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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 Rushworth¹, David J. Torpy², Henrik Falhammar^{3,4,5}

¹School of Medicine, Sydney, The University of Notre Dame, NSW, Australia; ²Endocrine and Metabolic Unit, Royal Adelaide Hospital and University of Adelaide, Adelaide, SA, Australia; ³Department of Endocrinology, Metabolism and Diabetes, Karolinska University Hospital, Stockholm, Sweden; ⁴Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; ⁵Menzies 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.

Keywords adrenal insufficiency · incidence · risk factors · morbidity · mortality

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

23 **Incidence and Mortality**

24

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.

38 **Diagnosis and Clinical Considerations**

39

40 Although there is no universally accepted definition of an AC, there is general agreement
41 regarding its underlying pathophysiology and clinical presentation. Briefly, ACs are acute disturbances
42 of physiology that happen when the circulating levels of adrenal steroid hormones are insufficient for
43 physiological requirements. Haemodynamic compromise, manifest primarily by hypotension, is the
44 cardinal physiological disturbance of an AC. Other symptoms and signs include: nausea; vomiting;
45 abdominal pain; fever; and delirium. Biochemical abnormalities comprising: hyponatraemia,
46 hyperkalaemia, hypoglycaemia (usually in children), and hypercalcaemia may also be present [10].

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

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

67

68

69 **Definition**

70

71 Despite consensus on the range of clinical features that comprise an AC, problems persist in
72 both its definition and identification. There is no universally accepted definition of an AC and the
73 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.

142

143

144 **Risk factors**

145

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

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

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

176 There are also other, as yet unknown, factors that appear to potentiate the AC risk in some
177 patients [10]. As has been mentioned, it is recognized that there is a subgroup of patients that has a
178 tendency to develop ACs and can experience multiple episodes. In contrast, other patients can be
179 observed for many years without an AC event, despite being at risk of an AC due to underlying AI. The
180 reasons for these differences in individual susceptibility to AC are not yet understood and this is an
181 important area of weakness in the current knowledge, as delineation of this predisposition could facilitate
182 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.

186
187 **Precipitating factors**
188

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 nmol/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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Future directions

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

332 morbidity data, although the extent to which this affects individual datasets is unknown. It is also
333 possible that the use of new indices may assist in a more thorough determination of trends in the severity
334 of admissions for AC and AI. These may include use of an AC/AI ratio as a way of assisting in the
335 interpretation of changes in presentation while controlling for possible fluctuations in baseline disease
336 rates.

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

343
344

345 **Conclusion**

346
347 Despite considerable efforts to reduce the health burden of ACs, these events continue to cause
348 morbidity and mortality, and are source of considerable anxiety for patients and their families. Research
349 studies have increased our understanding of the elements of an AC but many important aspects remain
350 unresolved. As a consequence, progress towards a reduction in the occurrence of ACs is at best
351 incremental and often disappointing. Outstanding issues variously relate to AC physiology, uncertain
352 and inconsistent AC definitions applied by multiple clinicians in different settings, and apparent failures
353 to pursue rigorous investigation of variations in predisposition to AC events in patient sub-groups,
354 among others. Available education strategies are logical and certainly useful in preventing or aborting
355 episodes but the apparent failure of education strategies to change the incidence of AC in treated AI
356 highlights the necessity for new ideas and approaches to AC prevention. The use of self-administered
357 subcutaneous parenteral hydrocortisone holds promise but strong confirmatory evidence for its benefit in
358 situations of incipient AC is lacking. Development of a preloaded syringe, comparable to the Epipen®,
359 which can be used to administer the dose of hydrocortisone may be useful but appears to have
360 insufficient support from industry or government for its introduction.

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363

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366

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368

369 **Compliance with Ethical Standards:**

370
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372
373 Conflict of Interest:

374
375 R. Louise Rushworth declares that she has no conflict of interest.

