



# Professional practices in the management of adrenal insufficiency in two tertiary referral hospitals (Tunis, Tunisia)

## Pratiques professionnelles de prise en charge de l'insuffisance surrénalienne dans deux hôpitaux de référence tertiaire (Tunis, Tunisie)

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### ABSTRACT

**Background:** Adrenal insufficiency (AI) is a rare and life-threatening disease. Glucocorticoid replacement therapy and patient education are crucial. Few is known about physician practice in this topic.

**Aims:** To describe physician practice in the management of AI and to identify the associated factors.

**Methods:** the physicians, all grades and specialties, from two university hospitals in Tunis, were invited to respond to a paper-based 16- multiple choice item-questionnaire about the management of AI and the prevention of acute AI. Each question was scored 1 if correct or 0 if incorrect. The global score was calculated by adding the score of the first 15 questions.

**Results:** 200 physicians responded to the questionnaire, sex ratio: 0.47, mean age:  $29.0 \pm 5.8$  years (24 - 60). The overall rate of correct answers was 59.6%. The rate of correct responses was good for the type of replacement therapy (92%), the lifelong duration of treatment (88%), the symptoms of overtreatment (73.5%), the type of diet indicated (77%), and the necessity of special measures during the peri operative period (100%). However, the rate of correct responses was low for the half-life of hydrocortisone (12.5%), biological signs suggesting acute AI (17.5%), situations during which an increase in the dose of glucocorticoid is required (26.5%) and the risks of intermittent fasting (2%). Endocrinology specialty and overall medical specialties were independently associated with a better global score.

**Conclusion:** physician practice in the management of AI need to be improved.

**Key words:** adrenal insufficiency; glucocorticoids; hormone replacement therapy; clinical practice; surveys and questionnaires; education.

### RÉSUMÉ

**Introduction :** l'insuffisance surrénale (IS) est une maladie rare et potentiellement mortelle. Le traitement substitutif par des glucocorticoïdes et l'éducation du patient sont cruciales. Cependant, peu de données sont disponibles sur les pratiques des médecins à ce sujet.

**Objectifs :** Décrire les pratiques des médecins dans la prise en charge de l'IS et identifier les facteurs associés.

**Méthodes :** les médecins, tous grades et spécialités confondus, de deux hôpitaux universitaires de Tunis, ont été invité à répondre à un questionnaire en format papier fait de 16 questions à choix multiples concernant la prise en charge de l'IS et la prévention de l'IS aigue. Les réponses ont été cotées 1 quand elles étaient correctes et 0 quand incorrectes. Le score global a été calculé en additionnant les scores des 15 premières questions.

**Résultats :** 200 médecins ont répondu au questionnaire, sex-ratio : 0,47, âge moyen :  $29,0 \pm 5,8$  ans (24 - 60). Le taux global de réponses correctes était de 59,6 %. Le taux de réponses correctes était bon pour le type de traitement substitutif (92%), la durée du traitement à vie (88%), les symptômes de surdosage (73,5%), le type de régime alimentaire indiqué (77%) et la nécessité de mesures particulières pendant la période péri-opératoire (100%). En revanche, le taux de réponses correctes était faible pour la demi-vie de l'hydrocortisone (12,5%), les signes biologiques suggérant une IS aigue (17,5%), les situations au cours desquelles une augmentation de la dose de glucocorticoïde est nécessaire (26,5%) et les risques du jeûne intermittent (2%). La spécialité en endocrinologie et les autres spécialités médicales étaient indépendamment associées à un meilleur score global.

**Conclusion :** les pratiques des médecins dans la prise en charge de l'IS doivent être améliorées.

**Mots clés :** insuffisance surrénalienne ; glucocorticoïdes ; traitement hormonal substitutif ; pratiques cliniques ; enquêtes et questionnaires ; éducation.

