Adrenal crises: perspectives and research directions

Article *in* Endocrine · December 2016

DOI: 10.1007/s12020-016-1204-2

3 authors:

Louise Rushworth
University of Notre Dame Australia
49 PUBLICATIONS **420** CITATIONS
SEE PROFILE

David J Torpy
Royal Adelaide Hospital
178 PUBLICATIONS **4,632** CITATIONS
SEE PROFILE

Henrik Falhammar
Karolinska Institutet
98 PUBLICATIONS **1,691** CITATIONS
SEE PROFILE

Endocrine
DOI 10.1007/s12020-016-1204-2

REVIEW

Adrenal crises: perspectives and research directions

R. Louise Rushworth[1] · **David J. Torpy**[2] · **Henrik Falhammar**[3,4,5]

Received: 18 October 2016 / Accepted: 8 December 2016

Abstract Adrenal crises are life-threatening complications of adrenal insufficiency. These events have an estimated incidence of between 5 and 10 adrenal crises/100 patient years and are responsible for some of the increased morbidity and excess mortality experienced by patients with adrenal insufficiency. Treatment involves urgent administration of IV/IM hydrocortisone and IV fluids. Patient education regarding preventive measures, such as increasing the dose of replacement therapy ("stress dosing") when sick, using parenteral hydrocortisone as necessary and accessing medical assistance promptly, is still considered the best approach to averting the onset of an adrenal crisis at times of physiological stress, most commonly an infection. However, recent evidence has demonstrated that patient education does not prevent many adrenal crisis events and the reasons for this are not fully understood. Furthermore, there is no widely accepted definition of an adrenal crisis. Without a validated adrenal crisis definition it is difficult to interpret variations in the incidence of adrenal crises and determine the effectiveness of preventive measures. This article aims to review the clinical aspects of adrenal crisis events, to explore the epidemiology, and to offer a definition of an adrenal crisis and to offer a perspective on future directions for research into adrenal crisis prevention.

Keywords Adrenal insufficiency · Incidence · Risk factors · Morbidity · Mortality

Introduction

Adrenal crises (ACs) are serious, life threatening complications of adrenal insufficiency (AI). These acute episodes constitute one cause of the increased morbidity and mortality in AI [1–6], and account for a substantial proportion of all AI deaths [1–4, 6]. Most ACs occur in the context of exposure to a physiological stressor, such as an infection or injury, when the concentration of cortisol in the circulation is insufficient for requirements. However, knowledge of the physiological processes that contribute to the development of ACs is incomplete and, furthermore, there is no agreed definition of an AC.

Education is a necessary and important component of AC prevention. All patients should be instructed on stress dosing and parenteral glucocorticoid administration; carry a steroid dependency card; and wear a MedicAlert bracelet or similar identification. Despite these innovations, however, ACs continue to occur even among patients who have been well educated in preventive strategies [7], and it is not surprising that they are a major source of anxiety for patients and their families [8]. Frequent reports of patients having problems accessing appropriate treatment for an AC

✉ R. Louise Rushworth
louise.rushworth@nd.edu.au

[1] School of Medicine, Sydney, The University of Notre Dame, Sydney, NSW, Australia

[2] Endocrine and Metabolic Unit, Royal Adelaide Hospital and University of Adelaide, Adelaide, SA, Australia

[3] Department of Endocrinology, Metabolism and Diabetes, Karolinska University Hospital, Stockholm, Sweden

[4] Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

[5] Menzies School of Health Research and Royal Darwin Hospital, Darwin, NT, Australia

Published online: 19 December 2016

are highly regrettable and contribute to the difficulties in preventing ACs in treated AI [9, 10].

AC prevention, therefore, continues to be an important conundrum in endocrinology and the path towards a reduction in the incidence of these events remains uncertain. The objective of this paper is to assess the current knowledge regarding ACs; review the definition of an AC in this context; highlight areas where knowledge is deficient; and suggest topics for further investigation. In doing so, we hope to encourage research that can address a number of outstanding issues, with the overall aim of reducing the incidence of AC events in the future.

Incidence and mortality

Estimates from a number of well-conducted studies utilizing various designs have demonstrated that the incidence of AC is between 5 and 10 ACs/100PY in treated AI (Table 1) [7, 10–15], with AC events being somewhat more frequent in primary adrenal insufficiency (PAI) than secondary adrenal insufficiency (SAI) [2, 13, 14, 16]. The associated mortality rate from AC in treated AI is 0.5/100 PY [7]. However, not all AC related deaths occur in patients who have been diagnosed with AI, and a fatal AC may be the first diagnosis of AI in some patients [17, 18]. Among those with treated AI, AC related deaths contribute substantially to the increased mortality rate experienced by patients [1–4], being responsible for up to 15% of all deaths in autoimmune AI [1, 4, 6, 10], and 42% of those in congenital adrenal hyperplasia (CAH) [2]. Reassuringly though, AC related fatality in hospital is uncommon (<1%), suggesting that access to timely treatment for an AC is largely successful [19]. Nevertheless, problems of recognition of an AC as a cause of death are pervasive. While an AC may be missed as a cause of death at any age, it is likely that this is more common among older patients who generally have a greater number of comorbid illnesses, and this may affect mortality estimates.

