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R Rushworth
University of Notre Dame Australia, louise.rushworth@nd.edu.au

D Torpy

H Falhammar

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Adrenal crises: perspectives and research directions

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

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

Corresponding author: R. Louise Rushworth; School of Medicine, The University of Notre Dame, 160 Oxford St, Darlinghurst, NSW 2010, Australia; E-mail: louise.rushworth@nd.edu.au; Tel.: + 61/2/8204 4450; Fax: + 61/2/9357 7680

Abstract

Adrenal crises (AC) are life-threatening complications of adrenal insufficiency (AI). These events have an estimated incidence of between 5 and 10 ACs/100 patient years (PY) and are responsible for some of the increased morbidity and excess mortality experienced by patients with AI. 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 AC at times of physiological stress, most commonly an infection. However, recent evidence has demonstrated that patient education does not prevent many AC events and the reasons for this are not fully understood. Furthermore, there is no widely accepted definition of AC. Without a validated AC definition it is difficult to interpret variations in the incidence of AC and determine the effectiveness of preventive measures. This article aims to review the clinical aspects of AC events; to explore the epidemiology; and to offer a definition for an AC and to offer a perspective on future directions for research into AC prevention.

1 Introduction

2 Adrenal crises (AC) are serious, life threatening complications of adrenal insufficiency (AI). These

3 acute episodes constitute one cause of the increased morbidity and mortality in AI [1-6], and account

4 for a substantial proportion of all AI deaths [1-4,6]. Most ACs occur in the context of exposure to a

5 physiological stressor, such as an infection or injury, when the concentration of cortisol in the circulation

6 is insufficient for requirements. However, knowledge of the physiological processes that contribute to

7 the development of ACs is incomplete and, furthermore, there is no agreed definition of an AC.

8 Education is a necessary and important component of AC prevention. All patients should be

9 instructed on stress dosing and parenteral glucocorticoid administration; carry a steroid dependency card;

10 and wear a Medicalert bracelet or similar identification. Despite these innovations, however, ACs

11 continue to occur even among patients who have been well educated in preventive strategies [7], and it is

12 not surprising that they are a major source of anxiety for patients and their families [8]. Frequent reports

13 of patients having problems accessing appropriate treatment for an AC are highly regrettable and

14 contribute to the difficulties in preventing ACs in treated AI [9,10].

15 AC prevention, therefore, continues to be an important conundrum in endocrinology and the

16 path towards a reduction in the incidence of these events remains uncertain. The objective of this

17 paper is to assess the current knowledge regarding ACs; review the definition of an AC in this context;

18 highlight areas where knowledge is deficient; and suggest topics for further investigation. In doing so,

19 we hope to encourage research that can address a number of outstanding issues, with the overall aim

20 of reducing the incidence of AC events in the future.

21

22

Incidence and Mortality

25 Estimates from a number of well-conducted studies utilizing various designs have demonstrated

26 that the incidence of AC is between 5 and 10 ACs/100PY in treated AI (Table 1) [7,10-15], with AC

27 events being somewhat more frequent in primary adrenal insufficiency (PAI) than secondary adrenal

28 insufficiency (SAI) [2,13,14,16]. The associated mortality rate from AC in treated AI is 0.5/100 PY [7].

29 However, not all AC related deaths occur in patients who have been diagnosed with AI, and a fatal AC

30 may be the first diagnosis of AI in some patients [17,18]. Among those with treated AI, AC related

31 deaths contribute substantially to the increased mortality rate experienced by patients [1-4], being

32 responsible for up to 15% of all deaths in autoimmune AI [1,4,6,10], and 42% of those in congenital

33 adrenal hyperplasia (CAH) [2]. Reassuringly though, AC related fatality in hospital is uncommon

34 (<1%), suggesting that access to timely treatment for an AC is largely successful [19]. Nevertheless,

35 problems of recognition of an AC as a cause of death are pervasive. While an AC may be missed as a

36 cause of death at any age, it is likely that this is more common among older patients who generally have

37 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: 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 (100mg IV stat followed by 200mg/24h given as a continuous infusion or frequent IV (or IM) boluses (50mg) every 6h, with subsequent doses tailored to the clinical response); intravenous fluids (generally normal saline (1000mL 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

74 clinically relevant with regards to immediate and longer-term management decisions and is also of

75 considerable significance to research into AC prevention.

