey completed by 841 patients. A retrospective study in Germany reported on 6.6 incidences of adrenal crises in 100py (63). The highest value (9.3 incidences/100py) was reported in patients after bilateral adrenalectomy for Cushing's syndrome (122). However, all of these study were conducted retrospectively, and thus inclined to biases (17). Currently, there is only one prospective study available (115). The obvious advantage of a prospective study is that evaluation is based on clear-cut criteria, and less susceptible to biases. 64 episodes of adrenal crisis were reported in 423 patients, resulting in 8.3 incidences/100py. Based on these data, one out of 12 or 13 patients will be subject to an adrenal crisis within the next twelve months (5). Ten patients died in this study, and four deaths were accounted to adrenal crisis. This is a particularly alarming result, since all of the participants were well instructed regarding dose adaptations and correct behavior in emergency situations.

Apart from precipitating factors described in chapter "Triggers for adrenal crisis", the risk for adrenal crisis is further increased by several other factors (17;120). Among them comorbidities are particularly prevalent. E.g., commencement of hypothyroidism therapy may trigger an adrenal crisis in patients with undetected adrenal insufficiency (5); diabetes mellitus, diabetes insipidus (secondary adrenal insufficiency), and hypogonadism may be additional risk factors (22;63;114;120), and preceding adrenal crisis events. For risks deriving from concomitant drugs please refer to chapter "Interfering drugs and food, and comorbidities". Furthermore, many risk factors are still unknown up to now (17). Hence, further research in that field will definitely help to improve the prevention strategy for adrenal crisis (113).

In summary it can be said that adrenal crisis is a frequent complication in patients suffering from adrenal insufficiency which may cause premature death even in well-educated patients.

3.2.4 Symptoms

First of all, it has to be mentioned that there exists no single characteristic symptom for the onset of an adrenal crisis (113). The clinical representation is typically hypovolemia

and volume depletion (5), which might be accompanied by many unspecific symptoms for glucocorticoid under-replacement as already listed in the chapter “Management and monitoring”. The definition by Rushworth *et al.* (113) gives excellent advice on the clinical appearance of adrenal crisis (see chapter “Definition”). According to the Japanese guidelines, the criteria for detection are as follows:

“II-1.0 Symptoms

(1) Various symptoms are observed, such as nausea, vomiting, abdominal pain, muscle pain, arthralgia, fatigue, high fever, low blood pressure or disturbance of consciousness. If the patient has more than a couple of these symptoms, he may be in adrenal crisis. Patients are sometimes misdiagnosed as having acute abdomen.

(2) As to physical examinations, signs suggesting the presence of chronic AI give high diagnostic values.

(3) The possibility of AI is suggested in patients who have received long-term continuous steroid treatment. Such patients may show Cushing phenomenon in their appearance.

II-2.0 Laboratory examinations

(1) Findings are almost the same but augmented compared with those observed in chronic AI.

(2) Patients in adrenal crisis are under strong physiological stress, and immediate diagnosis by occasional blood sampling should be the first priority.

(3) The following serum cortisol levels at occasional blood, <3–5 μg/dL suggest high possibility of adrenal crisis”

An important observation is that many symptoms resemble to the ones of an acute abdomen leading to erroneous diagnoses. Further potential symptoms are anorexia, diarrhea, pigmentation hyponatraemia, hyperkalaemia, hypoglycaemia, and seldom hypercalcaemia (15;17). They may have an aberrant cardiogram or even cardiomyopathy (123;124). Furthermore, they are frequently in hypotensive shock, and may have an impaired perception (15). Patients with undiagnosed adrenal insufficiency typically complain about the impression that their overall health decreased gradually over the last weeks, months or even years (17). Many have an extensive clinical track record

comprising endoscopy, imaging and might have diagnosed psychiatric illnesses (125;126), where the outbreak was triggered by a stress situation (17).

An important aspect of preventing the fatal effects of adrenal insufficiency is that it is diagnosed in time. While the median time elapsed between perceiving of first symptoms to an apparent emergency case is around one day (5), there are often cases where the crisis evolved in one hour (17). Based on the prospective study (115), Allolio reported in a later review (17) that median time was 135 min between first symptoms and contacting health professionals, however, the range encompassed values from 5 minutes to 7 days. Response times of 5 min are far beyond the reach of health care professionals. Thus, such situations can be handled by well-trained patients only.

3.2.5 Therapeutic intervention

The two major components in fighting adrenal crisis are (i) sufficient glucocorticoid replacement and, (ii) rapid rehydration. Vitally important is the consideration that glucocorticoid under-replacement might cause fatality, primarily since there seems to exist a “point of no return” where even ideal treatment will not be able to rescue the patient’s life (17). On the downside is that there are no dose-replacement studies (5), thus, recommendations are based purely on best-practice experiences (5). Particularly since short-term supraphysiological glucocorticoid levels do not seem to have tremendous side effects (105;127), and the dose must account for unexpected complications, the proposed dosage is residing rather at the upper limit (17). The generally agreed treatment strategy for adrenal crisis for adults is as follows (similar to the one for major surgery described in chapter “Dose adaptations in stress conditions”) (5;15;17;19;113):

- 100 mg hydrocortisone administered iv by a bolus injection; followed by 200 mg continuously infused iv for 24 hours or 50 mg boluses iv (or im) every six hours; the following days the dose shall be reduced to 100 mg/d; only in the case of unavailability of hydrocortisone, other glucocorticoids shall be used.
- 1000 mL of 0.9% NaCl or 5% glucose in isotonic solution within 60 min; followed by continuous infusion of isotonic NaCl solution depending on the patient’s need; fluid requirements shall be assessed based on central venous pressure,

haemodynamic monitoring to avoid fluid overload, and serum electrolytes; particular caution has to be taken for patients suffering from diabetes insipidus to prevent hyponatraemia.