376 David J. Torpy declares that he has no conflict of interest.

377 Henrik Falhammar declares that he has no conflict of interest

378
379
380 Ethical approval: This article does not contain any studies with animals performed by any of the
381 authors.

382
383 Ethical approval: This article does not contain any studies with human participants or animals
384 performed by any of the authors.

385
386
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388 **References**

389 1. Erichsen MM, Lovas K, Fougner KJ, Svartberg J, Hauge ER, Bollerslev J, Berg JP, Mella B,
390 Husebye ES. Normal overall mortality rate in Addison's disease, but young patients are at risk of
391 premature death. *Eur J Endocrinol*, 2009;160:233-237.

392 2. Falhammar H, Frisé L, Norrby C, Hirschberg AL, Almqvist C, Nordenskjöld A, Nordenström A,
393 Increased mortality in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *J*
394 *Clin Endocrinol Metab*, 2014;99(12):E2715-21.

395 3. Burman P, Mattsson AF, Johannsson G, Höybye C, Holmer H, Dahlqvist P, Berinder K, Engström
396 BE, Ekman B, Erfurth EM, Svensson J, Wahlberg J, Karlsson FA. Deaths among adult patients with
397 hypopituitarism: hypocortisolism during acute stress, and de novo malignant brain tumors contribute
398 to an increased mortality. *J Clin Endocrinol Metab*, 2013;98(4):1466-75.

399 4. Bergthorsdottir R, Leonsson-Zachrisson M, Oden A, Johannsson G. Premature mortality in patients
400 with Addison's disease: a population-based study. *J Clin Endocrinol Metab*, 2006;91:4849-4853.

401 5. Tomlinson JW, Holden N, Hills RK, Wheatley K, Clayton RN, Bates AS, Sheppard MC, Stewart
402 PM. Association between premature mortality and hypopituitarism. West Midlands Prospective
403 Hypopituitary Study Group. *Lancet*, 2001;357(9254):425-31.

404
405 6. Bensing S, Brandt L, Tabaroj F, Sjoberg O, Nilsson B, Ekblom A, Blomqvist P, Kampe O. Increased
406 death risk and altered cancer incidence pattern in patients with isolated or combined autoimmune
407 primary adrenocortical insufficiency. *Clin Endocrinol (Oxf)*, 2008;69:697-704.

408
409 7. Hahner S, Spinnler C, Fassnacht M, Burger-Stritt S, Lang K, Milovanovic D, Beuschlein F,
410 Willenberg HS, Quinkler M, Allolio B. High incidence of adrenal crisis in educated patients with
411 chronic adrenal insufficiency: a prospective study. *J Clin Endocrinol Metab*. 2015;100(2):407-16.

412
413 8. Chapman SC, Llahana S, Carroll P, Horne R. Glucocorticoid therapy for adrenal insufficiency:
414 nonadherence, concerns and dissatisfaction with information. *Clin Endocrinol (Oxf)*. 2016;84(5):664-
415 71.

416
417 9. Gargya A, Chua E, Hetherington J, Sommer K, Cooper M. Acute adrenal insufficiency: an aide-
418 memoire of the critical importance of its recognition and prevention. *Intern Med J*. 2016;46(3):356-9.