Diagnosis and clinical considerations

Although there is no universally accepted definition of an AC, there is general agreement regarding its underlying pathophysiology and clinical presentation. Briefly, ACs are acute disturbances of physiology that happen when the circulating levels of adrenal steroid hormones are insufficient for physiological requirements. Haemodynamic compromise, manifest primarily by hypotension, is the cardinal physiological disturbance of an AC. Other symptoms and signs include: nausea, vomiting, abdominal pain, fever, and delirium. Biochemical abnormalities comprising:

Table 1 Estimations of adrenal crisis incidence

Authors	Year	Location	Method of AC assessment	Study type	Population	Sample (n)	Incidence in All AI	Incidence in PAI	Incidence in SAI
White [21]	2010	Four countries	Self-report	Cross-sectional survey	Support groups	481	–	8%/year	–
Hahner [11]	2010	Germany	Self-report	Cross-sectional survey	Clinic, support group	444	6.3/100py	6.6/100py	5.8/100py
Reisch [15]	2012	Germany	Self-report, verified	Retrospective cohort	Clinic, support group	122	–	5.8/100py[a,b]	–
Ritzel [14]	2013	Various	Review	Review	Post-adrenalectomy	203	–	9.3/100py[c]	–
Hahner [7]	2015	Germany	Questionnaire,phone contact	Prospective cohort	Clinic	423	8.3/100py	–	–
Meyer [16]	2016	Germany	Record linkage	Retrospective cohort	Insurance enrollees	11691	4.8/100py	7.6/100py	3.2/100py
Smans [13]	2016	Netherlands	Record review	Retrospective cohort	University hospital clinic	458	4:1 /100py	5.2/100py	3.6/100py

[a] CAH only

[b] 4.9/100py from chart review

[c] Median

Table 2 Definitions of an adrenal crisis

Authors	Bornstein [23]	Allolio [7, 10]	Puar [24]	Smans [13]
Text	A medical emergency with hypotension, marked acute abdominal symptoms, and marked laboratory abnormalities, requiring immediate treatment	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	An acute deterioration in a patient with adrenal insufficiency	An acute impairment of general health requiring hospital admission and administration of intravenous saline and glucocorticoids in patients with AI
Added details	Symptoms: severe weakness, syncope, abdominal pain, nausea, vomiting, back pain, confusion. Signs: hypotension, abdominal tenderness/guarding, decreased consciousness, delirium. Laboratory results: hyponatraemia, hyperkalaemia, hypoglycaemia, hypercalcaemia	Grading: Grade 1: outpatient care only. Grade 2: hospital care (general ward). Grade 3: admission to intensive care unit. Grade 4: death from adrenal crisis (with or without parenteral glucocorticoid administration)	Symptoms: severe weakness, acute abdominal pain, nausea and vomiting, altered sensorium. Signs: hypotension, fever, abdominal tenderness/guarding, reduced consciousness. Biochemical: hyponatraemia, hyperkalaemia (primary AI), hypoglycaemia, hypercalcaemia	

hyponatraemia, hyperkalaemia, hypoglycaemia (usually in children), and hypercalcaemia may also be present [10].

Typically patients with PAI are at higher risk of an AC than those with SAI, as mentioned earlier. PAI patients are also considered to be more prone to hyperkalaemia. This is presumed to be due to an absence of aldosterone secretion and a complete loss of cortisol production in PAI, while aldosterone secretion is preserved in SAI and there may also be residual cortisol secretion in some patients. SAI due to sustained glucocorticoid exposure is common but AC events tend to be rare or mild, probably reflecting incomplete HPA axis suppression in many treated patients. For example, among renal transplant patients taking 5–10 mg prednisolone daily, one-third were found to have normal ACTH stimulated cortisol levels, indicating lack of suppression and likely low risk of AC events [20].

An AC is a medical emergency. Treatment in hospital involves: the urgent administration of hydrocortisone (100 mg IV stat followed by 200 mg/24 h given as a continuous infusion or frequent IV (or IM) boluses (50 mg) every 6 h, with subsequent doses tailored to the clinical response); intravenous fluids (generally normal saline (1000 mL within the first hour, with further crystalloid fluid being administered according to standard resuscitation guidelines, taking into account the patient's circulatory status, body size and relevant comorbidities, and administered with particular caution among patients with treated diabetes insipidus, as excessive fluids may lead to hyponatraemia)); treatment of the precipitating cause, if one is evident; and management of any existing comorbidities. After successful treatment and, in an attempt to prevent further ACs, it is advisable that the patient and their clinician assess the precipitants of the AC; review any risk factors; reiterate the steps for prevention; and re-evaluate the patient's competency in parenteral glucocorticoid administration.

Definition

Despite consensus on the range of clinical features that comprise an AC, problems persist in both its definition and identification. There is no universally accepted definition of an AC and the definitions that are used can differ substantially between clinicians and research studies [10]. This is clinically relevant with regards to immediate and longer-term management decisions and is also of considerable significance to research into AC prevention.

The AC definitions used in research, particularly in studies that involve smaller cohorts and the assessment of interventions, tend to be project specific and may be detailed in the study report [7, 13, 15, 21]. By comparison, studies using morbidity and mortality databases [4, 16] use diagnoses that have been coded according to the

Table 3 Definition of an adrenal crisis

Authors	Rushworth, Torpy and Falhammar
Text	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)
Added details	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

International Statistical Classification of Diseases and Related problems (ICD-10-CM), where the rubric E27.2—"Addisonian or adrenal crisis" (approximate synonym of severe adrenal insufficiency) [22] denotes the diagnosis of an AC. However, there is no detailed guidance given in the ICD-10-CM (or the previous ICD-9-CM) on the symptoms or signs that define an AC [22] and, as a consequence, the incidence of this code in health-related datasets represents the interpretation of the various clinical features of acute illness in AI by multiple doctors in accordance with their own preferred AC definition.

