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# Journal Pre-proof

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

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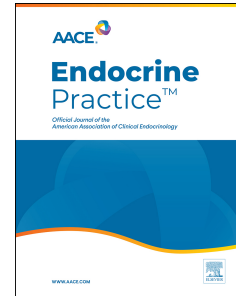
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## People with Adrenal Insufficiency who are in Adrenal Crisis are Frequently Unable to Self-Administer Rescue Injections

Running title: Failed Emergency Injections in Adrenal Crisis

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**1 ABSTRACT**

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

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

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

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

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

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**27 INTRODUCTION:**

28 Adrenal Insufficiency (AI) results from a complete or relative deficiency in the  
29 production and secretion of cortisol. Adrenal crisis is an acute hypotensive event and a severe  
30 manifestation of AI that requires rapid parenteral glucocorticoid administration. Adrenal crisis  
31 can be precipitated by various factors, including gastrointestinal illness, emotional stress or other  
32 physical stresses resulting from surgery, illness, or infection <sup>1-4</sup>. This is due to the inability to  
33 upregulate the endogenous secretion of cortisol by the hypothalamic pituitary adrenal (HPA) axis  
34 to meet stress-related demands. The time course, evolution, and severity of an adrenal crisis are  
35 related to the magnitude of the biologic stress. An absolute definition of adrenal crisis may be  
36 elusive, but untreated it can be deadly, with risk of adrenal crisis estimated to be between 6 and  
37 10 events per 100 patient-years, and risk of adrenal-crisis-associated death approximated to be  
38 0.3 to 0.5 deaths per 100 patient years. The risk extends across all subtypes, ages, countries, and  
39 educational achievement <sup>5-9</sup>. Adrenal crisis represents a treatable variety of shock but continues  
40 to have frequent poor outcomes, likely due to complex system failures and inadequate  
41 understanding of the clinical situation. The recent death of an eight-year-old girl while on a  
42 commercial airline flight illustrates the rapid progression and potential bad outcome from failure  
43 to diagnosis and initiate early treatment of adrenal crisis. An excellent review of adrenal crises  
44 with comprehensive definitions, descriptions, and management was recently published <sup>2</sup>.  
45 Although sometimes considered rare, with an estimate of up to 200,000 people affected by  
46 various forms of adrenal insufficiency in the US, adrenal crisis events could be in the range of  
47 20,000 cases per year.

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

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

## 54 **METHODS**

55 An online survey was posted on the National Adrenal Diseases Foundation (NADF)  
56 website inviting patients with AI and their caregivers to provide feedback on their experience  
57 with emergency glucocorticoid injections. The survey was anonymous and no data were  
58 collected on the identity, location, or demographics of the respondents; nor was there  
59 confirmation of AI diagnosis. Participants were asked to state their status as: 1) an adult with AI  
60 > 18 years of age, 2) a caregiver, spouse, or friend of an adult with AI, 3) a child with AI <18  
61 years of age, 4) a parent or other caregiver of a child with AI.

### 62 *Institutional review board*

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

### 65 *Data Collection*

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

### 69 *Data analysis*

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

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

## 77 **RESULTS**

78       There were 670 individuals who responded to the survey on emergency injections; 657  
79 responses were included for analysis. Respondents were categorized as patient with AI (n=566,  
80 86%) or caregiver (n=91, 14%). Caregivers were further classified as caregiver for adult AI  
81 patient (n= 33) and caregiver for a child with AI (n= 66). Eight respondents reported overlap of  
82 caregiver for either adult or child and AI patient. For overlap respondents they were analyzed as  
83 caregivers. There was a strong overall female predominance (n=586, 89%) in the responses and a  
84 mean (standard deviation) age of 51.3 (13.8) years. The age range was 19 to 87 years; no  
85 responses were received from participants younger than 18 years. Demographics by group are  
86 provided in Table 1 and a diagram of included and excluded participants shown in the online  
87 supplement.

### 88 ***History of adrenal crisis and emergency injection***

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

95 [86% (49/57) vs 59% (188/320),  $p=0.0002$ ]. Caregivers of adults and children were very  
96 similar in their responses (Table 1)

### 97 ***Outcomes of completed and failed injections***

98 Respondents were asked additional questions regarding outcomes depending on whether  
99 they were able to administer the needed emergency injection. Those able to administer the  
100 injection were asked whether the injection worked to stabilize the crisis situation. The completed  
101 injection was successful in stabilizing the crisis situation for 92% ( $n=218$  events stabilized of  
102 237 completed injections). Fifty of the 140 respondents (36%) who were unable to administer the  
103 emergency injection reported negative outcomes, such as patient became sicker, needed  
104 hospitalization, or died, from not being able to administer the injection. The combined  
105 unsuccessful group further reported which problems impeded them from completing the  
106 injection. The most frequently reported barrier to administering a glucocorticoid injection in a  
107 timely manner, which was unique to patients, was “confusion, feeling sick or difficulty  
108 thinking”. Further barriers were: being alone and needing help with the process, concerns about  
109 the correct dose, and worrying about injection pain (Figure 1).

