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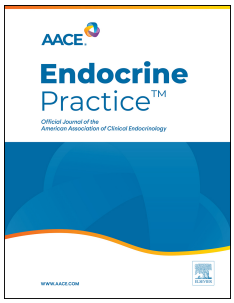

People with Adrenal Insufficiency who are in Adrenal Crisis are Frequently Unable to Self-Administer Rescue Injections

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Running title: Failed Emergency Injections in Adrenal Crisis

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ABSTRACT

Objectives: Individuals with adrenal insufficiency (AI) are at risk of acute adrenal crisis and death, particularly during illness or trauma, and may require rapid treatment with parenteral glucocorticoid such as hydrocortisone (HC) to manage a crisis. Current guidelines recommend timely self-injection in an evolving crisis. Little is known about the patient experience with emergency injections. We surveyed people with adrenal insufficiency regarding success with emergency injections.

Methods: In 2022 a survey was conducted through the National Adrenal Diseases Foundation website of individuals with AI or their caregivers about experience with managing an adrenal crisis. They reported on adrenal crisis events that required an emergency cortisol injection and the success or failure of the injection, context of the event and reasons for failure,

Results: Nearly half (41%) of adrenal insufficient patients were unable to self-administer an emergency glucocorticoid injection, citing effects of their crisis-associated illness and confusion as major barriers. Failed injections led to bad outcomes (sicker, need for hospitalization, or death) in 36% of cases.

Conclusions: Effective, timely, management of an impending adrenal crisis can prevent progression to hospitalization, multisystem failure requiring ICU care, and death. Reliance solely on patient self-injection may result in worse outcomes. Treating physicians should include patient education about injections and specific practical instruction in the technique, as well as the potential need for assistance in a crisis. FDA approval of a glucocorticoid auto injector, greater engagement with EMS clinicians, hospital emergency staff, and other healthcare professionals, are key for future success in managing adrenal crises.

Key words: adrenal crisis, emergency injections, hypotension, adrenal insufficiency, auto-injectors, education

INTRODUCTION:

Adrenal Insufficiency (AI) results from a complete or relative deficiency in the production and secretion of cortisol. Adrenal crisis is an acute hypotensive event and a severe manifestation of AI that requires rapid parenteral glucocorticoid administration. Adrenal crisis can be precipitated by various factors, including gastrointestinal illness~~,~~ emotional stress or other physical stresses resulting from surgery, illness, or infection [1-4]. This is due to the inability to upregulate the endogenous secretion of cortisol by the hypothalamic pituitary adrenal (HPA) axis to meet stress-related demands. The time course, evolution, and severity of an adrenal crisis are related to the magnitude of the biologic stress. An absolute definition of adrenal crisis may be elusive, but untreated it can be deadly, with risk of adrenal crisis estimated to be between 6 and 10 events per 100 patient-years, and risk of adrenal-crisis-associated death approximated to be 0.3 to 0.5 deaths per 100 patient years. The risk extends across all subtypes, ages, countries, and educational achievement [5-9]. Adrenal crisis represents a treatable variety of shock but continues to have frequent poor outcomes, likely due to complex system failures and inadequate understanding of the clinical situation. The recent death of an eight-year-old girl while on a commercial airline flight illustrates the rapid progression and potential bad outcome from failure to diagnosis and initiate early treatment of adrenal crisis. An excellent review of adrenal crises with comprehensive definitions, descriptions, and management was recently published [2]. Although sometimes considered rare, with an estimate of up to 200,000 people affected by various forms of adrenal insufficiency in the US, adrenal crisis events could be in the range of 20,000 cases per year.

Since an emergency self-injection is an uncommon requirement of a lay person to manage their health care, yet is a critical node in the care pathway for adrenal crisis, we

hypothesized that success in completing an injection would be an important factor in the ultimate outcome of crisis care. We conducted an online survey of a large, US-based patient advocacy group for individuals with AI and their caregivers regarding their experiences with emergency self-injection.