419
420 10. Allolio B. Extensive Experience in Endocrinology: Adrenal Crisis. *Eur J Endocrinol*
421 2015;172:R115–R124.
422
423 11. Hahner S, Loeffler M, Bleicken B, Drechsler C, Milovanovic D, Fassnacht M, Venz M, Quinkler
424 M, Allolio B. Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new
425 prevention strategies. *Eur J Endocrinol*. 2010;162(3):597-602
426
427 12. Odenwald B, Nennstiel-Ratzel U, Dörr HG, Schmidt H, Wildner M, Bonfig W.
428 Children with classic congenital adrenal hyperplasia experience salt loss and hypoglycemia:
429 evaluation of adrenal crises during the first 6 years of life. *Eur J Endocrinol*. 2016;174(2):177-86.
430
431 13. Smans LC, Van der Valk ES, Hermus AR, Zelissen PM. Incidence of adrenal crisis in patients
432 with adrenal insufficiency. *Clin Endocrinol (Oxf)*. 2016;84(1):17-22
433
434 14. Ritzel K, Beuschlein F, Mickisch A, Osswald A, Schneider HJ, Schopohl J, Reincke M. Clinical
435 review: Outcome of bilateral adrenalectomy in Cushing's syndrome: a systematic review. *J Clin*
436 *Endocrinol Metab*. 2013;98:3939-3948.
437
438 15. Reisch N, Willige M, Kohn D, Schwarz HP, Allolio B, Reincke M, Quinkler M, Hahner S,
439 Beuschlein F. Frequency and causes of adrenal crises over lifetime in patients with 21-hydroxylase
440 deficiency. *Eur J Endocrinol*. 2012;167(1):35-42
441
442 16. Meyer G, Badenhoop K, Linder R. Addison's disease with polyglandular autoimmunity carries a
443 more than 2.5-fold risk for adrenal crises: German Health insurance data 2010-2013. *Clin Endocrinol*
444 *(Oxf)*. 2016; 85(3):347-53.
445
446 17. Papierska L, Rabijewski M. Delay in diagnosis of adrenal insufficiency is a frequent cause of
447 adrenal crisis. *Int J Endocrinol*. 2013;2013:482370
448
449 18. Gidlöf S, Falhammar H, Thilén A, von Döbeln U, Ritzén M, Wedell A, Nordenström A. One
450 hundred years of congenital adrenal hyperplasia in Sweden: a retrospective, population-based cohort
451 study. *Lancet Diabetes Endocrinol*. 2013;1(1):35-42.
452
453 19. Rushworth RL, Torpy DJ. A descriptive study of adrenal crises in adults with adrenal
454 insufficiency: increased risk with age and in those with bacterial infections. *BMC Endocr Disord*.
455 2014 Oct 1;14:79.
456
457 20. Bromberg JS, Alfrey EJ, Barker CF, Chavin KD, Dafoe DC, Holland T, Naji A, Perloff LJ, Zellers
458 LA, Grossman RA. Adrenal suppression and steroid supplementation in renal transplant recipients. *J*
459 *Transplantation* 1991;31:385-390.
460
461 21. White K, Arlt W. Adrenal crisis in treated Addison's disease: a predictable but under-managed
462 event. *Eur J Endocrinol*. 2010;162(1):115-20.
463
464 22. World Health Organisation: International Statistical Classification of Diseases and Health Related
465 Problems, 10th Revision (ICD 10). Geneva: WHO; 2011.
466
467 23. Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke
468 DP, Murad MH, Stratakis CA, Torpy DJ. Diagnosis and Treatment of Primary Adrenal Insufficiency:
469 An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*, 2016;101(2):364-89.
470
471 24. Puar TH, Stikkelbroeck NM, Smans LC, Zelissen PM, Hermus AR. Adrenal Crisis: Still a Deadly
472 Event in the 21(st) Century. *Am J Med*. 2016;129(3):339.e1-9.
473