76 The AC definitions used in research, particularly in studies that involve smaller cohorts and

77 the assessment of interventions, tend to be project specific and may be detailed in the study report

78 [7,13,15,21]. By comparison, studies using morbidity and mortality databases [4,16] use diagnoses

79 that have been coded according to the International Statistical Classification of Diseases and Related

80 problems (ICD-10-CM), where the rubric E27.2 - "Addisonian or adrenal crisis" (approximate

81 synonym of severe adrenal insufficiency) [22] denotes the diagnosis of an AC. However, there is no

82 detailed guidance given in the ICD-10-CM (or the previous ICD-9-CM) on the symptoms or signs that

83 define an AC [22] and, as a consequence, the incidence of this code in health-related datasets

84 represents the interpretation of the various clinical features of acute illness in AI by multiple doctors in

85 accordance with their own preferred AC definition.

86 In an attempt to identify a unifying definition of an AC, a number of authors have proposed

87 new versions, although none to date has been universally accepted [10]. The most recent of these was

88 included in the 2016 guidelines on PAI management, and mandates the presence of hypotension,

89 "marked acute abdominal symptoms and marked electrolyte abnormalities" [23]. While electrolyte

90 abnormalities are required in this particular definition, these are now believed to occur less often in an

91 AC than was previously thought, possibly resulting in an under-enumeration of true cases of AC and

92 adversely affecting the utility of this definition in practice [10]. Another definition classifies an AC as "a

93 major health impairment" and specifies the presence of at least two symptoms or signs, including but not

94 mandating, electrolyte abnormalities, and requiring the administration of glucocorticoid [7] (Table 2). A

95 grading system using levels of hospitalization to denote AC severity was added to this, which assists in

96 interpretation, but its validity may be affected by variation in the services provided by different

97 hospitals, particularly with regard to grades 2 and 3 (Table 2) [7]. It may also be confounded by other

98 factors, such as age and comorbidities, as older patients and those with significant coexisting illnesses

99 are likely to be admitted to hospital or an intensive care unit at a lower threshold of illness at each level

100 than healthier younger patients.

101 By comparison, the two remaining definitions are more general and do not mandate the presence

102 of specific features (Table 2). One describes an AC as "a sudden deterioration in a patient with known

103 AI" [24], while noting in the manuscript that, "the principal manifestation of AC is hypotension or

104 hypovolaemic shock" [24]. The other defines an AC as "an acute impairment of general health

105 requiring hospital admission and administration of intravenous saline and glucocorticoids in patients

106 with AI" [13]. It is noteworthy that this last definition and the one by Hahner *et al.* (2015) mention

107 glucocorticoid treatment (but not the resolution of symptoms following its administration) presumably

108 in an effort to minimize the likelihood of misclassification of other diseases as an AC. For the same

109 reason, and in an extension of this idea, Allolio (2015) included a rider on the original definition by

110 Hahner *et al.* (2015), described above, requiring that there be a resolution of symptoms following

111 administration of intravenous hydrocortisone [10].

112 　　　Despite these efforts directed towards developing a universal AC definition, none to date has

113 been accepted and each has strengths and weaknesses. For this reason, a new definition is proposed in

114 this review (Table 3). Like those already described, it follows the general principle of aiming to be clear

115 and easy to apply, whilst minimising measurement error by reducing false positives (milder

116 physiological aberrations being classified as an AC, which are prone to occur in definitions that are very

117 general) and false negatives (actual ACs being classified as milder forms of AI, when the required

118 features for diagnosis are overly stringent). Central to considerations around this definition was an

119 understanding that there is no particular feature of an AC that is diagnostic, and even a set of common

120 clinical features has limited specificity for the diagnosis. However, there is general acknowledgement

121 that haemodynamic disturbance is the central physiological aberration of an AC and, for this reason

122 hypotension (either absolute or relative) was mandated in this definition (Table 2).