In an attempt to identify a unifying definition of an AC, a number of authors have proposed new versions, although none to date has been universally accepted [10]. The most recent of these was included in the 2016 guidelines on PAI management, and mandates the presence of hypotension, "marked acute abdominal symptoms and marked electrolyte abnormalities" [23]. While electrolyte abnormalities are required in this particular definition, these are now believed to occur less often in an AC than was previously thought, possibly resulting in an under-enumeration of true cases of AC and adversely affecting the utility of this definition in practice [10]. Another definition classifies an AC as "a major health impairment" and specifies the presence of at least two symptoms or signs, including but not mandating, electrolyte abnormalities, and requiring the administration of glucocorticoid [7] (Table 2). A grading system using levels of hospitalization to denote AC severity was added to this, which assists in interpretation, but its validity may be affected by variation in the services provided by different hospitals, particularly with regard to grades 2 and 3 (Table 2) [7]. It may also be confounded by other factors, such as age and comorbidities, as older patients and those with significant coexisting illnesses are likely to be admitted to hospital or an intensive care unit at a lower threshold of illness at each level than healthier younger patients.

By comparison, the two remaining definitions are more general and do not mandate the presence of specific features (Table 2). One describes an AC as "a sudden deterioration in a patient with known AI" [24], while noting in the manuscript that, "the principal manifestation of AC is hypotension or hypovolaemic shock" [24]. The other defines an AC as "an acute impairment of general health requiring hospital admission and administration of intravenous saline and glucocorticoids in patients with AI" [13]. It is noteworthy that this last definition and the one by Hahner et al. [41] mention glucocorticoid treatment (but not the resolution of symptoms following its administration) presumably in an effort to minimize the likelihood of misclassification of other diseases as an AC. For the same reason, and in an extension of this idea, Allolio [10] included a rider on the original definition by Hahner et al. [41], described above, requiring that there be a resolution of symptoms following administration of intravenous hydrocortisone [10].

Despite these efforts directed towards developing a universal AC definition, none to date has been accepted and each has strengths and weaknesses. For this reason, a new definition is proposed in this review (Table 3). Like those already described, it follows the general principle of aiming to be clear and easy to apply, whilst minimising measurement error by reducing false positives (milder physiological aberrations being classified as an AC, which are prone to occur in definitions that are very general) and false negatives (actual ACs being classified as milder forms of AI, when the required features for diagnosis are overly stringent). Central to considerations around this definition was an understanding that there is no particular feature of an AC that is diagnostic, and even a set of common clinical features has limited specificity for the diagnosis. However, there is general acknowledgement that haemodynamic disturbance is the central physiological aberration of an AC and, for this reason hypotension (either absolute or relative) was mandated in this definition (Table 3).

The other new aspect to this definition, like the addition of a demonstrated improvement after glucocorticoid administration by Allolio [10] to the original Hahner et al. [41] definition, is that there needs to be a documented improvement in the patient's clinical status after the administration of intravenous hydrocortisone. However, in this new definition a time frame for the improvement is included to increase the validity of the AC diagnosis. This is supported on physiological grounds by knowledge of the rapid pressor effects of hydrocortisone on blood pressure in the context of an AC, probably reflecting the known effects of hydrocortisone on the peripheral vasculature, which can be measured in vivo at the macro and microcirculation level

[25, 26]). The exact time frame of the pressor response in an AC has not been documented but clinical experience suggests that a response should be seen within an hour. Longer periods would indicate that another cause for shock may be present, or that the AC may have co-occurred with another severe illness, such as septic shock, which would affect the apparent resolution of the AC.

These extra criteria included in the proposed definition increase the likelihood that true AC events are identified as such, and that other, less severe episodes of illness, which are nonetheless important and significant in the context of AI management and surveillance, are not classified as an AC but rather a milder form of illness, which we suggest can be denoted as "symptomatic AI". In addition, a list of common features of an AC was also included in the present definition to assist in the diagnosis (Table 3). Scores from established metrics of illness severity, such as APACHE [27] could also be used to add information on the seriousness of an AC episode.

Risk factors

All patients with AI are at risk of an AC in situations, usually of physiological stress, where the requirement for cortisol is greater than its availability in the circulation. However, a number of studies have demonstrated that AC risk is not uniform across all patients and there are some demographic and personal characteristics of patients that may potentiate this risk [10, 16]. As has been mentioned, patients with PAI appear to be at greater risk of an AC than those with SAI, which may be related to a complete loss of adrenal function in PAI, or there may be other causes, including complications from endocrine comorbidities in patients with autoimmune PAI/APS. For example, thyroid disease is common in patients with PAI and thyrotoxicosis can precipitate an AC, as can the initiation of thyroid hormone replacement in a patient with undiagnosed AI [23, 28]. Patients with PAI also have an increased prevalence of type 1 diabetes mellitus, a comorbidity that may be associated with a higher AC risk [16]. Some pharmaceutical agents can also induce AI and, in doing so, increase AC risk [24].

It is also possible that there may be an association between the glucocorticoid replacement regimen used by the patient and AC risk. This may be an issue with the modern approach, which favors lower doses of shorter-acting glucocorticoids (hydrocortisone and cortisone acetate) in preference to the longer acting glucocorticoids (prednisolone and dexamethasone) [29]. Although this has not been identified in follow-up studies and, indeed, glucocorticoid replacement regimen and AC risk may not in fact be associated, it should be noted that in a recent meta-analysis of the relevant studies, the evidence base for this negative finding was considered to be weak [30, 31]. Another possible reason for this apparent lack of association is that patients who experience an AC event(s) may have their glucocorticoid dose escalated or altered to prednisolone, potentially masking any association between low dose glucocorticoid replacement and AC incidence. Newer formulations, such the dual (Plenadren®, Duocort®) or delayed release (Chronocort®) forms of hydrocortisone, have not been examined in terms of AC risk explicitly but to date no specific safety issues have emerged [32].