- 474 25. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve--an integrative interface
475 between two supersystems: the brain and the immune system. *Pharmacol Rev.* 2000;52(4):595-638.
476
- 477 26. Andrews RC, Herlihy O, Livingstone DE, Andrew R, Walker BR. Abnormal cortisol metabolism
478 and tissue sensitivity to cortisol in patients with glucose intolerance. *J Clin Endocrinol*
479 *Metab.* 2002;87(12):5587-93.
480
- 481 27. Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health
482 Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Crit Care*
483 *Med.* 2006;34(5):1297-10.
- 484 28. Naik D, Jebasingh KF, Thomas N. Delayed Diagnosis of Graves' Thyrotoxicosis Presenting as
485 Recurrent Adrenal Crisis in Primary Adrenal Insufficiency. *J Clin Diagn Res,* 2016;10 (4):OD20-2.
- 486 29. Rushworth RL, Torpy DJ. Adrenal Insufficiency in Australia: Is it Possible that the Use of Lower
487 Dose, Short-Acting Glucocorticoids has Increased the Risk of Adrenal Crises? *Horm Metab Res.*
488 2015;47(6):427-32.
489
- 490 30. Nofal AA, Bancos I, Benkhadra K, Ospina NM, Javed A, Kapoor E, Muthusamy K, Brito JP,
491 Turcu AF, Wang Z, Prokop L, Erickson DZ, Lteif AN, Natt N, Murad MH. Glucocorticoid
492 replacement regimens in chronic adrenal insufficiency: a systematic review and meta-analysis.
493 *Endocr Pract.* 2016 Sep 15.
494
- 495 30a Torpy DJ. Glucocorticoid replacement in adrenal insufficiency; evaluating the evidence for
496 optimal therapy. *Endocr Pract* Sept 2016; On Line before print. DOI: 10.4158/EP161591.CO
497
- 498 31. Reznik Y. Therapeutic innovations in endocrine diseases - Part 2: Modified-release glucocorticoid
499 compounds: What good do they provide to the adrenal insufficient patient? *Presse Med.* 2016 Jun;45(6
500 Pt 2):e205-10.
501
- 502 32. Rushworth RL, Falhammar H, Munns CF, Maguire AM, Torpy DJ. Hospitalisation in children
503 with Congenital Adrenal Hyperplasia: the importance of younger age, viral infections and acute
504 hypoadrenalism. *International Journal of Endocrinology,* 2016(2); DOI: 10.1155/2016/5748264
- 505 33. Elenkov IJ, Iezzoni DG, Daly A, Harris AG, Chrousos GP. Cytokine dysregulation, inflammation
506 and well-being. *Neuroimmunomodulation.* 2005;12(5):255-69
507
- 508 34. Yang S¹, Zhang L. Glucocorticoids and vascular reactivity. *Curr Vasc Pharmacol.* 2004;2(1):1-
509 12.
510
- 511 35. Quinkler M, Dahlqvist P, Husebye ES, Kämpe O A European Emergency Card for adrenal
512 insufficiency can save lives. *Eur J Intern Med.* 2015;1(1):75-6
513
- 514 36. Hahner S, Burger-Stritt S, Allolio B. Subcutaneous hydrocortisone administration for emergency
515 use in adrenal insufficiency. *Eur J Endocrinol.* 2013;169(2):147-54
516
- 517 37. Rushworth RL, Bischoff C, Torpy DJ. Preventing adrenal crises – home administered
518 subcutaneous hydrocortisone is an option. (in press, *Int Med Journal*)
- 519 38. Harbeck B, Brede S, Witt C, Sufke S, Lehnert H, Haas C. Glucocorticoid replacement therapy in
520 adrenal insufficiency--a challenge to physicians? *Endocr J.* 2015;62(5):463-8.
521
- 522 39. Kampmeyer D, Lehnert H, Moenig H, Haas CS, Harbeck B. A strong need for improving the
523 education of physicians on glucocorticoid replacement treatment in adrenal insufficiency: An
524 interdisciplinary and multicentre evaluation. *Eur J Intern Med.* 2016 Apr 20. pii: S0953-