123 　　　The other new aspect to this definition, like the addition of a demonstrated improvement after

124 glucocorticoid administration by Allolio (2015) to the original Hahner *et al* (2015) definition, is that

125 there needs to be a documented improvement in the patient's clinical status after the administration of

126 intravenous hydrocortisone. However, in this new definition a time frame for the improvement is

127 included to increase the validity of the AC diagnosis. This is supported on physiological grounds

128 because the pressor effects of hydrocortisone on blood pressure in the context of an AC are rapid,

129 probably reflecting the known effects of hydrocortisone on the peripheral vasculature, which can be

130 measured in vivo at the macro and microcirculation level (25,26). The exact time frame of the pressor

131 response in an AC has not been documented but clinical experience suggests that a response should be

132 seen within an hour. Longer periods would indicate that another cause for shock may be present, or

133 that the AC may have co-occurred with another severe illness, such as septic shock, which would affect

134 the apparent resolution of the AC.

135 　　　These extra criteria included in the proposed definition increase the likelihood that true AC

136 events are identified as such, and that other, less severe episodes of illness, which are nonetheless

137 important and significant in the context of AI management and surveillance, are not classified as an AC

138 but rather a milder form of illness, which we suggest can be denoted as "symptomatic AI". In addition, a

139 list of common features of an AC was also included in the present definition to assist in the diagnosis

140 (Table 2). Scores from established metrics of illness severity, such as APACHE [27] could also be used

141 to add information on the seriousness of an AC episode.

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143

144 **Risk factors**

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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, 30a]. 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 [31].

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

183 of AI patients who have persistently reduced well-being despite optimal replacement therapy and it is

184 possible that the unknown physiological factors which cause this phenomenon may be related to AC

185 risk, and this warrants further investigation.

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187 **Precipitating factors**
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189   An AC event can be precipitated by a number of factors, most commonly a physiological

190 stressor, such as an infection or injury. Indeed, infections are regarded as the most common

191 precipitants of an AC [7,10,11,19,24] and these can be both bacterial [13,19] and viral (especially in

192 children) [32]. An infection is a particularly potent AC precipitant because immunomodulation is

193 partly controlled by cortisol and, in an environment of insufficient circulating cortisol, excess pro-

194 inflammatory cytokines in the circulation can lead to the development of uncontrolled inflammation,

195 vasodilatation, impaired cardiac function, and shock [25,33]. These effects are amplified by the

196 absence of the facilitating role of cortisol on catecholamine action on the cardiovascular system (34).

197   Gastroenteritis is particularly hazardous in AI because vomiting and diarrhoea impair the

198 adequate absorption of glucocorticoids and also cause dehydration [10,24]. Emotional stress has been

199 cited as an AC precipitant but the underlying reasons for the association between psychological stress

200 and an AC are unknown and warrant further investigation. An abrupt discontinuation of

201 glucocorticoid therapy may also precipitate an AC, with or without a stressor. In addition, a

202 proportion of ACs, perhaps as many as 10%, has no identifiable precipitant [10].

203

204

205 **Prevention – is it possible?**
206

207   Clinically, the general approach to AC prevention involves a sequence of logical steps,

208 including: the administration of oral or parenteral glucocorticoids in increased doses when there is an

209 acute illness; the provision of glucocorticoid cover for surgical procedures, with doses varying

210 according to illness severity; avoidance of sudden withdrawal of glucocorticoid pharmacotherapy; the

211 use of a steroid card to inform practitioners of the glucocorticoid requirement for unwell patients [35];

212 and the use of a MedicAlert bracelet or similar to identify the patient as having AI when they are

213 unable to communicate.

214   Much of the success of AC prevention, however, relies on a patient's ability to take action to

215 avert the onset of an AC by recognizing an indicator of physiological stress, such as an infection, and

216 implementing stress dosing and/or self-administering parenteral glucocorticoids, where appropriate.

217 However, intensive patient education, which has long been considered the cornerstone of preventive

218 endeavors, does not appear to be sufficiently effective to enable many patients to take these steps

219 independently [10]. Indeed intensive education was not found to be more effective than routine

220 instruction in reducing the incidence of ACs in a recent trial [10]. Unsurprisingly, anxiety about ACs is

221 common [8] and may have a number of consequences including unnecessary attendance for medical care
222 when self-management at home is likely to be effective or inaction or delayed action in the face of a
223 significant and potentially life-threatening episode of illness.