- For hypoglycaemia, 0.5-1 g/kg dextrose or 2-4 mL/kg of D25W infused slowly in rates of 2-3 mL/min.
- Depending on the severity of the crises and concomitant illnesses, the patient must be taken to the intensive care unit, obtain low-dose heparin, and/or possibly antibiotic treatment (12).
- According to the European/American guidelines, cardiac monitoring is suggested, while the glucocorticoid dose is rapidly tapered, and the patient shall take glucocorticoids orally as soon as possible.
- There is no need for administering mineralocorticoids due to the mineralocorticoid effects of hydrocortisone, but in the tapering phase, mineralocorticoids must be administered for patients with primary adrenal insufficiency.
- When there are no clinical signs of improvement within 24 hours, other causes for these life-threatening circumstances have to be considered.

Of note, if there is adrenal crisis suspected, the treatment should start immediately without delay, particularly for patients with known adrenal insufficiency (15). For patients without preceding diagnosis, samples can be taken for testing ACTH, aldosterone, DHEAS, and renin, since these values may be useful for diagnosis, but must be avoided for unstable patients (128). In an unstable patient case, therapy shall be pursued until recovery, but ACTH testing should be performed as soon as possible to consider suppression of the HPA axis (15). However, full recovery might take from one day up to one week (17). Subsequent to recovery, the patient should be interviewed for precipitants, once more informed about preventive measures, and tested whether the patient is capable of administering glucocorticoids parenteral (113).

3.2.6 Prevention

The potentially fatal effects of adrenal crisis are deemed to be avertable by appropriate emergency actions (15;17). The prevention of this disease lies primarily in the hands of

the patient. Patients must autonomously adapt their medication in respect to stress conditions (see chapter “Dose adaptations in stress conditions”) (17). Permanent overdosing is no recipe to avert this disease, due to the cardiovascular and metabolic consequences, and interestingly, due to increased vulnerability to infectious disease, which may in turn precipitate adrenal crisis (129).

The most important measure for prevention seems to be the timely parenteral administration of glucocorticoids. In a prospective study it was shown that (115), although the patients were instructed to administer glucocorticoids parenteral in the presence of symptoms such as diarrhea or vomiting, the patients increased just their oral dose or did not change the dose at all in 42% of the cases of adrenal crisis where vomiting was involved. A potential cause for the reluctance of a parenteral replacement may be the necessity of iv or im injection. Thus, the subcutaneous injection is more frequently promoted due to its improved acceptance, despite its delayed but still timely effects (102). Furthermore, it is absolutely necessary to instruct the patient to apply the parenteral dose in cases where its necessity is uncertain (15). A further problem is that during illnesses patients are often unable to administer the drug themselves, hence, family members must be instructed too. Additionally, steroid cards and bracelets are highly recommended to inform practitioners about appropriate actions (130). Alarmingly, mortality due to adrenal crisis was even present in well-educated patients (102). However, it has been reported that some patients obviously did not obey the communicated instructions or had difficulties to act correspondingly. Positively, the reported incidence of adrenal crisis decreased in the well-educated group of patients in comparison to a preceding retrospective study (63).

From the current point of view, there is no replacement therapy possible to fully mimic the rapid responsiveness of an intact HPA axis (17). Lack of detailed knowledge about the molecular causes leading to fatality in adrenal crisis (113) precludes improved preventative approaches at the moment. As a result of the often short time intervals between onset of symptoms and outbreak of the crisis (that can only be 5 min), currently, only well-educated patients and family members can be the appropriate remedy to reduce the incidences and fatal effects of an adrenal crisis (11;17). Thus, quality controlled education approaches have to be implemented, promoted, and made available to patients (17) (see chapter “Patient education”).

3.3 Patient education

Primary adrenal insufficiency cannot be handled by physicians and medical persons alone. Critical situations typically occur in the absence of trained endocrinologists, and it should be considered that other health care providers are not so familiar with this disease due to its rare nature (18). It was reported that only two-thirds of adrenal crises occur at home, while one third was outside the home environment, e.g. overseas transit, house of acquainted person, hotel, work etc. (22). Consequently, patients suffering from adrenal insufficiency have to be prepared to adopt their dose appropriately and to perform measures preventing adrenal crisis (131). Therefore, thorough patient education is currently considered the most effective preventive strategy (63;108;121).

Patients shall be empowered to act appropriately in the various situations requiring dose adaptations (113), which is far from straightforward since they may have impaired perception and possibly benign symptoms of hypotensive shock (15). Moreover, through daily life, patients must strictly adhere to prescribed corticoid dose and administration regimens to maintain their well-being and avoid crisis precipitation. Such rigid medication requirements demand quite some self-discipline. In fact, patients have to manage their chronic illness from day to day and are in charge for their well-being (132), thus, the term self-management was introduced. For chronic diseases, self-management is widely accepted to be a compulsory part of the treatment (131). In order to cope with the demands of self-management, on the one hand, patients have to comprehend essential background knowledge to identify critical situations, and on the other hand, skills have to be learned to react and act appropriately, as has been shown for other chronic diseases (133).

3.3.1 Education and equipment

Patient education should emphasize on the early detection and treatment of adrenal crisis emergencies (15). For adrenal crisis prevention, the following steps are agreed upon in the community (5;14;17;113;134):

- Educate the patient to identify situations where dose adaptation is required and to act appropriately.
- Provide the patient with an emergency kit for parenteral hydrocortisone injection.