Age and significant comorbidities may also act as risk factors for the development of an AC in patients with AI, although the mechanism for this is less clear and may be specific to the individual comorbidity [16, 19]. Other factors that may increase a patient's predisposition to an AC include psychological and cognitive difficulties, and social isolation, as these may impair the patient's ability to manage their AI, especially the use of stress dosing and parenteral hydrocortisone. Non-compliance with treatment is particularly hazardous in AI, and failure to take glucocorticoid replacement according to instructions places a patient at increased AC risk.

There are also other, as yet unknown, factors that appear to potentiate the AC risk in some patients [10]. As has been mentioned, it is recognized that there is a subgroup of patients that has a tendency to develop ACs and can experience multiple episodes. In contrast, other patients can be observed for many years without an AC event, despite being at risk of an AC due to underlying AI. The reasons for these differences in individual susceptibility to AC are not yet understood and this is an important area of weakness in the current knowledge, as delineation of this predisposition could facilitate a considerable reduction in the total number of ACs occurring in a population. There is also a subgroup of AI patients who have persistently reduced well-being despite optimal replacement therapy and it is possible that the unknown physiological factors which cause this phenomenon may be related to AC risk, and this warrants further investigation.

Precipitating factors

An AC event can be precipitated by a number of factors, most commonly a physiological stressor, such as an infection or injury. Indeed, infections are regarded as the most common precipitants of an AC [7, 10, 11, 19, 24] and these can be both bacterial [13, 19] and viral (especially in children) [33]. An infection is a particularly potent AC precipitant because immunomodulation is partly controlled by cortisol and, in an environment of insufficient circulating cortisol, excess pro-inflammatory cytokines in the circulation can lead to the development of uncontrolled inflammation, vasodilatation, impaired cardiac function, and

shock [25, 34]. These effects are amplified by the absence of the facilitating role of cortisol on catecholamine action on the cardiovascular system [35].

Gastroenteritis is particularly hazardous in AI because vomiting and diarrhoea impair the adequate absorption of glucocorticoids and also cause dehydration [10, 24]. Emotional stress has been cited as an AC precipitant but the underlying reasons for the association between psychological stress and an AC are unknown and warrant further investigation. An abrupt discontinuation of glucocorticoid therapy may also precipitate an AC, with or without a stressor. In addition, a proportion of ACs, perhaps as many as 10%, has no identifiable precipitant [10].

Prevention—is it possible?

Clinically, the general approach to AC prevention involves a sequence of logical steps, including: the administration of oral or parenteral glucocorticoids in increased doses when there is an acute illness; the provision of glucocorticoid cover for surgical procedures, with doses varying according to illness severity; avoidance of sudden withdrawal of glucocorticoid pharmacotherapy; the use of a steroid card to inform practitioners of the glucocorticoid requirement for unwell patients [36]; and the use of a MedicAlert bracelet or similar to identify the patient as having AI when they are unable to communicate.

Much of the success of AC prevention, however, relies on a patient's ability to take action to avert the onset of an AC by recognizing an indicator of physiological stress, such as an infection, and implementing stress dosing and/or self-administering parenteral glucocorticoids, where appropriate. However, intensive patient education, which has long been considered the cornerstone of preventive endeavors, does not appear to be sufficiently effective to enable many patients to take these steps independently [10]. Indeed intensive education was not found to be more effective than routine instruction in reducing the incidence of ACs in a recent trial [10]. Unsurprisingly, anxiety about ACs is common [8] and may have a number of consequences including unnecessary attendance for medical care when self-management at home is likely to be effective or inaction or delayed action in the face of a significant and potentially life-threatening episode of illness.

One area of particular concern is the time that elapses between the onset of symptoms and the initiation of parenteral therapy, a delay that is often due to a patient's reluctance or an inability to transfer from oral stress doses to intramuscular injection of hydrocortisone, particularly in situations where there are symptoms of vomiting and diarrhea, which impair the absorption of oral glucocorticoids. Subcutaneous administration of hydrocortisone may address this problem, as this route is more acceptable to patients than the intramuscular approach, and its use can be considered preferable to a situation in which no parenteral hydrocortisone is given [10, 37, 38]. Recent research demonstrated that while cortisol levels of greater than 1000 mmol/l from subcutaneous injection were reached more slowly than through intramuscular injection, this was within an acceptable time limit among patients with a BMI of less than 27 who were not in shock [37]. Another alternative in this situation may be rectal hydrocortisone suppositories, providing there is no diarrhea [23, 38]. Emergency self-care could be improved by the introduction of a preloaded hydrocortisone syringe, which obviates the need for an unwell patient to draw up and then inject hydrocortisone [10]. Unfortunately, this product is not available and there are no current prospects for its introduction [10].

Other barriers to successful AC prevention relate to problems with health care delivery, including inadequate levels of knowledge about AI/AC among clinicians [8, 39, 40]. Ignorance about the importance of an AC as a medical emergency can result in patients communicating the need for urgent treatment to hospital staff, only to be ignored or have the treatment refused, some with severe consequences [9, 10]. The ability of emergency service personnel to administer parenteral glucocorticoids also varies between jurisdictions and delays may occur in the response to calls for assistance by emergency services. Inadequate responsiveness of triaging systems in hospitals and poor timeliness in the initiation of definitive treatment can also influence the outcome of acute illness in AI patients [41].