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## INTRODUCTION

Adrenal insufficiency (AI) is a life-threatening rare disease. Its prevalence is about 300 cases per million inhabitants [1-2]. The incidence of acute AI is about 4.4 to 17 per 100 patients per year with a mortality of 0.5% per 100 patient years [3-4]. Primary AI is caused by a destruction of the adrenal glands whereas secondary and tertiary AI are caused by a dysfunction of the pituitary gland or the hypothalamus. Adrenal insufficiency is characterized by a deficiency in glucocorticoids (GC) that is associated with a deficit in mineralo-corticosteroids in primary AI. The treatment consists of lifelong hormone replacement therapy. The aims of the management and monitoring of AI are to prevent over and under treatment complications and particularly acute AI and to restore a good quality of life [5-6]. Patient education is crucial and is generally performed by the endocrinologist. However, patients with AI might consult a general or any specialist practitioner for any other disease. Therefore, all practitioners should know about this disease, its risks, its treatment and how to prevent acute AI. Moreover, studies showed insufficient understanding of the patients regarding their disease and its management [7-9]. All this shows the importance of a well knowledge of AI by the practitioners. However, there is a lack of studies in this field and little is known about physicians' knowledge and practices regarding AI. The aims of this study were to describe physician practices in the management of AI and to identify the associated factors.

## METHODS

It is a cross sectional study conducted in the two main university hospitals of Tunis, la Rabta and Charles Nicolle, between September and November 2020. In each of these hospitals there is a department of endocrinology with hospitalization units and a specialized consultation. All physicians were invited to participate in the study. Physicians from all grades and all specialties who accepted to participate in the study were included. They were asked to reply to a paper-based questionnaire specially designed for the study. The questionnaire was inspired by that of Harbeck B et al [10]. It included 16 multiple choice questions. The questionnaire was written in French, the language used in the medical field in Tunisia. It was tested and revised by five physicians in order to verify the comprehensibility of the questions and avoid eventual misunderstanding. Age, gender, professional degree and specialty were determined. The number of patients with AI followed up by the practitioner was also specified. Anonymity was respected on the questionnaire form.

Each question was scored 1 if correct or 0 if incorrect. Apart question 3, the questions were considered correct if all the correct responses were marked with no marked incorrect answer. In question 3, either of these two options 'hydrocortisone' or 'prednisone/prednisolone' were considered correct. A global score (GS) was calculated by adding the scores of the 15 first questions noted each one 0 or 1 and was expressed in percentage of correct answers (total points x 100 / number of

questions). The question 16 concerning Ramadan fasting was not included in the GS. The GS was considered low if it was between 0 and 33.3%, intermediate if it was between 33.4 and 66.6%, and good if it was between 66.7 and 100%.

## Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 23. Results were expressed as means  $\pm$  standard variations for quantitative variables and number of cases and percentages for qualitative variables. Student test and non-parametric Mann-Whitney U test were used to compare quantitative variables. Pearson's Chi-squared test was used to compare qualitative variables or, failing that, Fisher's exact test was used. Multiple linear regression analysis using backward elimination was used to assess the relationship between a dependent variable and independent variables with a  $p < 0.20$ . P value  $< 0.05$  was considered significant. The alpha Cronbach coefficient was calculated to assess the internal consistency of the questionnaire.

## RESULTS

Out of the 250 questionnaire forms distributed, 203 fulfilled ones were collected. Three were excluded for insufficient number of responses ( $< 2/3$  of the questions). Thus, the responses of 200 physicians were studied; 138 (69%) from la Rabta University hospital and 62 (31%) from Charles Nicolle University hospital. There were 136 females and 64 males and the mean age was  $29.0 \pm 5.8$  years (24 - 60). The majority (82.5%) were younger than 30 years. According to their grade, 50 were interns (25%), 34 were family medicine residents (17%), 92 were specialty residents (46%) and 24 (12%) were seniors. The different specialties of the participants are detailed in table 1. Ten (5%) practitioners have followed up more than 50 patients with AI, 16 (8%) followed up between 11 and 50 patients, 100 (50%) followed up between one and 10, and 74 (37%) have never followed up a patient with AI.

The responses to the different questions are presented in table 2. The mean GS i.e. the overall correct response rate was  $59.6 \pm 15.5\%$  (20-93). The GS was considered low in 14 (7%) practitioners, intermediate in 136 (68%) and good in 50 ones (25%). The analysis of the GS according to the characteristics of the physicians is presented in table 3. The gender, the specialty (endocrinology or not), the surgical or medical specialty, and the number of patients with AI followed up ( $\leq 10$  or  $> 10$ ) were entered into the model of multiple linear regression analysis to determine independent factors associated with the GS. The analysis showed that the endocrinology specialty and the medical specialties were independently associated with the GS (Standardized coefficient  $\beta$  : -0.42, t: -4.83, p: 0.000 and Standardized coefficient  $\beta$  : -0.32, t: -3.98, p: 0.000, respectively). The gender and the number of patients with AI followed up were no longer associated with the GS. The Cronbach coefficient of the questionnaire was 0.55.