- Provide the patient with a steroid emergency card, and medical alert bracelet or necklace.

The patient actions are outlined in the so-called “sick day rules”, which are essentially nothing more than a concise summary of the dose adaptations reviewed in the chapter “Dose adaptations in stress conditions”. Due to the potential presence of impaired perception and possibly hypotension in patients in the benign state of an adrenal crisis (15), the patient herself/himself is often not able anymore to act appropriately. Thus, it is recommended that the patient and her/his family should participate in the educative actions (19;131). The sick day rules were summarized by the European/American guidelines as follows (5):

“Sick day rule 1: need to double the routine oral glucocorticoid dose when the patient experiences fever or illness requiring bed rest; when requiring antibiotics for an infection; or before a small outpatient procedure (eg, dental work)”

“Sick day rule 2: need to inject a glucocorticoid preparation im or iv in case of severe illness, trauma, persistent vomiting, when fasting for a procedure (colonoscopy!), or during surgical intervention. 100 mg hydrocortisone iv, im, or sc followed by 200 mg hydrocortisone per continuous iv infusion, alternatively repeated bolus doses (iv or im) every 6 h”

While these two rules contain the most essential points for crisis prevention, they seem to be too abridged to act appropriately in all situations. Thus, I want to raise attention to the more detailed description of required dose adaptations in the chapter “Dose adaptations in stress conditions”, which are supported by other publications as well (15;17;131;135). However, there is disagreement in literature at which temperature the dose has to be doubled and tripled. Some literature recommend doubling and tripling the dose at 37.5 °C and 38.5 °C, respectively, and others at 38 °C and 39 °C, respectively. Furthermore, the Japanese guidelines recommend the following points, whose communication to the patient is essential in my opinion (19):

“(1) Do not stop the oral intake of GC by your own judgment.

(2) During physical stress, for example, flu, fever, tooth extraction or strong exercise (such as a long walk), take 1.5–3.0 times the usual dose of Cortril®.

(3) Recognize that missed doses or insufficient steroid doses at a time of stress could cause adrenal crisis, which is characterized by remarkable general malaise, nausea, vomiting, fever, abdominal pain and symptoms such as low blood pressure. When the condition becomes more severe, consciousness disorder and hypovolemic shock can occur.

(4) Carry an emergency card including the disease name, treatment, a contact person and details of the doctor in charge of your care at all times."

The instructor should particularly take care that patients comprehend the rationale for dose adaptations, and situations necessitating dose adaptations shall be discussed. Additionally, the instructor should explain real life emergency cases so that patients can recognize signs and symptoms of adrenal crisis (5). An essential point is to teach the patient and her/his family the skills for parenteral glucocorticoid administration, which must be practiced in the education session (22;131). Furthermore, the patient must comprehend the necessity for a visiting hospital after an emergency injection (5). It is highly recommended that the conveyed knowledge is reinforced at least annually in patients without problems, and more frequently when specific problems are/were present or adrenal crisis occurred. The mandatory annual visits are an excellent opportunity for this purpose. For traveling, the patients must take their oral medication on the plane, and must have an emergency kit, a letter from the doctor (in English and local language), prescription for medication, and have information about local emergency facilities (15).

According to European/American guidelines, patients shall be equipped with (5): (i) sufficient quantities of hydrocortisone and fludrocortisone to adapt the doses correspondingly at sick days; (ii) glucocorticoid emergency kit consisting of vials containing 100 mg hydrocortisone (or other glucocorticoids such as prednisolone), syringes and needles; (iii) leaflet containing emergency instructions for health care professionals, i.e. immediate bolus injection of 100 mg hydrocortisone, followed by continuous infusion of 200 mg/24h; (iv) emergency phone number of an endocrine specialist team. Furthermore, since around one third of emergencies occur outside home,

the patient must be advised to carry always their steroid emergency card and the medical alert bracelet/necklace with them (5;12;14;136).

3.3.2 Sources of information

Recently, a German study reported on the sources of information patients (n = 33) are using for educating themselves about their disease (13). The vast majority of the patients (97%) indicated their physician to be their primary source of information. 39% acquired further knowledge by brochures and 24% by the internet. Although only 6% looked for advice at other patients, 44% were part of an adrenal insufficiency support group. However, particularly the experience exchange between fellow patients proved to be beneficial on the self-management (131).

The authors of (13) attributed primary reliance on physicians, despite the presence of excellent material in the internet. This was attributed to the age of the patients. This situation might be dangerous, particularly since Allolio described the principle of crisis prevention as follows (17): “The well-informed patient (or her/his relative) guides the poorly informed health-care professional!”. Actually, 30% of patients reported difficulties in convincing health care professionals to increase or even continue their indispensable glucocorticoid replacement (13) (21% with nurses, 6% with general practitioners, 9% with other healthcare professionals). Similar things were reported in UK, e.g. a general practitioner advised a patient even to stop glucocorticoid replacement (137). In the same study, they found out that most of the patients see the health professionals as experts, and they follow their instructions even though these instructions do not cohere with their knowledge of the disease. Furthermore, it was reported that practitioners disregarded emergency cards and were unable to administer glucocorticoids parenteral (138). This situation might result from the belief that glucocorticoids shall not be administered in the presence of infectious diseases because of their immunosuppressive effects (134). As a consequence, e.g. Prof. Allolio of the Endocrine Unit, Department of Internal Medicine in Würzburg provides his patients with a written letter to be signed by emergency physicians, stating that there might be a crisis impending, and that steroid card and emergency kit were presented. In such a situation, a signature would document gross negligence in cases where glucocorticoids were not administered parenteral (17). A recent study compared physicians regarding knowledge on adrenal insufficiency.