### 110 ***System Issues***

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

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

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

### 127 *Importance of Patient Education*

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

### 139 **DISCUSSION**

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

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

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

164         New technologies such as glucocorticoid autoinjectors are an important and time-critical  
165 goal for future development that could address the need for rapid injections and minimize the  
166 difficulties of managing a complex process for both patients and caregivers. Similar devices are  
167 used to deliver epinephrine during anaphylaxis and glucagon for acute severe hypoglycemia <sup>12</sup>.  
168 Survey participants responded enthusiastically to the idea of an autoinjector. Of our respondents,  
169 97% believed that having a prefilled automatic injector would have better allowed them to  
170 accomplish the injection. However, while autoinjectors are an important technology that are  
171 badly needed, they will not solve all of the issues. Some patients will require more extensive care  
172 in addition to the initial injection, including volume expansion, and subsequent diagnosis and  
173 treatment of the underlying cause of the crisis.

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

184 disease and adrenal crisis management, as well as increasing confidence in completing an  
185 emergency injection <sup>5,13</sup>.

### 186 *Health Care System*

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

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



207 and wallet cards <sup>16,17</sup>. These items communicate that the wearing patient is “steroid dependent,”  
208 and when presenting with symptoms of an adrenal crisis (Table 3), is in urgent need of  
209 glucocorticoids. In cases where rapid-acting hydrocortisone is unavailable, other glucocorticoids  
210 can be administered <sup>1</sup>.

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

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

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

### 231 *Comprehensive Redesign of Care*

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

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

252 strain the health care system; as ongoing and worsening hypotension and hypoglycemia lead to  
253 multiorgan failure and critical illness (8). Our data emphasize the urgency and importance of  
254 gathering the stakeholders to initiate the comprehensive redesign of emergency care for patients  
255 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.	55		
ii. Occasionally I will, if I am concerned about either injury or distance from medical care	117		
iii. I do usually carry an injection kit	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 $\geq 20$ 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 $\geq 20$ mm Hg lower than usual

## Figure Legends

### **Figure 1. Patient and Caregiver Reported Barriers to Injection.**

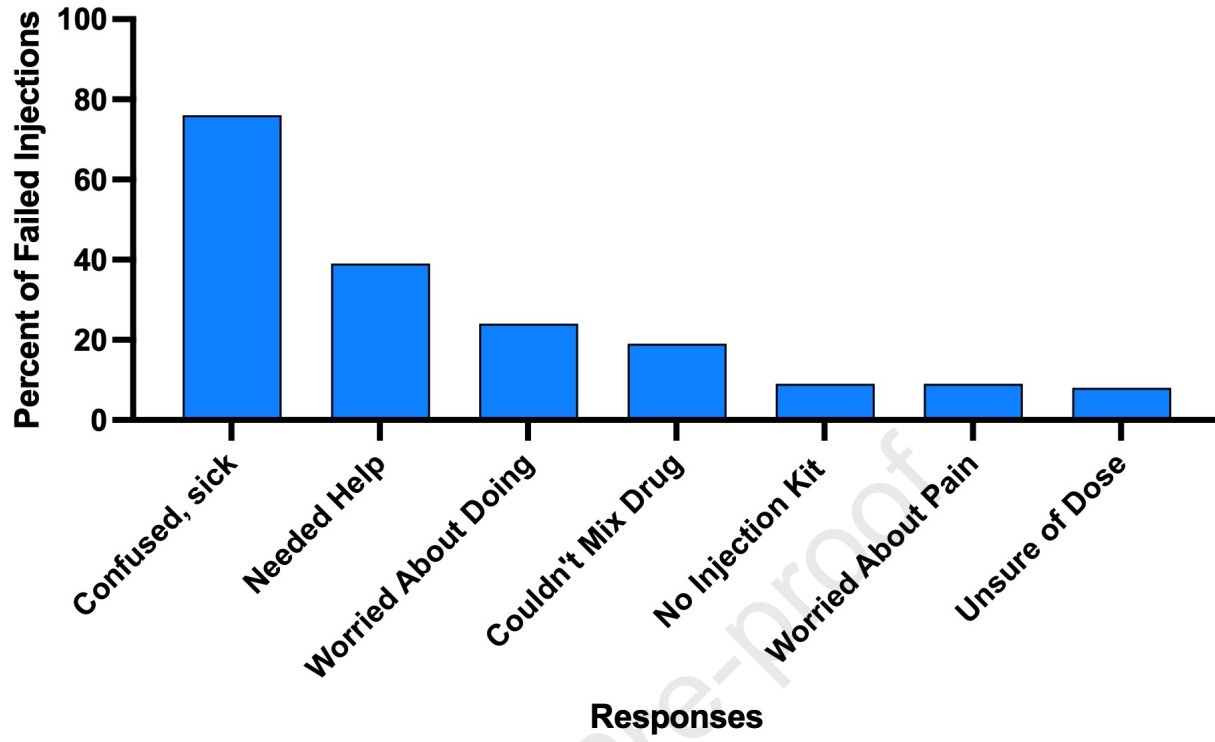
Patients were asked about problems that hampered their ability to administer an emergency injection. The most common response was that they were “confused, sick or having difficulty thinking due to the impending crisis”. Additional responses also reflected specific impacts of the illness on their ability 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.

