




Adrenal Crisis – Definition, Prevention and Treatment: Results from a Delphi Survey

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ABSTRACT

Based on recent data, a total number of about 29 000 patients with adrenal insufficiency can be calculated for Germany, and about 1500 fatalities due to adrenal crises have to be expected within the next decade. Management of adrenal crises is still unsatisfactory. The objectives of this study were to establish consensus for diagnostic criteria, prevention strategies, and treatment recommendations for adrenal crises. The study was conducted from January 2022 to April 2023, using Delphi technique. Four rounds of questionnaires were sent to 45 experts, selected by a coordinating group on behalf of the adrenal section of the German Society of Endocrinology. The survey was implemented online using the REDCap web application. Responses were captured anonymously. During the Delphi process the expert panel developed diagnostic criteria to identify patients likely to have an adrenal crisis. Education about adrenal insufficiency among patients as well as non-endocrine medical personnel were regarded as highly important. It was suggested that recommendations for the management of adrenal insufficiency have to be simplified and made widely available. This study provides pragmatic strategies to identify and treat patients prone to adrenal crisis, thereby highlighting the need for an improved management of patients with adrenal insufficiency.

Introduction

Adrenal crisis is a potentially life-threatening complication in patients with adrenal insufficiency. It can occur when an acutely increased cortisol demand is not met by adequate cortisol supply. Inappropriate glucocorticoid adjustment in gastrointestinal or febrile infections, surgical procedures, intensive physical activity, major psychological or social stress and, occasionally, a so far undiagnosed adrenal insufficiency are common triggers of an adrenal crisis [1]. Several studies demonstrated a higher risk for adrenal crises as formerly assumed. A 2-year prospective follow-up of more than 400 patients with adrenal insufficiency detected a prevalence of 8.3 adrenal crises per 100 patient years [2]. Life-time risk of adrenal crisis was calculated at about 50% [3]. Patients with primary adrenal insufficiency are at higher risk than patients with secondary adrenal insufficiency with prevalence rates of 7.6 vs. 3.2 per 100 patient years as reported in a retrospective study [4].

Excess mortality has been shown in patients with primary [5, 6] as well as secondary adrenal insufficiency [7]. Adrenal crises substantially contribute to this excess mortality [8]. A large Swedish study demonstrated that 42% of all deaths among patients with congenital adrenal hyperplasia were due to adrenal crisis [9]. In the prospective study mentioned above, mortality of adrenal crisis was 6.3% [2]. It can therefore be concluded that 1 out of 200 adrenal insufficient patients will die from an adrenal crisis per year, whereby regional differences may exist. For Germany, a prevalence for adrenal insufficiency of about 348 per million has been determined, thereof 222 per million for secondary and 126 per million for primary adrenal insufficiency [4].

Based on these data, a total number of about 29 000 patients with adrenal insufficiency can be calculated for Germany, and about 1500 fatalities due to adrenal crises have to be expected within the next decade. Since there are measures to prevent and treat an adrenal crisis, this projection is deplorable and alarming.

In the last decade, several projects were carried out to improve prevention as well as awareness and treatment of adrenal crises. A standardized, pan-European emergency card for patients with adrenal insufficiency was introduced in 2014 by modifying the original Swedish emergency card [10–12]. This European Emergency card in a credit card format is nowadays available in multiple languages. The card bears an English text on one side and the same text in the patient's native language on the other. In the same year, the German Society of Endocrinology (Deutsche Gesellschaft für Endokrinologie, DGE) developed and implemented a nation-wide structured and certified educational program for patients with adrenal insufficiency and their relatives [13]. Beyond that, structured training programs and written information for medical staff and paramedics were developed or updated, respectively.

Despite these efforts, management of adrenal crises is still unsatisfactory. A German retrospective analysis demonstrated a delay above an accepted time limit between declaration of symptoms suspicious for an adrenal crisis and initiation of parenteral glucocorticoid treatment in over 40% of patients [14]. It has to be assumed that comparable outcome data could also be observed elsewhere in Europe.

The objectives of this study were to establish consensus for diagnostic criteria, prevention strategies, and treatment recommendations for adrenal crises, with the aim that in ten years no one will die from an adrenal crisis anymore.