Disturbingly, physicians were by far more aware of signs for glucocorticoid over-replacement (71% identified all symptoms) than of the life-threatening under-replacement (only 24% identfied all symptoms) (139). According to these facts, in addition to the patient education, there is a clear requirement present for further training of physicians regarding adrenal insufficiency (140).

3.3.3 How well equipped are patients

Table 1 gives an overview about reported availability of steroid cards emergency bracelet/necklace and emergency kits, and the percentage of patients able to use the kit. The data is obtained from 4 studies conducted in Germany, the Netherlands, and the United Kingdom (13;131;135;137). Since patients were educated in the course of some studies, this influencing variable was indicated by the column "Instructed in the course of the study" in Table 1. In addition, there has been a prospective study in Germany (115) consisting of the largest cohort of 423 patients with adrenal insufficiency. However, in this study, the behavioral changes of patients depending on adrenal crisis events were investigated, thus, these data could not be so easily transferred to informative values in Table 1. Therefore, results of this study are discussed in-line in the text only.

The steroid or emergency card should help health professionals to provide patients with an impending adrenal crisis with an emergency glucocorticoid replacement. The patients were most frequently equipped with an emergency card or steroid card, ranging from 58-100% (Hahner *et al.* reported 96%). As such, this preventative measure seems to be the most accepted one by patients. Based on a Swedish model, a newer European version of the card was already implemented, containing on one side instructions in English, and on the other side instructions in the domestic language (130;134). Currently, the European version was implemented in several countries such as Germany, and UK and Spain provide similar versions. Emergency bracelets/necklaces were present in around two thirds of the patients. The bracelet/necklace is for the immediate identification of glucocorticoid replacement requiring patients by health personal, which is essential in case of unconsciousness. The reduced usage of the bracelet (59-69%) has been attributed to the potential impression of being marked as different from others by a disease diagnosis (118).

Table 1: Patient education and equipment.
In the study of Repping-Wuts, the patients were evaluated six months before, and six months after the glucocorticoid group meeting.

	Country	Number of patients involved	Instructed in the course of the study	Instructed by HCP at diagnosis	Steroid card
Shepherd *et al.* (137)	United Kingdom	10	NO	90%	100%
van der Meij *et al.* (135)	Netherlands	83	YES	n.i.	95%
Repping-Wuts *et al.* before (131)	Netherlands	246	NO	n.i.	58%
Repping-Wuts *et al.* after (131)	Netherlands	183	YES	n.i.	82%
Kampmeyer D *et al.* (13)	Germany	33	NO	n.i.	88%

Table 1 (continued)

	Emergency bracelet/necklace	Emergency kit	Parenteral glucocorticoid administration	Aware of all under-replacement symptoms	Detected symptoms for under-replacement (Mean)
Shepherd *et al.* (137)	60%	20%	0%	n.i.	n.i.
van der Meij *et al.* (135)	63%	87%	75%	n.i.	n.i.
Repping-Wuts *et al.* before (131)	59%	95%	57%	n.i.	n.i.
Repping-Wuts *et al.* after (131)	69%	96%	82%	n.i.	n.i.
Kampmeyer D *et al.* (13)	n.i.	65%	36%	21%	58%

Table 1 (continued)

	Aware of all over-replacement symptoms	Detected symptoms for over-representation (Mean)	Experienced difficulties with HCP	Satisfied with education	Member of self-help group
Shepherd *et al.* (137)	n.i.	n.i.	10%	0%	10%
van der Meij *et al.* (135)	n.i.	n.i.	n.i.	n.i.	n.i.
Repping-Wuts *et al.* before (131)	n.i.	n.i.	n.i.	n.i.	n.i.
Repping-Wuts *et al.* after (131)	n.i.	n.i.	n.i.	n.i.	n.i.
Kampmeyer D *et al.* (13)	18%	53%	30%	n.i.	44%

n.i. no information

The presence of having the live-saving emergency kit varied highly. While one study of the UK reported on 80% of patients possessing an emergency kit (22), in another small cohort, only 20% had actually one (137). Coverage in Germany and the Netherlands ranged from two-third to almost complete coverage. However, in contrast to this, the findings of Hahner *et al.* (115) indicated a much lower value of 30% in Germany, at the beginning of the study, which is far from optimal. Even worse is the statistics on patients who can actually use the emergency kit, which will be dealt with in chapter "Patients' knowledge on adrenal insufficiency".

3.3.4 Patients' knowledge on adrenal insufficiency

In this chapter, actual knowledge of the patients is reviewed. It surveys their actual knowledge on symptoms to assess the criticality of a situation (Table 1 and Table 2) and on appropriate countermeasures (Table 2), e.g. dose adaptations, their actual skills for parenteral glucocorticoid administration (Table 1), and knowledge on the replacement medication.

There are hardly any studies available showing the patients' ability to detect over- or under-replacement. Only very recently, a German study pursued this topic and reported quite poor results on this latter topic (13). About on fifth of the patients (n=33) could correctly identify all symptoms for under- and over-replacement in a multiple choice test. However, it must be noted that 82% and 67% of the patients correctly assessed the prominent symptoms weight gain and nausea, respectively, while mainly symptoms requiring further medical assistance were unknown. Nevertheless, one third of the patients not recognizing the frequent system nausea for under-replacement is far from optimum. Moreover, patients were not familiar with available medication for glucocorticoid replacement. While patients knew hydrocortisone quite well (88%), only 27% knew prednisolone, 15% retarded formulations, and a mere 9% dexamethasone. These results indicate definitely the necessity of more and/or better education regarding background knowledge (13).