224   One area of particular concern is the time that elapses between the onset of symptoms and the
225 initiation of parenteral therapy, a delay that is often due to a patient's reluctance or an inability to
226 transfer from oral stress doses to intramuscular injection of hydrocortisone, particularly in situations
227 where there are symptoms of vomiting and diarrhea, which impair the absorption of oral
228 glucocorticoids. Subcutaneous administration of hydrocortisone may address this problem, as this route
229 is more acceptable to patients than the intramuscular approach, and its use can be considered preferable
230 to a situation in which no parenteral hydrocortisone is given [10,36,37]. Recent research demonstrated
231 that while cortisol levels of greater than 1000 mmol/l from subcutaneous injection were reached more
232 slowly than through intramuscular injection, this was within an acceptable time limit among patients
233 with a BMI of less than 27 who were not in shock [36]. Another alternative in this situation may be
234 rectal hydrocortisone suppositories, providing there is no diarrhea [23,37]. Emergency self-care could be
235 improved by the introduction of a preloaded hydrocortisone syringe, which obviates the need for an
236 unwell patient to draw up and then inject hydrocortisone [10]. Unfortunately, this product is not
237 available and there are no current prospects for its introduction [10].

238   Other barriers to successful AC prevention relate to problems with health care delivery,
239 including inadequate levels of knowledge about AI/AC among clinicians [8,38,39]. Ignorance about
240 the importance of an AC as a medical emergency can result in patients communicating the need for
241 urgent treatment to hospital staff, only to be ignored or have the treatment refused, some with severe
242 consequences [9,10]. The ability of emergency service personnel to administer parenteral
243 glucocorticoids also varies between jurisdictions and delays may occur in the response to calls for
244 assistance by emergency services. Inadequate responsiveness of triaging systems in hospitals and poor
245 timeliness in the initiation of definitive treatment can also influence the outcome of acute illness in AI
246 patients [40].

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250 **Future directions**
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252   There are many issues that remain unresolved in the pursuit of AC event reduction and targeted
253 research may help in making progress towards this goal. Importantly, a number of aspects of AC
254 physiology are not yet understood and a suite of specifically designed research projects should assist in
255 improving the knowledge base. Among these is the need for a more thorough elucidation of the
256 physiological response to infection. It is thought that inflammatory cytokine induced HPA axis
257 activation occurs in combination with rapid cleavage of corticosteroid binding globulin (CBG) by
258 tissue elastases to enhance cortisol delivery to inflamed tissues [41]. CBG cleavage is an early feature

259   of this [42], and the cleavage is associated with increased cortisol secretion and reduced CBG

260   production. Consequent depletion of circulating CBG may contribute to inadequate cortisol supply to

261   inflamed tissues, resulting in heightened tissue damage, as cellular processes become overwhelmed by

262   unfettered NfKB activation [41]. However, the relative importance of these processes to the onset of

263   an AC has not been evaluated and research to determine the range of cytokine/CBG/circulating

264   hydrocortisone and catecholamine levels at the time of AC presentation, along with relevant

265   inflammatory markers is needed.

266   Cortisol is also involved in catalyzing the conversion of adrenomedullary noradrenaline to

267   adrenaline via the phenylethanolamine N-methyltransferase enzyme, the levels of which are known to

268   be low in AI (43). An adequate cortisol level is also required for adrenomedullary organogenesis and,

269   as a result, the loss of this conversion of noradrenaline to adrenaline may be more pronounced in

270   congenital forms of AI, such as CAH [44,45]. It is possible that insufficient concentrations of

271   circulating adrenaline may contribute to the tendency to vascular collapse in AI. However, the relative

272   contribution of both adrenaline and noradrenaline to the onset and progression of an AC is unknown

273   and should be the subject of further research.

274   It is also not known whether an AC event occurs in the context of a complete deficiency of

275   circulating glucocorticoid or a relative deficiency, where the level of circulating glucocorticoid is lower

276   than the concentration that is required for the degree of physiological stress imposed by an illness. There

277   have not been studies conducted to examine this issue, largely because of the temporal disconnect

278   between the determination of serum levels of glucocorticoids and their tissue action. However, this is of

279   considerable importance and warrants further examination.