METHODS

An online survey was posted on the National Adrenal Diseases Foundation (NADF) website inviting patients with AI and their caregivers to provide feedback on their experience with emergency glucocorticoid injections. The survey was anonymous and no data were collected on the identity, location, or demographics of the respondents; nor was there confirmation of AI diagnosis. Participants were asked to state their status as: 1) an adult with AI > 18 years of age, 2) a caregiver, spouse, or friend of an adult with AI, 3) a child with AI <18 years of age, 4) a parent or other caregiver of a child with AI.

Institutional review board

This project was reviewed by an Institutional Review Board and determined to be exempt as "Not Human Subjects Research".

Data Collection

The survey, provided in the on-line supplement, consisted of seventeen questions and included two optional text field responses for additional comments about available hospital access and general experiences with adrenal crisis.

Data analysis

Respondents were grouped for analysis as patient or caregiver, and only adult respondents were included. Survey response data was analyzed using descriptive statistics. Continuous variables were described as mean and standard deviation. Categorical variables were

described as number n (%) and were analyzed using chi-squared tests, and *p* values less than 0.05 for a two-sided test were considered significant. Statistical analysis was performed using R version 4.4.0.[10]. Content analysis was used to analyze free text field comments to the open questions.

RESULTS

There were 670 individuals who responded to the survey on emergency injections; 657 responses were included for analysis. Respondents were categorized as patient with AI (n=566, 86%) or caregiver (n=91, 14%). Caregivers were further classified as caregiver for adult AI patient (n= 33) and caregiver for a child with AI (n= 66). Eight respondants reported overlap of caregiver for either adult or child and AI patient. For overlap respondants they were analyzed as caregivers.There was a strong overall female predominance (n=586, 89%) in the responses and a mean (standard deviation) age of 51.3 (13.8) years. The age range was 19 to 87 years; no responses were received from participants younger than 18 years. Demographics by group are provided in Table 1 and a diagram of included and excluded participants shown in the online supplement.

History of adrenal crisis and emergency injection

Approximately 75% (n=423) of patients reported a previous hospitalization or emergency room visit with an adrenal crisis, and 57% (n=377) overall of both groups of patients and caregivers reported needing to perform an emergency glucocorticoid injection to manage an adrenal crisis. More than a third of these 377 patient and caregiver respondents (n=140; 37%) stated they were unable to administer the injection when it was needed. Caregivers reported significantly greater proportionate success than patients at administering the emergency injection

[86% (49/57) vs 59% (188/320), p=0.0002)]. Caregivers of adults and children were very similar in their responses (Table 1)

Outcomes of completed and failed injections

Respondents were asked additional questions regarding outcomes depending on whether they were able to administer the needed emergency injection. Those able to administer the injection were asked whether the injection worked to stabilize the crisis situation. The completed injection was successful in stabilizing the crisis situation for 92% (n=218 events stabilized of 237 completed injections). Fifty of the 140 respondents (36%) who were unable to administer the emergency injection reported negative outcomes, such as patient became sicker, needed hospitalization, or died, from not being able to administer the injection. The combined unsuccessful group further reported which problems impeded them from completing the injection. The most frequently reported barrier to administering a glucocorticoid injection in a timely manner, which was unique to patients, was "confusion, feeling sick or difficulty thinking". Further barriers were: being alone and needing help with the process, concerns about the correct dose, and worrying about injection pain (Figure 1).

System Issues

In 75% of situations (280/367 responses) a hospital or emergency room was potentially available to the patient when an injection was being considered. Content analysis of text field responses to the question of why a prehospital injection was still needed included: 1. long distance to the facility (hours), 2. rapid progression of symptoms, 3. endocrinologist instructions to inject first then go to the hospital, 4. previous experience with delays in treatment at a hospital, and 5. previous experience that emergency staff lacked knowledge about adrenal crisis. Respondents were also queried about what they thought was the time during which they needed

to accomplish the injection. Options included "very short" 10-30 minutes, "medium" 30 minutes up to 2 hours, and "longer" more than 2 hours. Responses were: very short time period = 230, medium time period = 144 and longer time period = 25.

In addition to patient/caregiver problems with injections, content analysis of the text field for other comments about caring for an adrenal crisis identified additional issues. These included (Table 2) previous experience with delays in getting timely treatment, perception that providers had inadequate knowledge of how to treat an adrenal crisis, physician resistance to administering glucocorticoids, and lack of standardized protocols for emergency prehospital care including regulatory variation by city, county, and state within the US.