There are more studies available assessing correct reaction based on sick day rules, presumably because these rules are the most substantial ones to prevent adrenal crisis. However, reported results are subject to high variations. A study in the United Kingdom (consisting of 10 patients only) reported on a good understanding in 90% of the

Table 2: Adequate patient behavior.
In the study of Repping-Wuts, the patients were evaluated six months before, and six months after the glucocorticoid group meeting. Shepherd *et al.* (137) reported only that 90% of the patients were well-educated, but there were no details given whether they would react appropriately in the various situations. In the study by van der Meij the threshold for doubling and tripling the dose at fever was 37.5 and 38.5 °C, respectively.

	Country	Number of patients involved	Instructed in the course of the study	Fever ≥ 38 °C	Fever ≥ 39 °C	Simple vomiting
van der Meij *et al.* (135)	Netherlands	83	YES	66%	75%	n.i.
Repping-Wuts *et al.* before (131)	Netherlands	183	NO	96%	n.i.	77%
Repping-Wuts *et al.* after (131)	Netherlands	183	YES	97%	n.i.	84%
Kampmeyer D *et al.* (13)	Germany	33	NO	73%	n.i.	n.i.

Table 2 (continued)

	Repeated vomiting	Mild surgery	Major surgery	Psychological stress	Intensive sports (> 30 min)	All correct
van der Meij *et al.* (135)	80%	72%	80%	74%	n.i.	48%
Repping-Wuts *et al.* before (131)	96%	n.i.	n.i.	n.i.	n.i.	n.i.
Repping-Wuts *et al.* after (131)	98%	n.i.	n.i.	n.i.	n.i.	n.i.
Kampmeyer D *et al.* (13)	82%	n.i.	n.i.	27%	36%	0%

n.i. no information

patients (137), however, there are no details provided whether all of the questions were answered satisfactorily. Results of the other studies are provided in Table 2, whereas the comparability of overall assessment is quite limited, since each study covered different parts of the dose adaptations. Furthermore, the assessment strategies were essentially different (multiple choice, telephone interview etc.). The overall results of the other studies (13;135) were quite in contrast to the UK study. In the Dutch study (135), only 48% of the participants provided the correct dose adaptations and emergency actions in all situations. In this study, appropriate actions correlated with patients' education level. Even worse were the results of the German study (13): not a single patient was able to act accordingly in all situations – an alarming result in view of the patients' mortality risk in case of inappropriate actions. In general, patients seem to act more appropriately in view of more frequent adrenal crisis precipitators such as fever and episodes including vomiting, while psychological stress and intensive sport was rarely identified as necessity for dose adaptations (13). Similar results were reported in the prospective study of Hahner *et al.*, but additionally, this study indicated that patients with preceding adrenal crisis events seemed to be more inclined to dose adaptations. Furthermore, it was shown that awareness and subsequently the adequacy of actions can be improved by self-management group meetings (131). Nonetheless, despite detailed provided dose instructions, 18% of patients facing deteriorations did not increase their oral glucocorticoid dose – a clear indicator for the necessity of enforced educational actions (115).

There is huge discrepancy in the rate of people who feel sufficiently trained for parenteral glucocorticoid injection (see Table 1). While none of the ten patients of the UK study felt able to perform this action (137), 82% of the participants in the education group meeting were confident in doing so. Thorough education in handling the emergency kit seems to be a key for good outcome. In another study (13), where only 50% of the possessors of an emergency kit felt confident in handling, 20% claimed that they were not instructed at all. Nonetheless, from previous data (22;115), it seems that even well-trained patients refrain from the life-saving parenteral glucocorticoid therapy, and it is unknown whether this is due to reluctance or inability (113). Indeed, despite explicit preceding training, only 41% of patients supplied glucocorticoids in case of vomiting (115). Even worse was the rate in a group without a specific training before the

evaluation (22). In this postal survey, only 12% of the participants surviving an adrenal crisis declared that they had given the injection themselves. In such an tremendous event, support from acquainted people seem to be of utmost importance, since further 17% announced that the injection was set by partner, relatives, friends or neighbors. Another study indicated that support by family substantially helped in the right diagnosis due to insistence on specific actions (137). Apart from educational aspects, subcutaneous (103) or rectal (5) glucocorticoid supply might be an option to lower the patient's threshold for a non-oral supply.

3.3.5 The case for structured education programs

Patients suffering from adrenal insufficiency must be able to autonomously, immediately and appropriately increase their glucocorticoid dose in stress situations to prevent adrenal crisis. Hence, patient education is regarded of supreme importance (131). However, adrenal crises occur frequently still, even in educated patients (115). Furthermore, there seems to be a gap in the patient's knowledge and its application, but for adrenal insufficiency, there are no studies available investigating the level of patients' comprehension and ability to apply it (137). Therefore, it is unclear whether the mental status of patients is deranged in an extend that avoids appropriate actions, or whether the patient lacks confidence for appropriate actions. In stress situations, many patients seem to trust rather family or health care professionals than their own judgment (137). A recent study showed that patients' knowledge was severely unsatisfactory (13). Others found out that knowledge increases with the education level (135), and improved adequacy of actions was observed in a questionnaire six months after an education group meeting that took three hours (131). There is plenty of evidence indicating that repetitive education is required to improve self-management, because patients simply forget information (135). Furthermore, the information shall be provided in a consistent and comprehensible manner to avoid confusion (13). Consequently structured education programs have to be implemented (134), where structured practitioner and patient protocols would be beneficial to document the educational actions (134), particularly since differences in quality and quantity of provided education was reported (137). Moreover, these protocols will subsequently help in identifying effective educational

instruments. Furthermore, family members should participate in education actions too, as patients seem to typically rely on their assessment in stress situations (137).