280   Another area that is worthy of further exploration is the interrelationship between AI and

281   glucose metabolism. It has been shown that morning glucose levels are lower in AI patients [45-47],

282   and recent evidence has demonstrated that occult nocturnal hypoglycaemia can occur in adults with AI

283   [48,49]. The underlying mechanism for this is likely to involve reduced nocturnal gluconeogenesis

284   during an overnight fast, a process that is partially dependent on glucocorticoids. However,

285   sympathoneural responses may become impaired in AI patients with recurrent nocturnal

286   hypoglycaemia and this may increase the predilection to, or severity of, AC events. For this reason, it

287   would be valuable to assess the frequency of hypoglycaemic events in patients who experience

288   frequent ACs, as one important element of an investigation into the reasons underlying some patients'

289   apparent predisposition to ACs.

290   In an extension of this idea, a comprehensive investigation into the variability in the apparent

291   propensity to AC between patients may uncover other factors that influence the risk of AC, such as a

292   vulnerability to hypoglycaemia, mentioned earlier, and this may be of potential benefit to all patients.

293   The underlying risk factors, precipitants and responses to stressors among patients who have repeated

294   episodes of AC should be assessed relative to those in a comparator group who do not have frequent

295 ACs, so that any physiological, management, personal or psychological factors that may act to increase

296 the AC risk can be identified.

297 A number of epidemiological aspects of AC also require further research and it is important

298 that, where possible, any methodological limitations of the studies are addressed. Generally, studies on

299 AC are either cohort studies of small patient groups or population-based studies linking records from

300 registers or other databases. Typically, cohort studies conducted on samples of patients offer the

301 detailed information on treatment and risk factors but may be affected by selection bias, as the study

302 subjects are often drawn from specialized clinics, offering lower levels of generalizability than well-

303 conducted population based studies [7,14,15]. Surveys of unselected patients, on the other hand,

304 including those that use convenience samples of patients recruited from AI support groups have lower

305 levels of validity and usually are affected by selection bias [8,21,50]. Measurement error is also likely to

306 be present in any study that relies on patient self-report of an AC, although independent record review

307 may help to minimize the misclassification of AI/AC that is inherent in this approach [15].

308 By comparison, population-based disease registers can be linked with other databases, such as

309 hospital admission and mortality records, to provide estimations of AC incidence and mortality [1,2,4].

310 Alternatively, morbidity databases can be examined to detect changes in incidence that may not be

311 apparent in a clinical setting, although these sources of information tend to contain fewer clinical details

312 and may have lower levels of reliability for key data items than well-maintained registers [21,51].

313 Ongoing monitoring of AC events using these data is important for the prevention of ACs, and is

314 particularly relevant given that changes in AI management, such as the transition from higher to lower

315 doses of glucocorticoid replacement therapy, can be initiated without the benefit of a randomized trial.

316 Changes in incidence are more likely to be identified earlier through ongoing surveillance than in an

317 individual clinic setting.

318 Trends in incidence can be assessed and age and sex specific rates or statistical modeling may be

319 used to determine whether a change is widespread in a patient population or is concentrated in a

320 subgroup(s) of patients. Such analyses of population-based data have recently uncovered a number of

321 new patterns in AC/AI incidence. A recent Australian study found an increase in hospital admissions for

322 AC between 2000 and 2012 and another on the same dataset identified geographic variations in AC

323 incidence [29,51]. Another study in Germany, reported higher AC incidence rates in patients with the

324 autoimmune polyendocrine syndrome (APS)/PAI [16], and a separate analysis in the same population

325 noted an increase in the incidence of PAI in women [52]. A further study on Australian patients found

326 a previously undetected increase in hospital admissions for AC during an interruption to the supply of

327 20-mg hydrocortisone tablets [53].

328 This new information illustrates the valuable contribution made by the analysis of incidence data

329 towards the understanding of the epidemiology of AC but it is noteworthy to remember that the value of

330 such analyses may be diminished by inconsistencies in the definition of AC. Coding errors or the

331 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.

Compliance with Ethical Standards:

12

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