Future directions

There are many issues that remain unresolved in the pursuit of AC event reduction and targeted research may help in making progress towards this goal. Importantly, a number of aspects of AC physiology are not yet understood and a suite of specifically designed research projects should assist in improving the knowledge base. Among these is the need for a more thorough elucidation of the physiological response to infection. It is thought that inflammatory cytokine induced HPA axis activation occurs in combination with rapid cleavage of corticosteroid binding globulin (CBG) by tissue elastases to enhance cortisol delivery to inflamed tissues [42]. CBG cleavage is an early feature of this [43], and the cleavage is associated with increased cortisol secretion and reduced CBG production. Consequent depletion of circulating CBG may contribute to inadequate cortisol supply to inflamed tissues, resulting in heightened tissue damage, as cellular processes become overwhelmed by unfettered NfKB activation [42]. However, the relative importance of these processes to the onset of an AC has not been evaluated and research to determine the range of cytokine/CBG/circulating hydrocortisone and

catecholamine levels at the time of AC presentation, along with relevant inflammatory markers is needed.

Cortisol is also involved in catalyzing the conversion of adrenomedullary noradrenaline to adrenaline via the phenylethanolamine *N*-methyltransferase enzyme, the levels of which are known to be low in AI [44]. An adequate cortisol level is also required for adrenomedullary organogenesis and, as a result, the loss of this conversion of noradrenaline to adrenaline may be more pronounced in congenital forms of AI, such as CAH [45, 46]. It is possible that insufficient concentrations of circulating adrenaline may contribute to the tendency to vascular collapse in AI. However, the relative contribution of both adrenaline and noradrenaline to the onset and progression of an AC is unknown and should be the subject of further research.

It is also not known whether an AC event occurs in the context of a complete deficiency of circulating glucocorticoid or a relative deficiency, where the level of circulating glucocorticoid is lower than the concentration that is required for the degree of physiological stress imposed by an illness. There have not been studies conducted to examine this issue, largely because of the temporal disconnect between the determination of serum levels of glucocorticoids and their tissue action. However, this is of considerable importance and warrants further examination.

Another area that is worthy of further exploration is the interrelationship between AI and glucose metabolism. It has been shown that morning glucose levels are lower in AI patients [46–48], and recent evidence has demonstrated that occult nocturnal hypoglycaemia can occur in adults with AI [49, 50]. The underlying mechanism for this is likely to involve reduced nocturnal gluconeogenesis during an overnight fast, a process that is partially dependent on glucocorticoids. However, sympathoneural responses may become impaired in AI patients with recurrent nocturnal hypoglycaemia and this may increase the predilection to, or severity of, AC events. For this reason, it would be valuable to assess the frequency of hypoglycaemic events in patients who experience frequent ACs, as one important element of an investigation into the reasons underlying some patients' apparent predisposition to ACs.

In an extension of this idea, a comprehensive investigation into the variability in the apparent propensity to AC between patients may uncover other factors that influence the risk of AC, such as a vulnerability to hypoglycaemia, mentioned earlier, and this may be of potential benefit to all patients. The underlying risk factors, precipitants and responses to stressors among patients who have repeated episodes of AC should be assessed relative to those in a comparator group who do not have frequent ACs, so that any physiological, management, personal or psychological factors that may act to increase the AC risk can be identified.

A number of epidemiological aspects of AC also require further research and it is important that, where possible, any methodological limitations of the studies are addressed. Generally, studies on AC are either cohort studies of small patient groups or population-based studies linking records from registers or other databases. Typically, cohort studies conducted on samples of patients offer detailed information on treatment and risk factors but may be affected by selection bias, as the study subjects are often drawn from specialized clinics, offering lower levels of generalizability than well-conducted population based studies [7, 14, 15]. Surveys of unselected patients, on the other hand, including those that use convenience samples of patients recruited from AI support groups have lower levels of validity and usually are affected by selection bias [8, 21, 51]. Measurement error is also likely to be present in any study that relies on patient self-report of an AC, although independent record review may help to minimize the misclassification of AI/AC that is inherent in this approach [15].

By comparison, population-based disease registers can be linked with other databases, such as hospital admission and mortality records, to provide estimations of AC incidence and mortality [1, 2, 4]. Alternatively, morbidity databases can be examined to detect changes in incidence that may not be apparent in a clinical setting, although these sources of information tend to contain fewer clinical details and may have lower levels of reliability for key data items than well-maintained registers [21, 52]. Ongoing monitoring of AC events using these data is important for the prevention of ACs, and is particularly relevant given that changes in AI management, such as the transition from higher to lower doses of glucocorticoid replacement therapy, can be initiated without the benefit of a randomized trial. Changes in incidence are more likely to be identified earlier through ongoing surveillance than in an individual clinic setting.

Trends in incidence can be assessed and age and sex specific rates or statistical modeling may be used to determine whether a change is widespread in a patient population or is concentrated in a subgroup(s) of patients. Such analyses of population-based data have recently uncovered a number of new patterns in AC/AI incidence. A recent Australian study found an increase in hospital admissions for AC between 2000 and 2012 and another on the same dataset identified geographic variations in AC incidence [29, 52]. Another study in Germany, reported higher AC incidence rates in patients with the autoimmune polyendocrine syndrome (APS)/PAI [16], and a separate analysis in the same population noted an increase in the incidence of PAI in women [53]. A further study on Australian patients found a previously undetected increase in hospital admissions for AC during an interruption to the supply of 20-mg hydrocortisone tablets [54].