3.4 Education programs

Currently, hardly any information can be derived from literature and websites how structured educational programs actually look like, in what form they are implemented, or whether there are any implementations at all. There are no strict guidelines for iterating the education, and there are no examples about proper documentation of the educative actions. Nevertheless, the agreed consensus is that patients must be educated and familiarized with the emergency equipment as described in chapter "Education and equipment", and that there is need for structured educational concepts. Thus, the presented concepts in this review are not strict specifications of the required actions, but can be rather seen as a summary of recommendations given by experts in the literature. These recommendations seem to consent on the following points:

- Patients must receive all relevant information and training for the emergency kit as soon as possible after diagnosis of the disease.
- Particular emphasis has to be placed on the correct handling of the emergency kit, since the emergency kit seems to be the most effective measure to prevent fatality from an adrenal crisis (115).
- Patient education must be repeated at least annually, and the patients' knowledge should be re-evaluated (3;15;131;135).
- Family members and/or close friends shall be involved in the education, since these are typically the people patients rely on in critical situations (15;137).
- Patients shall be informed about further sources of information, such as mnemonics and educative videos in the internet(135).

Some experts have even the opinion that annual re-education by the specialist is insufficient, and recommend improved education concepts (17;135). Furthermore, structured practitioner and patient protocols are recommended to document educational actions (134;137). Additionally, there are hints that education group meetings (131) and social networks (135) might be more effective communication forms than one-to-one patient-specialist consultations. The reason is that e.g. personal experiences can be

discussed, and a cases with fatal outcomes can be presented in groups for illustrative purposes, which are deemed to be inappropriate for an individual conversation (131). One publication (135) excellently summarizes the requirements for adequate patients' actions in stressful situations: "repetition, mnemonic, reassurance, learning from experience and optimize social support", where particularly feedback (including positive one) was suggested as adequate mean for causing behavioral changes towards the right direction. The patients of this study indicated that improved education shall be realized by repeated education consultation, group education, internet-based education, and reminders once a year. Thus, it seems that a constant teaching-evaluation-feedback cycle has to be maintained to guarantee for optimal self-management of patients.

3.4.1 Internet Sources

Provision of information for patients about adrenal insufficiency is gaining increasingly importance. For this purpose, internet portals are provided by the various endocrine societies. In this review, three portals were identified which provide extensive information about the disease: (i) the National Adrenal Diseases Foundation (NADF; http://www.nadf.us/) which is located in the USA, the German Society for Endocrinology (http://www.endokrinologie.net/krankheiten-nebenniereninsuffizienz.php), and the Dutch/European portal (https://www.bijniernet.nl or http://adrenals.eu). Patients can obtain there information about the disease, helpful mnemonics and often excellent videos which are even approved for children of four years of age. An overview of useful links is given in Table 3.

The NADF provides a comprehensive compilation of useful information about the disease, mnemonics for stress dosing and emergency injections at the website http://www.nadf.us/tools-for-life/ in English. This website contains not only information for patients, but for practitioners too. Thus, only the most relevant information for patients of this site is reflected in Table 3. Furthermore, the NADF provides crisis care instruction leaflets in English, French, German, Italian, Polish, Portuguese and Spanish, and contact details to support groups in the USA.

The German Society for Endocrinology provides as well much background information, but the page is rather focused on patients. Of particular interest are the mnemonics concerning stress dosing and parenteral emergency injections (see Table 3).

Table 3: Education material and videos on the internet.
Since not all of the languages are properly linked under the main page in English, sometimes more than one link is given