Importance of Patient Education

Of those who reported a need to administer an emergency injection, 25% (n=95) were not familiar with completing an emergency injection before the crisis situation (Table 1). More than half of all respondents (n=376, 58%), reported they had never had an opportunity to practice an emergency injection utilizing a syringe to draw the medication out of a vial. Those with successful injections had greater experience practicing injections (prior practice n=128, 68% vs. no prior practice n= 107, 58% in successful injections, p=0.053). Education for managing a crisis, including carrying an injection kit, was reported by 65% (n=426), although 8% (n=55) never carried an injection kit and 5% (n=34) had never received a prescription for an emergency injection kit. When asked where they learned to perform emergency injections, respondents identified: their healthcare team, (50%, n=322), independent research (37%, n=238), and the NADF website (17%, n=110) (Figure 2).

DISCUSSION

We found a disturbing failure rate for emergency injections of glucocorticoid in adrenal crisis, with 58% of patients and caregivers reporting that they needed to administer an emergency injection, but more than one third were unable to administer the injection. The most common reason that patients failed to administer the injection was due to the crisis itself, obstacles included the illness itself, confusion and a need for assistance to prepare the injection. Current, systematic reliance on patients to accomplish this complex task in the face of progressing illness is an unreliable care plan resulting in too many unsatisfactory outcomes. Within the survey sample, 36% (n=50) of those unable to administer the emergency injection reported there was a bad outcome (patient became sicker, needed hospitalization, or died) as a result. This worrisome statistic implies a serious patient safety problem for our health care system. Conversely, of those able to administer the emergency injection when needed, 94% (n=218) reported that the injection stabilized the crisis situation.

Caregivers of both adult and child AI patients were more successful than AI patients themselves in administering the emergency injection when it was needed, but we found that difficulties in emergency injections can be a barrier for both patients and caregivers. There are likely some circumstances with early crisis symptoms and a patient who is very comfortable with the process (perhaps medically trained) who can manage the injection, and can facilitate rapid care. Rapid injection is advantageous, as a previous study showed more rapidly completed self-injections were less likely to result in hospitalization [11]. However, the current method is excessively complex, requiring the patient or caregiver to depress the stopper on the SOLU-CORTEF® ACT-O-VIAL, agitate the vial to mix the liquid with the powder medication to create the solution, use a needle and syringe to extract the solution, and finally inject the solution

intramuscularly. In an acute setting, with the stress and cognitive impairment accompanying an adrenal crisis, it can be overwhelming.

New technologies such as glucocorticoid autoinjectors are an important and time-critical goal for future development that could address the need for rapid injections and minimize the difficulties of managing a complex process for both patients and caregivers. Similar devices are used to deliver epinephrine during anaphylaxis and glucagon for acute severe hypoglycemia [12]. Survey participants responded enthusiastically to the idea of an autoinjector. Of our respondents, 97% believed that having a prefilled automatic injector would have better allowed them to accomplish the injection. However, while autoinjectors are an important technology that are badly needed, they will not solve all of the issues. Some patients will require more extensive care in addition to the initial injection, including volume expansion, and subsequent diagnosis and treatment of the underlying cause of the crisis.

The majority of respondents reported that although they were familiar with administering an emergency injection, only 42% had had the opportunity to actually practice an emergency injection with needles and syringes. Our results showed that patient education mattered. Caregivers that practiced giving an emergency injection were more likely to successfully administer the injection than caregivers without previous practice. Guidelines suggest that patients and caregivers should be provided materials and educated on how to administer emergency injections [1], yet, only half of respondents learned how to perform emergency injections from their doctor or their staff, with 38% learning from their own research. Currently, there is a lack of standardized and disseminated educational curricula for managing the disease for patients and/or caregivers. Standardized education programs improve patient knowledge of

disease and adrenal crisis management, as well as increasing confidence in completing an emergency injection [5,13].