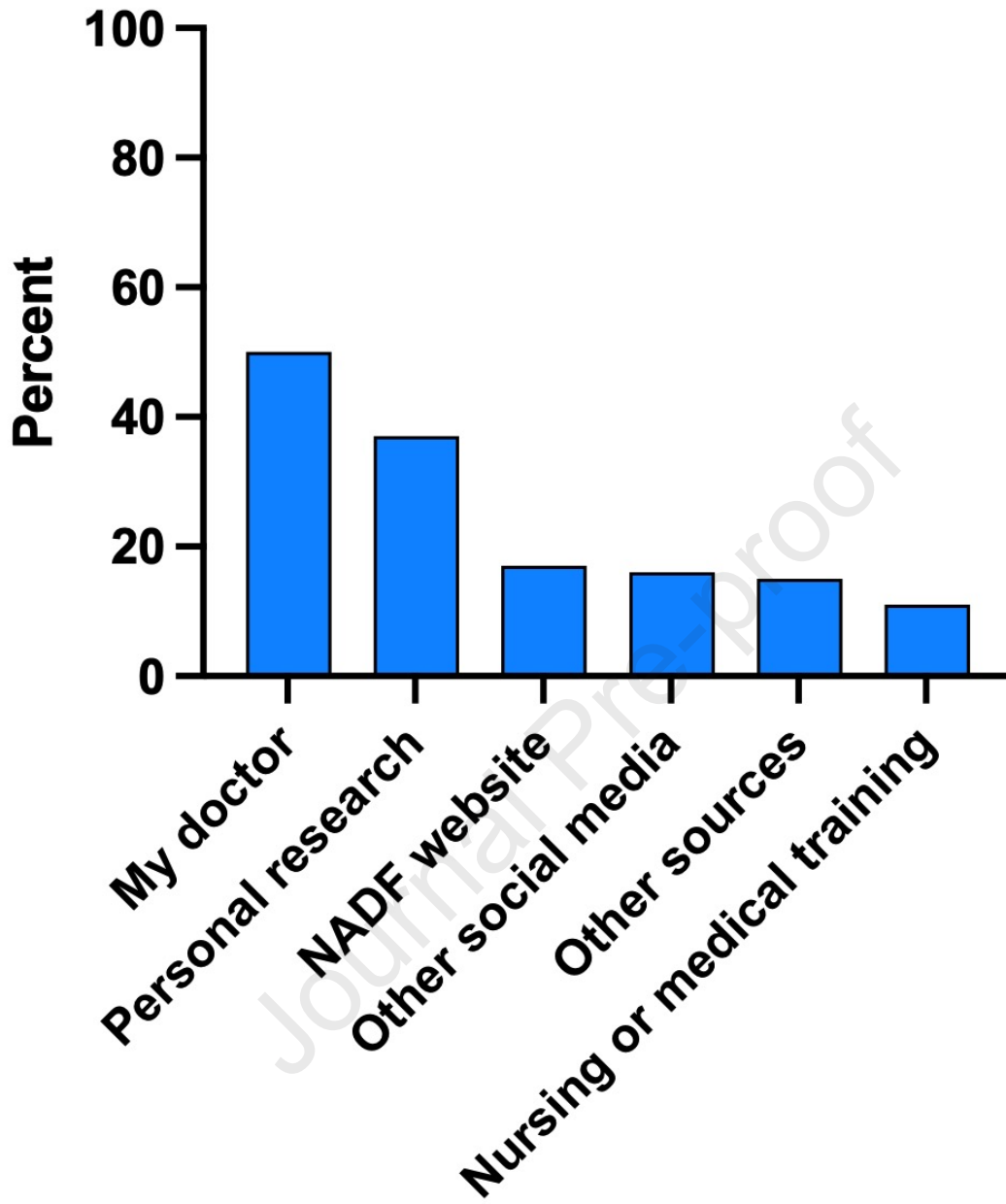
### **Figure 2. Educational sources for patients and caregivers for learning how to do an emergency injection.**

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.



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## 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.
- The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for this journal and was not involved in the editorial review or the decision to publish this article.
- 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.