Topic	Type	Language	URL
Stress dosing (CAH, 4+)	Video	AR,DE,EN,NL,TR	http://adrenals.eu/what-is-congenital-adrenal-hyperplasia-cah/
Stress dosing	Mnemonic (PPT)	DE	http://www.endokrinologie.net/files/download/glukokortikoide-notfallsituation.ppt
Stress dosing (incl. surgery)	Mnemonic (PDF)	EN	http://www.nadf.us/tools/Overview_of_stress_dosing.pdf
Stress dosing for surgery	Mnemonic (PDF)	DE	http://www.endokrinologie.net/files/download/hydrocortison-anpassung.pdf
Adrenal crisis (4+)	Video	AR,DE,EN,NL,TR	http://adrenals.eu/what-is-an-addison-crisis-4/
Adrenal crisis (12+)	Video	AR,DA,DE,EN,NL,TR	http://adrenals.eu/what-is-an-addison-crisis-12/
Adrenal crisis	Mnemonic (PDF)	EN	http://www.nadf.us/tools/WHAT_IS_AN_ADRENAL_CRISIS.pdf
Emergency injection	Video	AR,DA,DE,EN,NL,TR	http://adrenals.eu/how-an-emergency-injection-works/
Emergency injection	Mnemonic (PDF)	EN	http://www.nadf.us/tools/NIH_CRISIS_INJECTION_PICTORIAL.pdf
Adrenal crisis alert protocol	Mnemonic (PDF)	EN	http://www.nadf.us/tools/Addison's_Disease_Alert_Flyer_11-18-17.pdf
Adrenal crisis alert protocol including injection	Mnemonic (PDF)	DE	http://www.endokrinologie.net/files/download/glukokortikoide-hydrocortison.pdf
Caregiver (relative) information	Video	AR,DA,EN,NL,TR DE	http://adrenals.eu/what-can-carers-do/ http://adrenals.eu/de/betreuer-bei-einer-addison-krise/
Adrenal insufficiency and CAH (12+)	Video	AR,DA,DE,EN,NL,TR	http://adrenals.eu/what-is-cah/
HPA axis	Video	DE,NL	http://adrenals.eu/hpa-axis/
Handy app for download	App	DA,DE,EN,FR,NL	http://adrenals.eu/app/
Background information	Webpage	DA,EN,NL	http://adrenals.eu/basic-info/adrenal-insufficiency/
Background information	Webpage	DE	http://www.endokrinologie.net/krankheiten-nebenniereninsuffizienz.php
Background and awareness	Video	EN	https://www.youtube.com/watch?v=5fljd4jltlA
Information on medication	Webpage	EN	http://www.nadf.us/tools-for-life/adrenal-hormone-replacements/
Information on medication	Webpage	DE	http://www.endokrinologie.net/krankheiten-glukokortikoide.php
Information on medication	Webpage	EN	http://www.nadf.us/tools/ADRENAL_CRISIS_CARE_MEDICATION_INFO.pdf
Emergency health card	Emergency card (PDF)	DE	http://www.endokrinologie.net/files/download/glukokortikoide-notfallausweis.pdf
Travel compilation	Information (PDF)	EN	http://www.nadf.us/tools/TRAVEL_COMPILATION.pdf

PDF, Portable Document Format; PPT, Powerpoint;
AR, Arabic; DA, Danish; DE, German; EN, English; FR, French; NL, Dutch; TR, Turkish.

All of the available information is in German. This website refers to the "Netzwerk Glandula" (http://www.glandula-online.de/) which gives an overview of regional support groups. Of note, there are as well groups of Austria present which are located in Lienz (Tyrol), Linz (Upper Austria), and Vienna.

An extremely interesting educational approach was initiated by the Dutch Endocrine Society realized in the BijnierNET (or AdrenalNET; https://www.bijniernet.nl), who addressed most of the educational aspects such as stress dosing, adrenal crisis, and emergency injections in easily comprehensible cartoons, which are available on their website and on YouTube in the adrenalchannel at https://www.youtube.com/user/adrenalchannel. Some of these videos are so simple that they are approved for children of four years of age. The resonance to these cartoons seems to have been so positive that a corporate European homepage was founded (http://adrenals.eu). Many of the originally Dutch videos were translated to Arabic, Danish, German, English, and Turkish, and were approved by local endocrine societies, such as the Danish and the German ones. A detailed overview of the available videos regarding adrenal insufficiency and the available languages is given in Table 3. According to the web page, it seems that further translations in French, Russian and Spanish are planned (some of them are already supported by subtitles). Moreover, even an application for the mobile is provided, i.e. the AdrenalApp.

3.4.2 Psychological aspects

While there is quite good agreement upon the knowledge and skills patients shall have, there is limited information available why patients might not be able to apply the acquired knowledge and skills. There are hardly any studies available addressing the psychological aspects of patients' misbehavior in stress situations.

The authors of one study (135) reported the following reasons: (i) patients were unaware that they were in a severe condition requiring dose adaptations; (ii) many patients did not pay much attention to their disease and became incautious; (iii) some patients were worried about the adverse effects of hydrocortisone, and deliberately ignored sufficient dose adaptions; (iv) many patients simply forgot the information provided in educational session – some were not able to reproduce the information in face of the physical stress situation. The authors concluded that educating patients once

or twice does not seem to be appropriate and recommended frequent education and frequent assessment of the patient's actual knowledge. Another study reported too that patients deliberately changed their glucocorticoid dose in fear of the adverse effects (85), where weight gain, osteoporosis and unknown side effects were the major reasons. In this study, only 15% fully adhered to the prescribed dose in respect to dosage and particular time for intake. Furthermore, they showed that all patients were unsatisfied with the amount of provided information regarding potential problems adherent to glucocorticoid intake. They wanted to be better informed about side effects, how to behave in case of side effects, and whether there are interactions with other medication. The results of this study showed that non-adherence to prescribed medication positively correlated with concerns about glucocorticoids as a result of insufficient information. In this study, the authors concluded that better information might help to improve patients' adherence to medication. In a third study (88), it was shown that strong beliefs of the necessity of hydrocortisone replacement and concerns about adverse effects influenced the perception of the illness negatively in respect to lower treatment control. Here, they proposed a multi-phase approach for endocrinologists to alleviate the psychological burden of the disease:

1. Provide clear reasons why hydrocortisone is necessary.
2. Patients shall be evaluated regarding their concerns, and these issues shall be addressed in detail.
3. In cases where these concerns cannot be addressed by more information and reassurance, the help of a medical psychologist may be considered. This might help to improve the perception of the disease and develop improved self-management.
4. Further obstacles negatively impeding the patient's constant hydrocortisone usage should be addressed, and supportive actions/advice should be given to achieve permanent and correct adherence to dosage.

4 Discussion

This systematic review provides an overview of state-of-the-art therapies for adrenal insufficiency. Particular emphasis was placed on strategies for prevention of life-threatening adrenal crisis. As such, patient education holds promise to avert this event, or at least its fatality (63;108;121). Thus, subsequent to provide information on therapies and adrenal crisis, this review focuses on patient education, and provides as such detailed information about recommendations for education programs.