Materials and Methods

Delphi technique was used for this consensus analysis [15]. This method uses a series of questionnaires sent to participants who were selected for their expertise in the management of adrenal insufficiency and adrenal crisis by a coordinating group (TD, SH, JH, MK, MQ, NR, NR, HSW, TK, GM) on behalf of the "Section for adrenal, steroids and hypertension" of the German Society of Endocrinology (Sektion Nebenniere, Steroide und Hypertonie der DGE). The process included 45 experts from 32 centers, including in the majority endocrinologists, but also intensive care physicians (n = 7), pediatric endocrinologists (n = 4), endocrine nurses and patient voices (n = 2), neurosurgeons (n = 2), endocrine surgeons (n = 1), as well as laboratory physicians (n = 1).

In total, this Delphi process required four rounds of questionnaires to reach an adequate consensus. First round of the survey comprised five group of themes (definition of adrenal crisis, current deficits, management by medical staff, measures of self-management by patients, future projects), including 20 items in total. In the second round, experts received a summary of the answers and comments provided in the first round, requesting their review. Third round enfolded a compilation of questions based on panelists' comments and eight adapted questions about topics where a consent could not be achieved by then. In the fourth round, four final items were forwarded, each regarding still pending consensus.

The survey was implemented online using REDCap, a secure web application for building and managing online surveys [16]. Responses were captured anonymously. Replies were monitored by two coordination group members (TK and GM). The study was conducted from January 2022 to April 2023. Response rates reached 78% in the first round, 55% in the second, 53% in the third and 58% in the final round of the survey.

Results

Definition of adrenal crisis

Experts agreed that objective criteria need to be identified that help patients, their families and medical staff to recognize adrenal crises (96% agreement in first round of questionnaire). To define adrenal crisis the criteria established by Allolio in 2015 were suggested [17]. According to this definition, an adrenal crisis is a major impairment of general health with at least two of the following signs/symptoms: arterial hypotension (systolic blood pressure < 100 mmHg), nausea or vomiting, severe fatigue, fever, somnolence, hyponatremia (≤ 132 mmol/l) or hyperkalemia, and/or hypoglycemia. In addition, parenteral glucocorticoid (usually hydrocortisone) must be administered, followed by clinical improvement. Although 86% of experts agreed with this definition in the first round of the questionnaire, numerous comments were raised demanding a further specification of this definition. Therefore, a different definition based on the experts' suggestions was developed (► **Table 1**). In addition, experts were reminded to base their decision on the intention to help non-endocrinologists, medical staff and emergency personnel not experienced with adrenal insufficiency and unsure about administration of glucocorticoids in case of an adrenal crisis. Keeping this goal in mind, in the final round of the questionnaire 65% of experts

▶ **Table 1** Definition of adrenal crisis.

Adrenal crisis must be considered if ≥ 1 type A criterion and ≥ 2 type B criteria can be applied:

Type A criteria:

- History of adrenal insufficiency or previous glucocorticoid therapy for other diseases
- Hyponatremia ≤ 132 mmol/l
- Hyperkalemia

Type B criteria:

- Severe weakness or fatigue
- Impaired consciousness
- Nausea and/or vomiting
- Fever
- Hypotension with systolic blood pressure ≤ 100 mmHg

preferred the revised definition in comparison to the definition by Allolio (35 %).

Current deficits

Without doubt, according to experts there is no sufficient access for patients and their families to structured education programs (agreement of 82 %). While most centers also do not have enough time for educating and instructing patients about adrenal insufficiency (73 % agreement), most of the experts estimate more than 60 % of their patients to be appropriately educated about their disease and emergency measures (61–80 % of patients in 38 % of experts' practices/clinics; 81–100 % of patients in 19 % of experts' practices/clinics). However, in 29 % of the experts' working institutions only 41–60 % of patients are estimated to be educated well, and 14 % of the experts estimated that only 21–40 % of their adrenal insufficient patients know about their disease and emergency measures. Importantly, while some experts work in the same institution, there may still be a different education level of the patients under their supervision. Therefore, subgroup differentiation was made per expert if several experts came from the same institution.