Health Care System

The current lack of autoinjector options and the potential severity of an evolving crisis point to a need for greater assistance from the emergency care system. As a relatively rare condition, emergency physicians and EMS clinicians often encounter difficulty in appropriately responding to acute adrenal crises.. Many endocrinologists recommend that their patients try to accomplish a first glucocorticoid self-injection before seeking additional care, to expedite the treatment and avoid the consequences of delay. Anecdotal and survey reports of prolonged treatment delays or complete failure to provide the needed glucocorticoid within an emergency room or hospital facilities, that result in ICU admissions or death, are disturbingly too common [14,15]. AI patients in crisis may also be under-treated in the prehospital or emergency room setting, in part, due to physicians' discomfort with a glucocorticoid injection [15]. Current guidelines do emphasize the importance of early injection and avoiding delays for diagnostic testing or other reasons [1]. The risk of administering an emergency injection is minimal and the consequence of inaction is well established. Failure to administer timely parenteral glucocorticoid treatments places the patient at risk for more severe crisis and progression to hypotension, shock, and ultimately multiorgan injury or death [8].

Within the EMS, hospital, and emergency room settings, recognition and acceptance of the patient history and the written treatment recommendations from treating endocrinologists should be viewed as valued data to save a life, and not as a limitation on physician autonomy. Delays in treatment when patients present with clear documentation of disease are not justified. There are ongoing efforts to provide AI patients with disease identifying bracelets, necklaces,

and wallet cards [16,17]. These items communicate that the wearing patient is "steroid dependent," and when presenting with symptoms of an adrenal crisis (Table 3), is in urgent need of glucocorticoids. In cases where rapid-acting hydrocortisone is unavailable, other glucocorticoids can be administered [1].

Emergency physicians and EMS clinicians may encounter patients who are aware they have adrenal insufficiency, carry an injection kit, and provide detailed instructions for emergency injections; but they may also encounter those who are confused and unable to effectively communicate their condition and needs. Additionally, it has been estimated that 50% of AI patients are initially diagnosed with AI as a result of an adrenal crisis and may have no information to provide EMS clinicians [18]. Many lives have been saved by astute diagnoses of adrenal insufficiency in the emergency setting, but retaining a high index of suspicion for AI is important. In the near term, the solution should be both standardized education programs and Electronic Medical Record (EMR) alerts with drug and dosing information to reduce the barriers to providing adequate care and meeting treatment guidelines.

Our survey and findings represent a large and important source of information on real-world patient experiences that can be used to improve care and outcomes. The study has some limitations due to its anonymous nature and internet basis that limited verification of disease status or diagnostic records. However, the robust number of respondents in the context of a rare disease, with consistent findings and familiarity with AI care, is an important source of information. Obtaining patient-centered data is essential to improving care and outcomes. In addition, the recruited participants were active in a large patient advocacy group that provides its members with extensive educational programs, and thus the injection expertise in the surveyed

group was likely to be greater than the general population of adrenal insufficient patients. A previous report from the United Kingdom found much lower rates (12%) of injection success [19].

Comprehensive Redesign of Care

A redesign of adrenal crisis care needs to address the spectrum of abilities and situations for patients and caregivers, and also address the severity of crisis, location of event, available resources, and patient response to initial treatment. Education about the condition and its treatment is central to this process for all stakeholders. Stakeholders in the redesign process should include endocrinologists, patient educators, patients, caregivers, emergency physicians, primary care providers, insurers, biopharmaceutical manufacturers, EMS clinicians, hospital and emergency room staff (including nurses), and hospital quality assessment staff. We have identified patient/caregiver difficulty with emergency injections, lack of consistent protocols for EMS clinicians, lack of knowledge across the emergency care system about the critical need for rapid treatment, and some apparent reluctance on the part of physicians to use a safe and effective treatment. The finding that patients and caregivers, as well as treating endocrinologists, often opt for prehospital emergency injections instead of immediate referral to hospital and emergency room care reflects both the importance of a rapid response to a crisis and also the real experiences of failed current care systems.

Adrenal insufficiency is also a hidden risk factor for the ever-expanding number of people who are treated with chronic, exogenous glucocorticoids for various conditions (respiratory, rheumatologic and other). Cancer immunotherapy, increasing prevalence of autoimmune conditions, and other drug-induced adrenal insufficiency are increasing the potential for adrenal crises. Emergency parenteral rapid-acting glucocorticoids should be administered as soon as possible for adrenal crisis. Delayed treatment can cause significant harm to patients and

strain the health care system; as ongoing and worsening hypotension and hypoglycemia lead to multiorgan failure and critical illness (8). Our data emphasize the urgency and importance of gathering the stakeholders to initiate the comprehensive redesign of emergency care for patients with adrenal insufficiency.