**Table 1.** The specialties of the 200 physicians included in the study of medical practices in the management of adrenal insufficiency conducted in 2020 in two university hospitals La Rabta and Charles Nicolle of Tunis.

	Specialty; n (%)	Interns	Residents	Seniors	Total
Medical specialties	Endocrinology	-	15 (7.5)	4 (2)	19 (9.5)
	Infectious disease	-	1 (0.5)	-	1 (0.5)
	Cardiology	-	7 (3.5)	-	7 (3.5)
	Nephrology	-	8 (4)	1 (0.5)	9 (4.5)
	Gastroenterology	-	6 (3)	2 (1)	8 (4)
	Internal medicine	-	4 (2)	3 (1.5)	7 (3.5)
	Occupational Medicine	-	3 (1.5)	4 (2)	7 (3.5)
	Rheumatology	-	5 (2.5)	-	5 (2.5)
	Emergency	-	6 (3)	1 (0.5)	7 (3.5)
	Dermatology	-	4 (2)	-	4 (2)
	Haematology	-	3 (1.5)	-	3 (1.5)
	Neurology	-	2 (1)	-	2 (1)
	Medical intensive care	-	3 (1.5)	1 (0.5)	4 (2)
	Anaesthesia and resuscitation	-	1 (0.5)	-	1 (0.5)
Surgical specialties	General surgery	-	1 (0.5)	-	1 (0.5)
	Ophthalmology	-	1 (0.5)	-	1 (0.5)
	Oto-rhino-laryngology	-	8 (4)	4 (2)	12 (6)
	Cardio-vascular surgery	-	7 (3.5)	3 (1.5)	10 (5)
	Urology	-	7 (3.5)	-	7 (3.5)
General practitioners		50 (25)	34 (17)	-	84 (42)
Total		50 (25)	126 (63)	24 (12)	200 (100)

**Table 2.** Survey questions and responses on medical practice in the management of adrenal insufficiency of 200 physicians in two university hospitals, La Rabta and Charles Nicolle of Tunis in 2020.

Questions	Responses	Number of responses (%)	Correct responses (%)
1-The normal daily cortisol production rate in healthy individuals is:	5-10mg	43 (21.5)	103 (51.5)
	<b>10-20mg</b>	103 (51.5)	
	20-30mg	36 (18)	
	30-40mg	8 (4)	
2-The physiological peak of cortisol secretion occurs at:	<b>6-8 a.m</b>	150 (75)	150 (75)
	8-10 a.m	41 (20.5)	
	4-6 p.m	4 (2)	
	10-12 p.m	5 (2.5)	
3-Glucocorticoid preparation(s) that can be used for replacement therapy is (are):	<b>Hydrocortisone</b>	187 (93.5)	184 (92)
	<b>Prednisone/ prednisolone</b>	43 (21.5)	
	Betamethasone	3 (1.5)	
	Dexamethasone	13 (6.5)	
4-The half-life of hydrocortisone is:	<b>1-2 hours</b>	25 (12.5)	25 (12.5)
	8-12 hours	130 (65.5)	
	12-16 hours	22 (11)	
	16-20 hours	19 (9.5)	
5-The duration of replacement therapy is:	Short duration	1 (0.5)	176 (88)
	Long duration	23 (11.5)	
	<b>Lifelong</b>	176 (88)	

**Table 2.** Survey questions and responses on medical practice in the management of adrenal insufficiency of 200 physicians in two university hospitals, La Rabta and Charles Nicolle of Tunis in 2020. (Suite)