All experts agreed that patients with a diagnosis of adrenal insufficiency should be identifiable at any time by medical personnel (i. e., by a tag/note in an electronic patient record). They also believed that the European emergency card in its current form and content is sufficiently known (91 %). However, 29 % of experts believe that the European emergency card for adrenal insufficiency in its current form and content is not appropriate to improve emergency management. In the third round of the questionnaire, we therefore suggested according to the annotations of several experts, that the European emergency card should include a QR code with a link that provides information about treatment of adrenal crisis which 91 % of experts considered to be a valuable improvement. A majority (52 %) preferred the QR link to guide the user to the website of the German Society of Endocrinology, 29 % favored a website of the European Society of Endocrinology.

Management of adrenal insufficiency by medical staff

For improvement of adrenal crisis emergency management education of emergency personnel and paramedics was considered to have highest priority (91 %). Installing common standard operating procedures (SOPs) for download on the website of a (national) professional society was rated to be important, too (86 % categorized the latter measure as second highest priority). In comparison, having national or regional consulting services for endocrine emergencies (similar to poison control centers) and establishing specialized centers for endocrine emergencies (like a Chest Pain Unit) have minor priority according to experts (third priority for consulting services in 81 % and lowest priority for endocrine emergency centers in 81 %).

There is consent that each surgical center, which performs adrenalectomies should locally establish an interdisciplinary SOP for perioperative management in these patients (100 %). Furthermore, following pituitary surgery or radiotherapy, every patient should see a physician experienced in diagnosing adrenal insufficiency and also undergo a postinterventional dynamic stimulation test of the adrenal axis (within 3–6 months after surgery) for confirmation or exclusion of adrenal insufficiency (95 % agreement). Also, after an adrenal crisis, every patient should be seen by a physician experienced in diagnosing and educating patients on adrenal insufficiency (95 % agreement).

With respect to the management of febrile episodes occurring at home (sick day rule 1), experts regarded doubling (if fever $> 38^\circ\text{C}$) or tripling (if fever $> 39^\circ\text{C}$) of oral glucocorticoid until recovery (usually after 2–3 days) as appropriate (95 % agreement). If a patient is unable to tolerate oral medication (e. g., due to vomiting and/or diarrhea, trauma, high fever, or clinical deterioration) (sick day rule 2), 100 mg hydrocortisone should be given parenteral (i. e., intramuscular or subcutaneous (the latter off-label)) and health professionals should be contacted in case of initial self-treatment (91 % agreement).

There was consent on current recommendations about management of acute adrenal crisis (90 % agreement in second round of questionnaires): Patients should receive sufficient intravenous volume replacement and 100 mg hydrocortisone as an intravenous bolus injection followed by 200 mg hydrocortisone as a continuous infusion over 24 hours (for children dose adjustment according to body weight or body surface area). If hydrocortisone is not available, alternative glucocorticoids (i. e., prednisolone in a dosage of at least 25 mg) can be used for emergency treatment of acute adrenal crisis (agreement of 86 % to add this information in guidelines). In major surgery with general anesthesia, trauma, delivery, or disease that requires intensive care, 100 mg hydrocortisone as intravenous injection followed by continuous intravenous infusion of 200 mg hydrocortisone over 24 hours should be given (agreement of 91 % in second round of questionnaires). A large number of comments addressed the need for a more liberal approach to dosages of glucocorticoids in adrenal crisis. Therefore, in the final round of questionnaires there was consent that in patients with a longer history of adrenal insufficiency experienced physicians may suggest lower doses (in case of an adrenal crisis and major surgery) according to individual patient needs. This is also true for minor or moderate surgical stress where 100 mg hydrocortisone as an intravenous bolus should be given with the beginning of anesthesia

► **Table 2** Management of adrenal crisis and risk situations.

Management of an acute adrenal crisis	Sufficient intravenous volume replacement and 100 mg hydrocortisone as an intravenous bolus injection followed by 200 mg as a continuous infusion over 24 h *# (for children dose adjustment according to body weight or body surface area)
Major surgery with general anesthesia, trauma, delivery or disease that requires intensive care	100 mg hydrocortisone as intravenous injection followed by continuous intravenous infusion of 200 mg over 24 h *#
Minor or moderate surgical stress	100 mg hydrocortisone as an intravenous bolus given with the beginning of anesthesia *#
Minor surgical stress in local anesthesia (i. e., dermatological or dental procedures)	Doubling of usual oral glucocorticoid dosage
Management of illness with fever at home (sick day rule 1)	Doubling (if fever > 38 °C) or tripling (if fever > 39 °C) of oral hydrocortisone replacement dosing until recovery (usually after 2–3 days)
Inability to tolerate oral medication (vomiting and/or diarrhea, trauma, high fever and clinical deterioration) (sick day rule 2)	100 mg parenteral hydrocortisone; contacting health professionals in case of initial self-treatment#

* In patients with a longer history of adrenal insufficiency experienced physicians may suggest lower doses according to individual patient needs.; # If hydrocortisone is not available, alternative glucocorticoids (i. e., prednisolone in a dosage of at least 25 mg) can be used for emergency treatment of acute adrenal crisis.