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TABLES

Table 1.

	Patient	Caregiver for adult	Caregiver for child
Number (n=657)	566	33	66
Age Mean (SD)	52.4 (13.9)	50.5 (14.1)	41.9 (9.5)
Sex (Female)	505 (90%)	23 (70%)	65 (94%)
History of adrenal crisis	423 (75%)	27 (81%)	59 (89%)
Injection needed event	320 (57%)	24	42
Successful injection	188 (60%)	20 (83%)	36 (85%)
Injection stabilized the crisis	174 (93%)	17 (94%)	34 (94%)
Failed injection	132 (41%)	4 (17%)	6 (14%)
Bad outcome after failed injection	48 (32%)	1/4 (25%)	2/6 (33%)
Reason: no kit	0	11 (2%)	0
Reason: could not mix	0	25 (5%)	2 (3%)
Reason: unsure of dose	1 (3%)	9 (2%)	0
Reason: worried about hurting	2 (6%)	28 (5%)	5 (7%)
Reason: patient confused	2 (6%)	97 (18%)	2 (3%)
Reason: needed help	1 (3%)	47 (9%)	1 (1%)
Had opportunity to practice injection prior to event	210 (40%)	20 (63%)	42 (62%)
Had teaching by MD or Staff	263 (49%)	18 (55%)	47 (68%)
Would an autoinjector better allowed you to perform the emergency injection (of successful injections n=236)	165 (91%)	19 (95%)	36 (100%)
Would an autoinjector allowed you to perform the emergency injection (of failed injections n=135)	113 (97%)	4 (100%)	6 (100%)
Hospital or emergency room was available at the time	232 (78%)	18 (78%)	32 (78%)
Do you typically carry an emergency injection kit as either a patient or caregiver?			
i. No, never. ii. Occasionally I will, if I am concerned about either injury or distance from medical care iii. I do usually carry an injection kit	55 117 426		

Table 2. Selected Text Comments About Managing an Adrenal Crisis or Your Experiences

Respondant 1	"The way our system works, paramedics can't do the injection and a patient can't get meds in the ER until seen by a doctor & meds have been prescribed, then prepared by pharmacist... which can take hours unless unconscious. "
Respondant 2	"Despite emergency documents, ER nurses/ doctors are often unaware."
Respondant 3	"Drs in the ER need more training especially regarding crisis symptoms."
Respondant 4	"A lot of E.R. docs are resistant to giving Solu-Medrol"

Table 3. Symptoms and Signs of Adrenal Crisis

Symptoms	Abdominal pain, nausea, vomiting Severe weakness and fatigue Myalgia, or cramping Confusion Syncope Postural dizziness Salt craving Back and leg pain
Signs	Hyperpigmentation (only in primary adrenal insufficiency) Reduced levels of consciousness, delirium, confusion Pyrexia Abdominal tenderness or guarding Hypotension – systolic <100 mm HG or ≥20 mm Hg lower than usual Tachycardia Loss of consciousness Agitation Hyponatremia Hyperkalemia (primary adrenal insufficiency - reduced aldosterone secretion)
	Absolute or relative hypotension – systolic <100 mm HG or ≥20 mm Hg lower than usual