525 6205(16)30075-9.
526
527 40. Hahner S, Hemmelmann N, Quinkler M, Beuschlein F, Spinnler C, Allolio B. Timelines in the
528 management of adrenal crisis - targets, limits and reality. *Clin Endocrinol (Oxf)*. 2015;82(4):497-502.
529
530
531
532
533 41. Nenke MA, Rankin W, Chapman MJ, Stevens NE, Diener KR, Hayball JD, Lewis JG, Torpy DJ.
534 Depletion of high-affinity corticosteroid-binding globulin corresponds to illness severity in sepsis and
535 septic shock; clinical implications. *Clin Endocrinol (Oxf)*. 2015;82(6):801-7.
536
537 42. Meyer EJ, Nenke MA, Rankin W, Lewis JG, Torpy DJ. Corticosteroid-Binding Globulin: A
538 Review of Basic and Clinical Advances. *Horm Metab Res* 2016;48(06):359-371.
539
540 43. Betito K, Diorio J, Meaney MJ, Boksa P. Adrenal phenylethanolamine N-methyltransferase
541 induction in relation to glucocorticoid receptor dynamics: evidence that acute exposure to
542 high cortisol levels is sufficient to induce the enzyme. *J Neurochem*. 1992;58(5):1853-62.
543
544 44. Falhammar H, Filipsson Nystrom H, Wedell A, Thoren M. Cardiovascular risk, metabolic profile,
545 and body composition in adult males with congenital adrenal hyperplasia due to 21-hydroxylase
546 deficiency. *Eur. J. Endocrinol*. 2011;164(2), 285–293.
547
548 45. Charmandari E, Eisenhofer G, Mehlinger SL, Carlson A, Wesley R, Keil MF, Chrousos GP, New
549 MI, Merke DP. Adrenomedullary function may predict phenotype and genotype in classic 21-
550 hydroxylase deficiency. *J. Clin. Endocrinol. Metab*. 2002;87(7):3031-3037.
551
552 46. Falhammar H, Filipsson H, Holmdahl G, Janson PO, Nordenskjöld A, Hagenfeldt K, Thorén M.
553 Metabolic profile and body composition in adult women with congenital adrenal hyperplasia due to
554 21-hydroxylase deficiency. *J Clin Endocrinol Metab*. 2007;92(1):110-6.
555
556 47. Falhammar H, Filipsson H, Holmdahl G, Janson PO, Nordenskjöld A, Hagenfeldt K, Thorén M.
557 Increased liver enzymes in adult women with congenital adrenal hyperplasia due to 21-hydroxylase
558 deficiency. *Endocr J*. 2009;56(4):601-8.
559
560 48. Petersen KS, Rushworth RL, Clifton PM, Torpy DJ. Recurrent nocturnal hypoglycaemia as a
561 cause of morning fatigue in treated Addison's disease – favourable response to dietary management: a
562 case report. *BMC Endocrine Disorders* 2015 15:61 DOI: 10.1186/s12902-015-0058-6.
563
564 49. Meyer G, Hackemann A, Reusch J, Badenhoop K. Nocturnal hypoglycemia identified by a
565 continuous glucose monitoring system in patients with primary adrenal insufficiency (Addison's
566 disease). *Diabetes Technol Ther*. 2012;14(5):386–8.
567
568 50. Forss M, Batcheller G, Skrtic S, Johannsson G. Current practice of glucocorticoid replacement
569 therapy and patient-perceived health outcomes in adrenal insufficiency - a worldwide patient survey.
570 *BMC Endocr Disord*. 2012 Jun 13;12:8. doi: 10.1186/1472-6823-12-8.
571
572 51. Rushworth RL, Torpy DJ. Modern Hydrocortisone Replacement Regimens in Adrenal
573 Insufficiency Patients and the Risk of Adrenal Crisis. *Horm Metab Res*. 2015;47(9):637-42.
574
575 52. Meyer G, Neumann K, Badenhoop K, Linder R. Increasing prevalence of Addison's disease in
576 German females: health insurance data 2008-2012. *Eur J Endocrinol* 2014;170:367-373.
577
578 53. Rushworth RL, Slobodian P, Torpy DJ. Interruptions to supply of high-dose hydrocortisone
579 tablets and the incidence of adrenal crises. *Clin Endocrinol (Oxf)*. 2015;83(6):999-1000.

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580
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582
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584
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