(96% agreement). In minor surgical stress in local anesthesia (i. e., dermatological or dental procedures) doubling of usual oral glucocorticoid dosage is considered to be appropriate (100% agreement in third round of questionnaires). ► **Table 2** summarizes recommendations arising from this Delphi survey.

Measures for self-management of adrenal insufficiency and crisis

All patients with adrenal insufficiency have to be equipped with a standardized glucocorticoid emergency card and prescription for an additional supply of oral glucocorticoids as well as a hydrocortisone self-injection kit for emergency management (100%). All patients have to be educated in recognizing signs and symptoms of an adrenal crisis and in correct management of emergency events (sick day rules, training in hydrocortisone emergency self-injection (100%).

Bi-annual repetition of patient education was regarded unrealistic or inappropriate by 48% of experts. Therefore, experts agreed that repetition of patient education at least once yearly is a treatment goal (74% agreement).

Future projects

Experts were asked about the relevance of a (possibly mandatory) registry for the occurrence of adrenal crises in Germany/Europe to identify details in a structured manner (i. e., triggering factors, acute symptoms, latency from first symptoms until first contact with a physician or administration of glucocorticoids, convalescence). On a scale from 1 to 5, 20% considered such a platform as highly relevant (scale value 5; 36% for 4, 20% for 3 and 24% for 2). However, most experts would actively support such a registry (92%).

Discussion

During the last years progress has been made in treatment and management of patients with adrenal insufficiency. Educational

programs for patients and their families [13] as well as emergency equipment for situations with increased cortisol demand have contributed to this positive trend. However, adrenal crisis is still a major cause of death in patients with adrenal insufficiency and must not be missed [2]. Even more importantly, adrenal crisis can be prevented in many cases.

The Delphi technique used in the process of this survey has certain limitations as it represents the opinion of selected experts in the field. However, in rare diseases it needs experts to identify shortcomings of current patient care.

Despite guidelines on adrenal insufficiency [17–20], especially non-endocrinologists are often unsure about diagnosis of adrenal crisis, even when confronted with emergency cards about adrenal insufficiency from patients or the patients' relatives. Since most physicians and emergency personnel rarely encounter an adrenal crisis, there is a high risk it can be overlooked. In addition, there is often doubt about administration of glucocorticoids in situations where an infection can be the underlying cause of an adrenal crisis [21]. In fact, stress doses of short acting glucocorticoids (i. e., hydrocortisone or prednisolone) administered short-term, are not known to lead to relevant adverse events [20], but can be life-saving.

In 2015, Alolio suggested a definition of adrenal crisis that does not only address signs and symptoms of a crisis, but also demands parenteral glucocorticoid administration followed by clinical improvement [17]. The definition was developed from a scientific objective to investigate the incidence of adrenal crises prospectively [2]. Until then, no clear definition of adrenal crisis had been made, making research in this field difficult.

A large majority of our experts agreed with the definition by Alolio in our Delphi survey, but not without pointing out the definition's pitfalls. For scientific questions, a clear definition of what is regarded as adrenal crisis is important. Establishing a clear definition in this regard is challenging per se. Based on published definitions, for example, patients who died of a crisis because no glu-

cocorticoid was administered would not be counted, while patients who generously administered parenteral glucocorticoid for fear of a crisis would be counted. In the clinical setting, the definition of adrenal crisis seems less relevant than the identification of situations that pose a threat to patients with adrenal insufficiency and require appropriate action to prevent a severe course.