6-The symptom(s) of glucocorticoid over replacement is (are):	Low blood pressure	7 (3.5)	147 (73.5)
	<b>High blood pressure</b>	182 (91)	
	<b>Weight gain</b>	158 (79)	
	Weight loss	21 (10.5)	
	Hypoglycemia	7 (3.5)	
	<b>Hyperglycemia</b>	188 (94)	
7-The symptom(s) of glucocorticoid under replacement is (are):	<b>Low blood pressure</b>	188 (94)	124 (62)
	High blood pressure	5 (2.5)	
	Weight gain	21 (10.5)	
	<b>Weight loss</b>	130 (65)	
	<b>Hypoglycemia</b>	189 (94.5)	
	Hyperglycemia	188 (94)	
8-The measure(s) required in patients with AI is (are):	<b>Delivery of an emergency card</b>	190 (95)	99 (49.5)
	Prescription of glucagon	15 (7.5)	
	<b>Information of patient's close relatives</b>	165 (82.5)	
	Regular monitoring with adrenal ultrasound	14 (7)	
	Regular monitoring with serum cortisol at 8a.m	62 (31)	
	Any of these measures is necessary	6 (3)	
9-The type (s) of diet indicated is (are):	Low in salt	37 (18.5)	154 (77)
	<b>Normal in salt</b>	154 (77)	
	Low in calories	1 (0.5)	
	High in carbohydrate	8 (4)	
10-Specific measures should be undertaken during the peri operative period:	<b>Yes</b>	200 (100)	200 (100)
	No	0 (0)	
11-The medication(s) that should be avoided is (are):	Anti-inflammatory	45 (22.5)	78 (39)
	<b>Laxative</b>	107 (53.5)	
	Vitamin K antagonists	5 (2.5)	
	<b>Diuretics</b>	151 (75.5)	
12-Clinical sign(s) suggesting acute AI is (are):	<b>Vomiting</b>	166 (83)	114 (57)
	<b>Abdominal pain</b>	165 (82.5)	
	<b>Hypotension</b>	166 (83)	
	<b>Symptoms of hypoglycemia</b>	158 (79)	
13-Biological sign(s) suggesting acute AI is (are):	Hyperglycemia	9 (4.5)	35 (17.5)
	<b>Hyperkalemia</b>	132 (66)	
	<b>Hyper uremia</b>	51 (25.5)	
	<b>Hyponatremia</b>	173 (86.5)	
14-The dose of glucocorticoids should be adjusted in case of:	<b>Prolonged and intense physical activity</b>	148 (74)	53 (26.5)
	Transient psychic stress	87 (43.5)	
	Rheumatic pain	17 (8.5)	
	<b>Fever &gt; 38°C</b>	145 (72.5)	
	Headache	7 (3.5)	
	<b>Acute severe disease</b>	183 (91.5)	

**Table 2.** Survey questions and responses on medical practice in the management of adrenal insufficiency of 200 physicians in two university hospitals, La Rabta and Charles Nicolle of Tunis in 2020. (Suite)

15-In case of an acute infectious disease without signs of severity (example: flu), replacement therapy should be adjusted as follow:	Omission for 1-2 days	2 (1)	127 (63.5)
	Dose reduced by 50%	12 (6)	
	<b>Dose increased by 2- to 5- fold</b>	127 (63.5)	
	Dose increased by 10- fold	0 (0)	
	No dose adjustment	59 (29.5)	
16-During the month of Ramadan, the patient:	Can fast without risks	5 (2.5)	4 (2)
	<b>Can fast with a risk of complications</b>	18 (9)	
	<b>Can fast after drug adjustment</b>	55 (27.5)	
	Cannot fast	126 (63)	

NB: Correct responses are indicated in bold letters.

**Table 3.** The global score of the questionnaire on medical practice in the management of adrenal insufficiency according to the characteristics of the 200 physicians included in the study conducted in 2020 in two university hospitals La Rabta and Charles Nicolle of Tunis

Parameters		Global Score Percentage of correct answers, means±SD
Gender	Male	54.4± 14.5
	Female	62.1 ± 15.4*
Age (years)	≤30	59.7 ± 15.3
	>30	58.9 ± 16.9
Grade	Intern	58.2± 14.9
	Family medicine resident	54.8 ± 12.4
	Specialty resident	61.9 ± 15.8
	Senior	60.3± 18.7
Hospital	La Rabta	60.0 ± 16.5
	Charles Nicolle	58.7± 13.4
Specialty	Endocrinology	79.0± 10.9*
	Other specialties	57.8± 14.8
Surgical specialty	Yes	50.1±14.4
	No	62.5±15.2*
Number of followed up patients with AI	≤10	58.5± 13.9
	>10	66.4 ± 22.6*

AI: adrenal insufficiency; SD: standard deviation

\*: p<0.05

## DISCUSSION

The study of medical practice in the management of AI of 200 physicians, from two university hospitals in Tunis, all grades and specialties included, showed that the overall percentage of correct answers was 59.6%. The endocrinology specialty and the medical ones were independently associated with a higher GS.