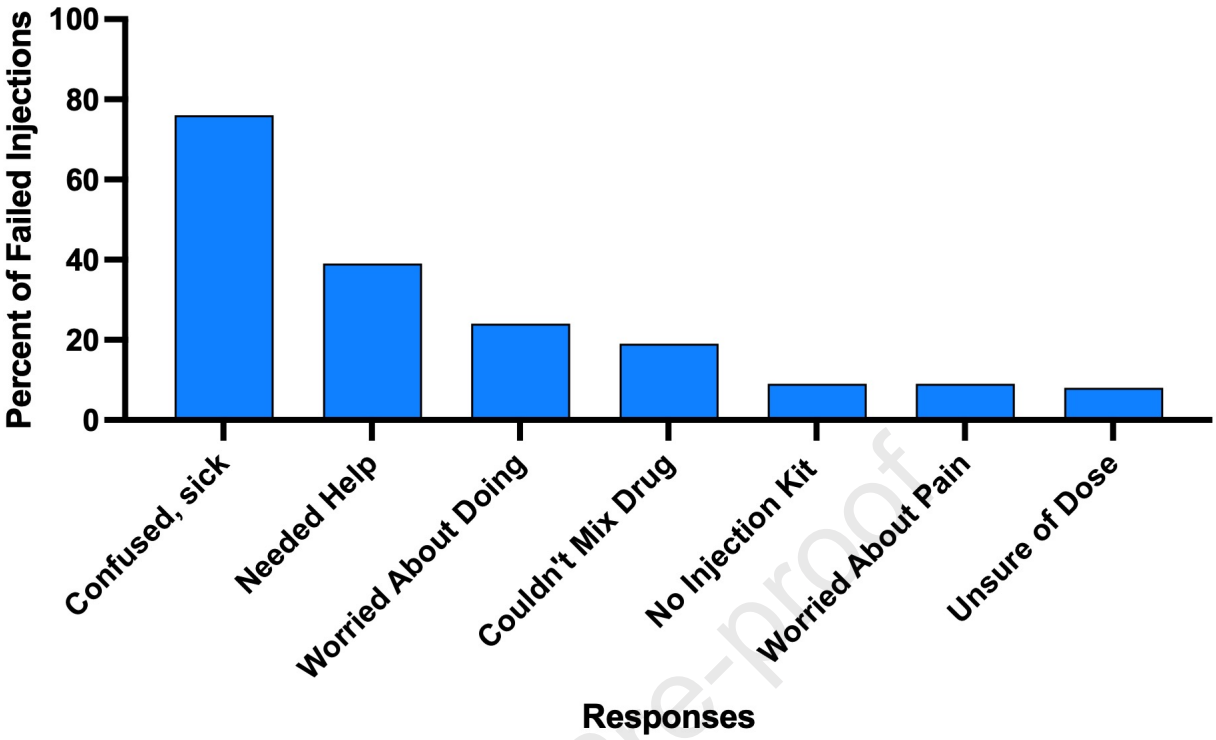
Figure Legends

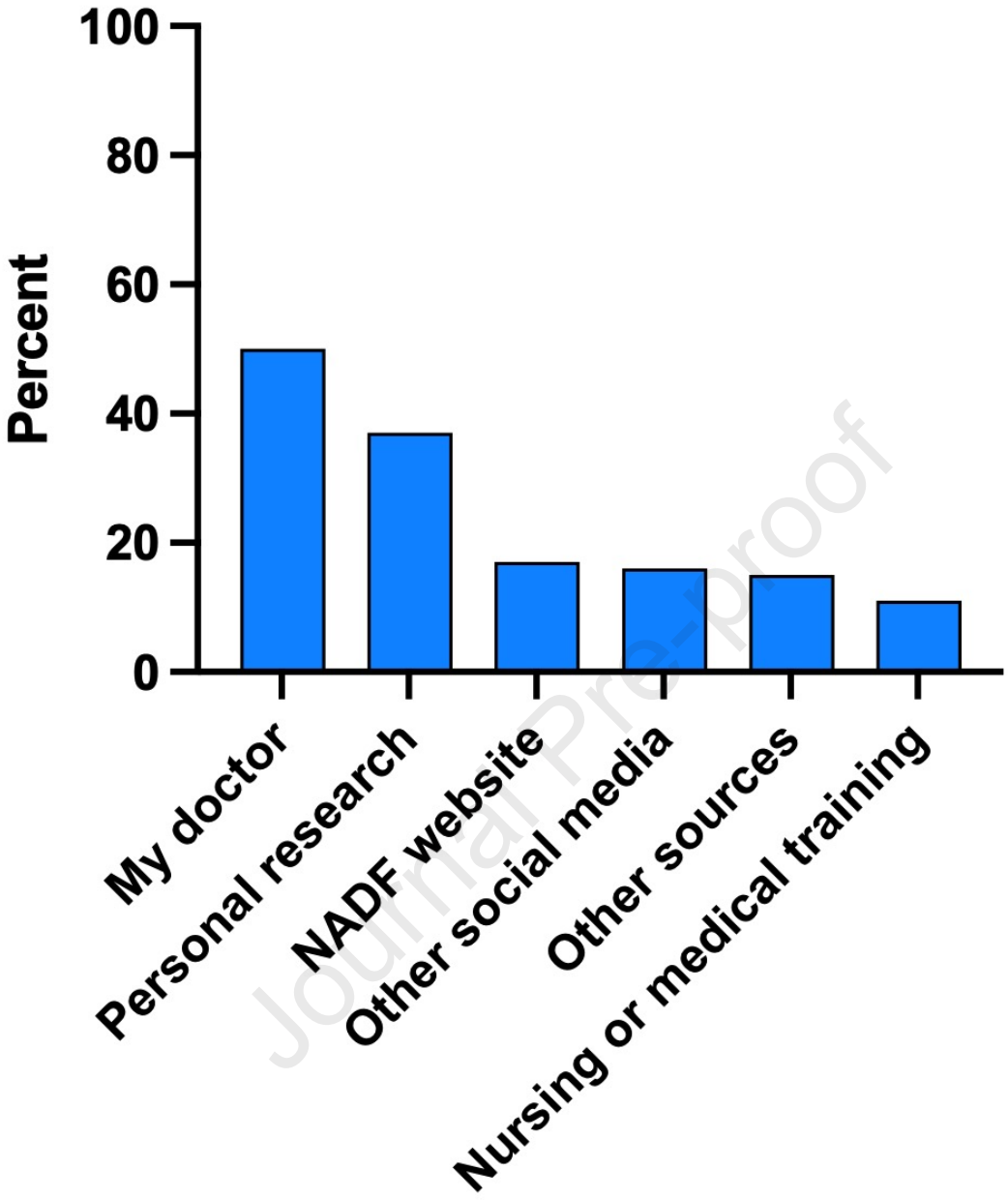
Figure 1. Patient and Caregiver Reported Barriers to Injection.

Patients were asked about problems that hampered their ability to administer an emergency injection. The most common response was that they were "confused, sick or having difficulty thinking due to the impending crisis". Additional responses also reflected specific impacts of the illness on their ability to perform an injection while in the situation of a crisis. Values shown were percent of the 140 respondents who reported they were unable to complete an emergency injection. More than one reason was permitted.

Figure 2. Educational sources for patients and caregivers for learning how to do an emergency injection.

The process to complete an emergency glucocorticoid injection involves multiple steps that are not commonly performed by non-medically trained people. In order to be prepared to perform an injection, current guidelines recommend that patients and caregivers be taught the process. Respondents were asked about whether they had received any teaching and what the source for the education was. About half had been taught by their treating endocrinologist or their staff, but sizable proportions had been left to seek the information from their own research and other sources. The figure shows percent of 647 respondents who identified an education source, and respondents were allowed to select more than one source.





Highlights:

Teaching points

Adrenal crisis is treatable variety of shock that is an ongoing risk for persons with adrenal insufficiency, and if not treated effectively can result in death or multisystem organ failure.

Emergency care may not be immediately available due to location of an acute injury or other precipitating factors leading to an adrenal crisis.

An emergency intramuscular or subcutaneous injection of cortisol by the patient or a caregiver is recommended by current treatment guidelines in order to manage or halt an evolving adrenal crisis.

Patient education regarding the risk of adrenal crisis and the recommended responses, including detailed teaching for emergency injections, is needed and should be reinforced annually.

Clinical Relevance
Patients in an adrenal crisis were often sick, or confused and failed to successfully complete a needed emergency injection, resulting in worse outcomes. Not all adrenal insufficiency patients were provided with prescriptions for injection kits (syringes, cortisol for injection and diluent if needed). More than half of patients had never practiced an injection. Those who had previous practice with injections had greater success in an emergency situation.

Declaration of Interest Statement

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Julia Anthony is Founder and Chief Strategy Officer for Solution Medical which is developing injector products for adrenal crisis treatment.