After reminding the experts that goal of this definition must be to not miss any adrenal crisis, two thirds of experts preferred our newly proposed definition compared to the original definition by Allolio (► **Table 1**). Its intention is to categorize situations where adrenal crisis is likely or very likely and where glucocorticoid administration must not be delayed. However, when a patient fails to improve, other causes of the clinical picture need to be considered. In contrast, for scientific objectives the definition by Allolio might be a more conclusive tool. Prospective studies will be needed to evaluate the value of our newly proposed definition in diagnosis of adrenal crisis and improvement of outcome.

There is no doubt that education of patients and their relatives is essential to prevent adrenal crises [13]. It empowers patients and families to act adequately in case of an impending adrenal crisis even when far away from an endocrine center. Patients need to be equipped with an emergency card (national and or international version) and with emergency medication such as glucocorticoid suppositories and/or glucocorticoid ampules [1].

During the last decade a structured nationwide educational program for patients with adrenal insufficiency has been established in Germany [13]. Today, this program is certified by the German Society of Endocrinology and is offered by more than 70 endocrine centers. Nevertheless, in the experts' opinion there is still a large discrepancy between the obvious need for patient education and its availability. While endocrinologists undertake considerable efforts to educate their patients, 43% of the experts estimated that only 21–60% of their patients have a good knowledge about their disease and emergency measures. This fits well with studies investigating into knowledge of patients who receive treatment at specialized centers [13, 22, 23]. Of course, our expert panel also included specialties that may not have direct and regular contact with adrenal insufficient patients or take part in education programs (i. e., laboratory medicine, intensive care medicine). However, only 9% of participants in the anonymous questionnaire declared not to be an endocrinologist. 72% of experts work in a university hospital or clinic and 32% in an outpatient clinic. Importantly, 96% of experts who answered the questionnaire declared that a structured patient training takes place in their center. Keeping this in mind, it is highly relevant that in most centers there is not enough time and resources for instructing and educating patients. One underlying reason may be that time and effort for educational programs in adrenal insufficiency is still not reimbursed by insurances in Germany, unlike for diabetes educational programs, for example. Accordingly, a biannual education of patients in recognizing adrenal crisis and acting appropriately seems too ambitious and may not be needed in all patients. An annual repetition is recommended, though.

For improvement of emergency management of adrenal insufficiency, it seems to be of utmost priority to involve emergency staff and paramedics in order to broaden knowledge about adrenal crisis. While the European emergency card is sufficiently known,

one third of our experts has doubts about its role in improving emergency management. Currently, it gives basic instructions for glucocorticoid stress dosing in case of an adrenal crisis, but does not provide further information on diagnosis of an adrenal crisis or management of situations with increased cortisol demand and risk to develop into a crisis [12]. In comparison, this information is given in the current form of the national emergency card by the German Society of Endocrinology [24, 25]. That is why a QR code implemented on the European emergency card and leading to official guidelines from the national Society of Endocrinology as suggested by our expert panel might add to the quality of emergency management of adrenal insufficiency. This could be of benefit especially in situations where medical staff not experienced with adrenal insufficiency is involved and simplified instructions are needed.

Instead of focusing on specialized centers that treat endocrine emergencies, experts generally agree that knowledge about adrenal insufficiency has to be spread widely in order to decrease mortality from adrenal crisis. In this light, there was a lively discussion during the Delphi process of how to simplify instructions for non-endocrinologists while still allowing individual approaches for patients and physicians that are experienced with the disease.

All patients with a history of adrenal crisis and after surgery or radiotherapy of the pituitary should be seen by a physician that is experienced with adrenal insufficiency and followed-up. In management of adrenal crisis, surgery that requires general anesthesia, trauma or delivery our expert panel largely agrees with current recommendations (► **Table 2**) [17, 18]. In minor surgical procedures that require only local anesthesia (such as dental or dermatological interventions) doubling of the usual oral glucocorticoid dosage is recommended. However, for patients with a long history of adrenal insufficiency and physicians very experienced with their patients' course of the disease, alternative doses may be recommended individually.

Conclusion

From this study diagnostic criteria have been developed to identify patients likely to have an adrenal crisis and to allow immediate initiation of emergency measures. Emergency management needs to be simplified in order to be applied by a broad field of national and international medical personnel as well as patients themselves. Recommendations and instructions evolving from our Delphi survey aim to be a pragmatic tool to recognize emergency situations and act appropriately. This will hopefully add to our declared goal that no more patients must die from an adrenal crisis.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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