This new information illustrates the valuable contribution made by the analysis of incidence data towards the understanding of the epidemiology of AC but it is noteworthy to remember that the value of such analyses may be diminished by inconsistencies in the definition of AC. Coding errors or the intentional upgrading of codes to reflect greater disease severity may be a potential limitation of morbidity data, although the extent to which this affects individual datasets is unknown. It is also possible that the use of new indices may assist in a more thorough determination of trends in the severity of admissions for AC and AI. These may include use of an AC/AI ratio as a way of assisting in the interpretation of changes in presentation while controlling for possible fluctuations in baseline disease rates.

Monitoring mortality rates is also an essential component in the drive to improve health outcomes in AI and disease registers or linked morbidity and mortality databases can be used for this purpose [1–4]. However, there is still much that is unknown about the processes that cause death from an AC, and detailed investigations aimed at determining whether patients suffering an AC were misdiagnosed and, therefore, not treated for an AC, or whether there were unrecognized complications due to comorbidities, may assist in reducing the burden of mortality from AC in treated AI.

Conclusion

Despite considerable efforts to reduce the health burden of ACs, these events continue to cause morbidity and mortality, and are source of considerable anxiety for patients and their families. Research studies have increased our understanding of the elements of an AC but many important aspects remain unresolved. As a consequence, progress towards a reduction in the occurrence of ACs is at best incremental and often disappointing. Outstanding issues variously relate to AC physiology, uncertain and inconsistent AC definitions applied by multiple clinicians in different settings, and apparent failures to pursue rigorous investigation of variations in predisposition to AC events in patient sub-groups, among others. Available education strategies are logical and certainly useful in preventing or aborting episodes but the apparent failure of education strategies to change the incidence of AC in treated AI highlights the necessity for new ideas and approaches to AC prevention. The use of self-administered subcutaneous parenteral hydrocortisone holds promise but strong confirmatory evidence for its benefit in situations of incipient AC is lacking. Development of a preloaded syringe, comparable to the Epipen®, which can be used to administer the dose of hydrocortisone may be useful but appears to have insufficient support from industry or government for its introduction.

Acknowledgments HF is supported by the Magnus Bergvall Foundation, Karolinska Institutet, and the Stockholm County Council.

Funding No funding was received for this review.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. M.M. Erichsen, K. Lovas, K.J. Fougner, J. Svartberg, E.R. Hauge, J. Bollerslev, J.P. Berg, B. Mella, E.S. Husebye, Normal overall mortality rate in Addison's disease, but young patients are at risk of premature death. Eur. J. Endocrinol. **160**, 233–237 (2009)
2. H. Falhammar, L. Frisén, C. Norrby, A.L. Hirschberg, C. Almqvist, A. Nordenskjöld, A. Nordenström, Increased mortality in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J. Clin. Endocrinol. Metab. **99**(12), E2715–E2721 (2014)
3. P. Burman, A.F. Mattsson, G. Johannsson, C. Höybye, H. Holmer, P. Dahlqvist, K. Berinder, B.E. Engström, B. Ekman, E.M. Erfurth, J. Svensson, J. Wahlberg, F.A. Karlsson, Deaths among adult patients with hypopituitarism: hypocortisolism during acute stress, and de novo malignant brain tumors contribute to an increased mortality. J. Clin. Endocrinol. Metab. **98**(4), 1466–1475 (2013)
4. R. Bergthorsdottir, M. Leonsson-Zachrisson, A. Oden, G. Johannsson, Premature mortality in patients with Addison's disease: a population-based study. J. Clin. Endocrinol. Metab. **91**, 4849–4853 (2006)
5. J.W. Tomlinson, N. Holden, R.K. Hills, K. Wheatley, R.N. Clayton, A.S. Bates, M.C. Sheppard, P.M. Stewart, Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. Lancet. **357**(9254), 425–431 (2001)
6. S. Bensing, L. Brandt, F. Tabaroj, O. Sjoberg, B. Nilsson, A. Ekbom, P. Blomqvist, O. Kampe, Increased death risk and altered cancer incidence pattern in patients with isolated or combined autoimmune primary adrenocortical insufficiency. Clin. Endocrinol. (Oxf). **69**, 697–704 (2008)
7. S. Hahner, C. Spinnler, M. Fassnacht, S. Burger-Stritt, K. Lang, D. Milovanovic, F. Beuschlein, H.S. Willenberg, M. Quinkler, B. Allolio, High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. J. Clin. Endocrinol. Metab. **100**(2), 407–416 (2015)
8. S.C. Chapman, S. Llahana, P. Carroll, R. Horne, Glucocorticoid therapy for adrenal insufficiency: nonadherence, concerns and dissatisfaction with information. Clin. Endocrinol. (Oxf). **84**(5), 664–671 (2016)
9. A. Gargya, E. Chua, J. Hetherington, K. Sommer, M. Cooper, Acute adrenal insufficiency: an aide-memoire of the critical importance of its recognition and prevention. Intern. Med. J. **46**(3), 356–359 (2016)
10. B. Allolio, Extensive experience in endocrinology: adrenal crisis. Eur. J. Endocrinol. **172**, R115–R124 (2015)