Although our study concerned two large hospitals, our results cannot be generalized to all Tunisian physicians as we did not include those from non-university hospitals, dispensaries, and clinics. In fact, it has been shown that the perception on AI management of internists working in university hospitals was higher than that of their colleagues from non-university hospitals [11]. On the same way, 88% of our population did not achieve their hospital internships. However, in young physicians, the medical course on AI was more recent. The main difficulty of the study was the design of the questionnaire as there is not a valid one in the literature. Only one questionnaire was published [10]. Nine questions of our questionnaire were inspired by that of Harbeck B et al [10]. The Cronbach coefficient of our questionnaire was 0.55, indicating that the internal consistency was sufficient but not satisfactory. So, the questionnaire has to be improved.

In the study of Kampmeyer et al, involving 209 physicians from different specialties and centers in Germany, where a 10-multi-choice-questionnaire was used, the percentage of correct answers was 72.9% [11]. This data was not mentioned in the study of Harbeck et al that included 69 physicians from a department of internal medicine in Germany evaluated by an 11-question questionnaire [10]. Makin V. et al evaluated the perception and practice in AI management of 51 primary care physicians using four clinical questions and showed gaps in particular in the management of the disease [12]. The questionnaire as well as the way to calculate the questions scores were different in the different studies making the comparison difficult. In fact, in our study, the strictest way to score the questions was used; the all or nothing rule.

The type of GC used in replacement therapy was well known as well as the life-long duration of treatment, the symptoms of overtreatment, the type of diet indicated, and the fact that special measures are required during the peri operative period. Hydrocortisone was recognized by the majority of the physicians (> 92%) of the different studies as a GC used for replacement therapy in patients with AI [10-11]. Symptoms of overtreatment were also well known in the



other studies (>70% of the physicians) [10-11]. In fact, these symptoms are those of side effects of long-term treatment with GC. Symptoms of overtreatment are important to know as overtreatment is associated with weight gain, insulin resistance, impaired glucose tolerance, and dyslipidemia with an increased cardio vascular risk as well as an increased risk of bone mineral density loss [13-15].

Clinical and biological signs of acute AI were insufficiently known, respectively 57% and 35% in our study. Symptoms of under treatment were known by 62% of our physicians compared to only 10% in the other studies [10-11]. Symptoms of under treatment and those of acute AI should be well known by the physicians for early diagnosis and treatment of this life-threatening disease but also for patients' education [16-17]. Likewise, the causes of acute AI should be well known by the physicians and the patients. The main causes are infections and particularly gastro intestinal ones, surgical interventions, intense physical activity and the withdrawal of replacement therapy [16]. In stressful situations, the doses of GC should be increased in order to prevent adrenal crisis. In our study, the situations during which GC replacement therapy has to be adjusted were known by 26.5% of the physicians. The majority of the physicians, 91.5% in our study and 87.6% in that of Kampmeyer et al, knew that the dose of GC should be adjusted in case of an acute severe disease [11]. In our study, 43.3% of the practitioners thought that replacement therapy has to be adjusted during a transient psychic stress. The need to increase the dose of GC replacement therapy depends on the severity and the duration of the physical or psychic stress [18-19].

The half-life of hydrocortisone and the risks of Ramadan fasting were poorly known. The short half-life of hydrocortisone was known by only 12.5% of our physicians and by 19.6% and 29.7% in the other studies. It is only in recent years that intermittent fasting in patients with AI has aroused the interest of researchers resulting in publications on this subject. The physicians should know that intermittent fasting is associated with complications in patients with AI [20] and that lower levels of interstitial glucose were observed during the fasting period [21]. These complications were explained by the short half-life of hydrocortisone that is the most used drug for replacement therapy. A literature review was recently published and guidelines have been proposed for fasting in patients with AI according to the levels of risk of complications and the measures that should be undertaken to reduce the risk of complications [22].

In our study as well as in that of Makin V. et al [12], female gender was associated with a better global score on univariate analysis. However, on multivariate analysis, female gender was no longer associated with the GS in our study. It was rather the endocrinology specialty and the medical specialties that were independently associated with more appropriate medical practices.

This study showed that physician practice in the management of AI needs to be improved. Decision-makers and medicine curriculum designers should be aware of this and courses to upgrade the levels of knowledge, skills, and attitudes regarding AI should be organized. Furthermore, a valid questionnaire is mandatory for the evaluation of physician practice. This questionnaire could also be used for formative evaluation.

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