Prevention of adrenal crisis depends on timely increase of glucocorticoid dose in stress situations (99) based on the patients' judgment. In cases of gastrointestinal illnesses where vomiting and diarrhea are included or onsets of adrenal crisis, there is a clearly defined algorithm to avert the fatality of the event (5;15;17;19;113): 100 mg hydrocortisone administered iv or im by a bolus injection; followed by 200 mg continuously infused iv for 24 hours or 50 mg boluses iv (or im) every six hours. Nonetheless, mortality and morbidity caused by adrenal crisis is still quite high (115). Since elapsed time between perceiving of first symptoms to an explicit adrenal crisis might be short (even only 5 minutes were reported (17)), and medical staff familiar with adrenal insufficiency are typically absent in such situations, the life-rescuing interventive actions must be inevitably accomplished by the patients or their families themselves (15). Therefore, patients must meticulously follow strict dose regimens (amount and time of intake is important) to preserve their quality of life (19), and comprehensive patient education is generally accepted to be an indispensable necessity to permit patients' self-management (17). In fact, the patient must have sufficient knowledge for identifying critical situations and skills for appropriate actions (17), where especially parenteral glucocorticoid administration is considered to be the most effective measure (115). Furthermore, patients shall possess an emergency kit for parenteral injection, and always carry a steroid card and medical alert necklace/bracelet with them to immediately inform health professionals of the urgent glucocorticoid requirement.

While there are currently many recommendations for a structured education program (3;17;131;135;137), there is hardly any information available whether such programs were already implemented and how. The urgent need for structured education programs has primarily emerged by the fact that even in well-educated patients, the incidence of adrenal crisis did not significantly decrease, and alarmingly, even such

patients died in consequence of an adrenal crisis (115). This initiated discussions whether extensive patient education might be the proper way to reduce the mortality risk inherent to adrenal crisis (113), since crises occur frequently still, even in educated patients (115). Indeed, there seems to be a huge difference in the rate of people comprehending taught subject and the ultimate ability to apply the knowledge under physical stress (137). It was proven that many patients have enormous problems to act correspondingly under physical stress (3;141;142). Patients prefer rather to follow instructions of health care professionals than their own judgment, even though these instructions disagree to their acquired knowledge in educational sessions (137). A recent survey indicated that many patients suffer from knowledge deficits (13), and another recent study showed that the education provided to patients varies highly (137). Moreover, correct behavior in adrenal crisis situations seems to correlate with educational level (135). There is profound evidence present that frequent re-education and re-evaluation of knowledge is required to increase the number of patients acting appropriately in stressful situations (131;135), and that information must be made available in easily comprehensible and coherent manner, possibly in group meetings of fellow sufferers, involvement in social networks, and educational videos (131;135). In respect to educational videos, the efforts of the Dutch AdrenalNET (http://adrenals.eu/video) have to be highlighted, in which the most important aspects of adrenal crisis and adrenal insufficiency are depicted in simplistic cartoons which are comprehensible by children. Moreover, these videos are already available in several languages. Recently, three studies reported on psychological aspects why patients do not adhere to dose regimens (85;88;135). The results identified the most common reasons to be unawareness of severity, concerns of long-term side effects, such as osteoporosis and weight gain, insufficient knowledge of the interrelationship of glucocorticoids and stress, and simple carelessness and forgetfulness. Taken together, there are further investigations warranted to detect reasons for the gaps between provided knowledge, its comprehension, and its life-rescuing application.

In summary, from the current point of view, there is quite some room for improvement of available instruments for patient education. It is evident that structured and sophisticated education concepts have to be established to improve the prevention and outcome of adrenal crisis (17). Moreover, the approaches have to be quality

controlled to guarantee that information has been made accessible to each individual patient (17) in a catchy, coherent and comprehensible form that even addresses the psychological aspects of patients suffering from adrenal crisis (a medical psychologist might help in some situations (88)). And in no case, the education of family members, and further education of health personnel has to be underestimated, since these are typically the people patients rely on when suffering from impaired consciousness (15;137).

4.1 Conclusion and Outlook

The prevention of adrenal crisis and subsequent mortality resides to a great extent on the shoulders of the patients. Well-educated patients are required to reduce the still high mortality rate inherent to this disease. This circumstance is particularly regrettable, since appropriate and timely actions typically antagonize this health threat. While a recent study questioned the efficacy of extensive patient education (113), there are studies showing that patients have severe knowledge deficits (13;137). In particular, repeated education and evaluation of knowledge seems to be beneficial for self-management skills under physical stress, where the success strategy can be summarized as follows: "repetition, mnemonic, reassurance, learning from experience and optimize social support" (135). Conclusively, structured and quality-controlled education strategies are required (17). Only by repeatedly instructing patients on the background and preventive strategies of adrenal insufficiency, there might be a chance to reduce the high death-toll. Consequently, such education programs are highly desirable for the University Hospital in Graz and should be anticipated. In the development of such a program, it is recommended from the very beginning to consider the importance of repetitive measures, place emphasis on the comprehensibility, to provide psychologically-balanced information on long-term effects of medication including sufficient background information, and include family members in the education. Emphasis shall be placed on teaching parenteral glucocorticoid self-administration, particularly since timely substitution is fundamental to avoid fatality (15). In this respect, it can be stated that more and easily intelligible information provided by frequent repetitions and controlled by knowledge assessments will prove advantageous on patient's self-management, and as such possibly lead to a reduced mortality and morbidity rate.

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