11. S. Hahner, M. Loeffler, B. Bleicken, C. Drechsler, D. Milovanovic, M. Fassnacht, M. Ventz, M. Quinkler, B. Allolio, Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new prevention strategies. Eur. J. Endocrinol. **162**(3), 597–602 (2010)
12. B. Odenwald, U. Nennstiel-Ratzel, H.G. Dörr, H. Schmidt, M. Wildner, W. Bonfig, Children with classic congenital adrenal hyperplasia experience salt loss and hypoglycemia: evaluation of adrenal crises during the first 6 years of life. Eur. J. Endocrinol. **174**(2), 177–186 (2016)
13. L.C. Smans, E.S. Van der Valk, A.R. Hermus, P.M. Zelissen, Incidence of adrenal crisis in patients with adrenal insufficiency. Clin. Endocrinol. (Oxf). **84**(1), 17–22 (2016)
14. K. Ritzel, F. Beuschlein, A. Mickisch, A. Osswald, H.J. Schneider, J. Schopohl, M. Reincke, Clinical review: outcome of bilateral adrenalectomy in Cushing's syndrome: a systematic review. J. Clin. Endocrinol. Metab. **98**, 3939–3948 (2013)
15. N. Reisch, M. Willige, D. Kohn, H.P. Schwarz, B. Allolio, M. Reincke, M. Quinkler, S. Hahner, F. Beuschlein, Frequency and causes of adrenal crises over lifetime in patients with 21-hydroxylase deficiency. Eur. J. Endocrinol. **167**(1), 35–42 (2012)
16. G. Meyer, K. Badenhoop, R. Linder, Addison's disease with polyglandular autoimmunity carries a more than 2.5-fold risk for adrenal crises: German Health insurance data 2010-2013. Clin. Endocrinol. (Oxf). **85**(3), 347–353 (2016)
17. L. Papierska, M. Rabijewski, Delay in diagnosis of adrenal insufficiency is a frequent cause of adrenal crisis. Int J Endocrinol **2013**, 482370 (2013)
18. S. Gidlöf, H. Falhammar, A. Thilén, U. von Döbeln, M. Ritzén, A. Wedell, A. Nordenström, One hundred years of congenital adrenal hyperplasia in Sweden: a retrospective, population-based cohort study. Lancet Diabetes Endocrinol. **1**(1), 35–42 (2013)
19. R.L. Rushworth, D.J. Torpy, A descriptive study of adrenal crises in adults with adrenal insufficiency: increased risk with age and in those with bacterial infections. BMC. Endocr. Disord. **14**, 79 (2014)
20. J.S. Bromberg, E.J. Alfrey, C.F. Barker, K.D. Chavin, D.C. Dafoe, T. Holland, A. Naji, L.J. Perloff, L.A. Zellers, R.A. Grossman, Adrenal suppression and steroid supplementation in renal transplant recipients. J. Transpl. **31**, 385–390 (1991)
21. K. White, W. Arlt, Adrenal crisis in treated Addison's disease: a predictable but under-managed event. Eur. J. Endocrinol. **162**(1), 115–120 (2010)
22. World Health Organisation: International statistical classification of diseases and health related problems, 10th Revision (ICD 10). Geneva: WHO (2011)
23. S.R. Bornstein, B. Allolio, W. Arlt, A. Barthel, A. Don-Wauchope, G.D. Hammer, E.S. Husebye, D.P. Merke, M.H. Murad, C. A. Stratakis, D.J. Torpy, Diagnosis and treatment of primary adrenal insufficiency: An Endocrine Society Clinical Practice Guideline. J. Clin. Endocrinol. Metab. **101**(2), 364–389 (2016)
24. T.H. Puar, N.M. Stikkelbroeck, L.C. Smans, P.M. Zelissen, A.R. Hermus, Adrenal crisis: still a deadly event in the 21(st) century. Am. J. Med. **129**(3), 339.e1–e9 (2016)
25. I.J. Elenkov, R.L. Wilder, G.P. Chrousos, E.S. Vizi, The sympathetic nerve—an integrative interface between two supersystems: the brain and the immune system. Pharmacol. Rev. **52** (4), 595–638 (2000)
26. R.C. Andrews, O. Herlihy, D.E. Livingstone, R. Andrew, B.R. Walker, Abnormal cortisol metabolism and tissue sensitivity to cortisol in patients with glucose intolerance. J. Clin. Endocrinol. Metab. **87**(12), 5587–5593 (2002)
27. J.E. Zimmerman, A.A. Kramer, D.S. McNair, F.M. Malila, Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. Crit. Care. Med. **34**(5), 1297–1210 (2006)
28. D. Naik, K.F. Jebasingh, N. Thomas, Delayed diagnosis of graves' thyrotoxicoisis presenting as recurrent adrenal crisis in primary adrenal insufficiency. J. Clin. Diagn. Res **10**(4), OD20–OD22 (2016)
29. R.L. Rushworth, D.J. Torpy, Adrenal insufficiency in Australia: is it possible that the use of lower dose, short-acting glucocorticoids has increased the risk of adrenal crises? Horm. Metab. Res **47**(6), 427–432 (2015)
30. A.A. Nofal, I. Bancos, K. Benkhadra, N.M. Ospina, A. Javed, Kapoor E, Muthusamy K, Brito JP, Turcu AF, Wang Z, Prokop L, Erickson DZ, Lteif AN, Natt N, Murad MH. Glucocorticoid replacement regimens in chronic adrenal insufficiency: a systematic review and meta-analysis. Endocr. Pract. (2016) Sep 15 [Epub ahead of print]
31 D.J. Torpy Glucocorticoid replacement in adrenal insufficiency; evaluating the evidence for optimal therapy. Endocr. Pract. (2016) On Line before print. doi:10.4158/EP161591.CO
32. Y. Reznik, Therapeutic innovations in endocrine diseases—Part 2: modified-release glucocorticoid compounds: what good do they provide to the adrenal insufficient patient? Presse. Med. **45**(6 Pt 2), e205–e210 (2016)
33. R.L. Rushworth, H. Falhammar, C.F. Munns, A.M. Maguire, D.J. Torpy, Hospitalisation in children with Congenital Adrenal Hyperplasia: the importance of younger age, viral infections and acute hypoadrenalism. Int. J. Endocrinol. (2016). doi:10.1155/2016/5748264
34. I.J. Elenkov, D.G. Iezzoni, A. Daly, A.G. Harris, G.P. Chrousos, Cytokine dysregulation, inflammation and well-being. Neuroimmunomodulation. **12**(5), 255–269 (2005)
35. S. Yang, L. Zhang, Glucocorticoids and vascular reactivity. Curr. Vasc. Pharmacol. **2**(1), 1–12 (2004)
36. M. Quinkler, P. Dahlqvist, E.S. Husebye, O.A. Kämpe, European emergency card for adrenal insufficiency can save lives. Eur. J. Intern. Med. **1**(1), 75–76 (2015)
37. S. Hahner, S. Burger-Stritt, B. Allolio, Subcutaneous hydrocortisone administration for emergency use in adrenal insufficiency. Eur. J. Endocrinol. **169**(2), 147–154 (2013)
38. R.L. Rushworth, C. Bischoff, D.J. Torpy, Preventing adrenal crises—home administered subcutaneous hydrocortisone is an option. Int. Med. Journal (in press)
39. B. Harbeck, S. Brede, C. Witt, S. Süfke, H. Lehnert, C. Haas, Glucocorticoid replacement therapy in adrenal insufficiency—a challenge to physicians? Endocr. J. **62**(5), 463–468 (2015)
40. D. Kampmeyer, H. Lehnert, H. Moenig, C.S. Haas, B. Harbeck, A strong need for improving the education of physicians on glucocorticoid replacement treatment in adrenal insufficiency: an interdisciplinary and multicentre evaluation. Eur. J. Intern. Med. S0953-6205(16), 30075–30079 (2016)
41. S. Hahner, N. Hemmelmann, M. Quinkler, F. Beuschlein, C. Spinnler, B. Allolio, Timelines in the management of adrenal crisis—targets, limits and reality. Clin. Endocrinol. (Oxf). **82**(4), 497–502 (2015)
42. M.A. Nenke, W. Rankin, M.J. Chapman, N.E. Stevens, K.R. Diener, J.D. Hayball, J.G. Lewis, D.J. Torpy, Depletion of high-affinity corticosteroid-binding globulin corresponds to illness severity in sepsis and septic shock; clinical implications. Clin. Endocrinol. (Oxf). **82**(6), 801–807 (2015)
43. E.J. Meyer, M.A. Nenke, W. Rankin, J.G. Lewis, D.J. Torpy, Corticosteroid-binding globulin: a review of basic and clinical advances. Horm. Metab. Res. **48**(06), 359–371 (2016)
44. K. Betito, J. Diorio, M.J. Meaney, P. Boksa, Adrenal phenylethanolamine *N*-methyltransferase induction in relation to glucocorticoid receptor dynamics: evidence that acute exposure to high cortisol levels is sufficient to induce the enzyme. J. Neurochem. **58**(5), 1853–1862 (1992)
45. H. Falhammar, H. Filipsson Nystrom, A. Wedell, M. Thoren, Cardiovascular risk, metabolic profile, and body composition in

adult males with congenital adcrenal hyperplasia due to hydroxylase deficiency. Eur. J. Endocrinol. **164**(2), 285–293 (2011)
46. E. Charmandari, G. Eisenhofer, S.L. Mehlinger, A. Carlson, R. Wesley, M.F. Keil, G.P. Chrousos, M.I. New, D.P. Merke, Adrenomedullary function may predict phenotype and genotype in classic 21-hydroxylase deficiency. J. Clin. Endocrinol. Metab. **87**(7), 3031–3037 (2002)
47. H. Falhammar, H. Filipsson, G. Holmdahl, P.O. Janson, A. Nordenskjöld, K. Hagenfeldt, M. Thorén, Metabolic profile and body composition in adult women with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J. Clin. Endocrinol. Metab. **92**(1), 110–116 (2007)
48. H. Falhammar, H. Filipsson, G. Holmdahl, P.O. Janson, A. Nordenskjöld, K. Hagenfeldt, M. Thorén, Increased liver enzymes in adult women with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Endocr. J. **56**(4), 601–608 (2009)
49. K.S. Petersen, R.L. Rushworth, P.M. Clifton, D.J. Torpy, Recurrent nocturnal hypoglycaemia as a cause of morning fatigue in treated Addison's disease—favourable response to dietary management: a case report. BMC. Endocr. Disord. **15**, 61 (2015). doi:10.1186/s12902-015-0058-6
50. G. Meyer, A. Hackemann, J. Reusch, K. Badenhoop, Nocturnal hypoglycemia identified by a continuous glucose monitoring system in patients with primary adrenal insufficiency (Addison's disease). Diabetes Technol. Ther. **14**(5), 386–388 (2012)
51. M. Forss, G. Batcheller, S. Skrtic, G. Johannsson, Current practice of glucocorticoid replacement therapy and patient-perceived health outcomes in adrenal insufficiency—a worldwide patient survey. BMC. Endocr. Disord. **12**, 8 (2012). doi:10.1186/1472-6823-12-8
52. R.L. Rushworth, D.J. Torpy, Modern hydrocortisone replacement regimens in adrenal insufficiency patients and the risk of adrenal crisis. Horm. Metab. Res. **47**(9), 637–642 (2015)
53. G. Meyer, K. Neumann, K. Badenhoop, R. Linder, Increasing prevalence of Addison's disease in German females: health insurance data 2008-2012. Eur. J. Endocrinol. **170**, 367–373 (2014)
54. R.L. Rushworth, P. Slobodian, D.J. Torpy, Interruptions to supply of high-dose hydrocortisone tablets and the incidence of adrenal crises. Clin. Endocrinol. (Oxf). **83**(6), 999–1000 (2015)