Lessons from rare diseases: pathophysiology of stress-related diseases and organization and evaluation of care for patients with Cushing's syndrome

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CHAPTER 8

CURRENT CLINICAL PRACTICE FOR THROMBOPROPHYLAXIS MANAGEMENT IN PATIENTS WITH CUSHING'S SYNDROME ACROSS REFERENCE CENTERS OF THE EUROPEAN REFERENCE NETWORK ON RARE ENDOCRINE CONDITIONS (ENDO-ERN)

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ABSTRACT

Background

Cushing's syndrome (CS) is associated with an hypercoagulable state and an increased risk of venous thromboembolism (VTE). Evidence-based guidelines on thromboprophylaxis strategies in patients with CS are currently lacking. We aimed to map the current clinical practice for thromboprophylaxis management in patients with CS across reference centers (RCs) of the European Reference Network on Rare Endocrine Conditions (Endo-ERN), which are endorsed specifically for the diagnosis and treatment of CS. Using the EU survey tool, a primary screening survey, and subsequently a secondary, more in-depth survey were developed.

Results

The majority of the RCs provided thromboprophylaxis to patients with CS (n = 23/25), although only one center had a standardized thromboprophylaxis protocol (n = 1/23). RCs most frequently started thromboprophylaxis from CS diagnosis onwards (n = 11/23), and the majority stopped thromboprophylaxis based on individual patient characteristics, rather than standardized treatment duration (n = 15/23). Factors influencing the initiation of thromboprophylaxis were 'medical history of VTE' (n = 15/23) and 'severity of hypercortisolism' (n = 15/23). Low-Molecular-Weight-Heparin was selected as the first-choice anticoagulant drug for thromboprophylaxis by all RCs (n = 23/23). Postoperatively, the majority of RCs reported 'severe immobilization' as an indication to start thromboprophylaxis in patients with CS (n = 15/25). Most RCs (n = 19/25) did not provide standardized testing for variables of hemostasis in the postoperative care of CS. Furthermore, the majority of the RCs provided preoperative medical treatment to patients with CS (n = 23/25). About half of these RCs (n = 12/23) took a previous VTE into account when starting preoperative medical treatment, and about two-thirds (n = 15/23) included 'reduction of VTE risk' as a goal of treatment.

Conclusions

There is a large practice variation regarding thromboprophylaxis management and perioperative medical treatment in patients with CS, even in Endo-ERN RCs. Randomized controlled trials are needed to establish the optimal prophylactic anticoagulant regimen, carefully
balancing the increased risk of (perioperative) bleeding, and the presence of additional risk factors for thrombosis.

BACKGROUND

Cushing's syndrome (CS) is characterized by excessive tissue exposure to glucocorticoids, caused by either exogenous administration of synthetic glucocorticoids, or excessive endogenous secretion of cortisol. Endogenous CS is rare, with an estimated incidence of 0.2–5.0 cases per million inhabitants per year in various populations, whereas its prevalence is close to 39–79 cases per million inhabitants [1]. Endogenous CS is most commonly caused by a pituitary corticotroph adenoma (Cushing's Disease, CD), accounting for 70% of all CS cases, and least frequently by adrenocorticotropic hormone (ACTH)-secreting non-pituitary tumors (ectopic ACTH and corticotropin-releasing hormone syndrome, CRH). ACTH-independent CS, is most commonly caused by an unilateral adrenal adenoma, or in fewer cases by bilateral micronodular, or macronodular adrenal hyperplasia, or adrenal carcinoma [1].

In recent years, the association between CS and hypercoagulability has gained growing interest. Multiple cohort studies reported an increased risk for venous thromboembolism (VTE), which encompasses pulmonary embolism (PE) and deep vein thrombosis (DVT), in patients with CS, both during the active phase of disease, and in the postoperative period after transsphenoidal surgery or adrenalectomy, and even after biochemical remission [2]. In their systematic meta- analysis, Wagner et al. found an almost 18-fold higher incidence of VTE in patients with CS compared with the general population [3]. A national multicenter cohort study by Stuijver et al. [4] showed an incidence rate of VTE in CS of 14.6 per 1000 person-years, whereas the risk for postoperative VTE in patients with ACTH-dependent CS was 3.4%.

The underlying mechanisms of, and contributing factors for the hypercoagulable state in patients with CS are still under investigation, with observed/reported coagulation profiles in patients with CS being heterogeneously affected. The hemostatic abnormalities most consistently reported in the various studies include increased levels of procoagulant factors, e.g. von Willebrand Factor (vWF), and factor VIII, and increased levels of fibrinolytic inhibitors, e.g. plasminogen activator inhibitor-1 (PAI-1), thrombin activatable fibrinolysis inhibitor (TAFI), and alpha 2-antiplasmin. The currently available reports did not find a correlation between the severity of hypercortisolism and hemostatic abnormalities [2, 3].

However, to date, there have been no prospective studies that have evaluated the effects of prophylactic anticoagulation on the occurrence of VTE in patients with CS, and consequently, evidence-based guidelines on thromboprophylaxis strategies in patients with CS are lacking [5]. Only retrospective series showing a decrease in VTE associated mortality and morbidity after the introduction of postoperative antithrombotic prophylaxis with unfractionated heparin followed by warfarin [6], low-molecular weight heparin with or without mechanical interventions [7], or aspirin [8] have been reported. We, therefore, anticipated and hypothesized that European Reference Centers (RCs) applied various thromboprophylaxis strategies for patients with CS. Using the EU survey tool, a primary screening survey, and subsequently a secondary, more in-depth survey were developed and sent to RCs of the European Reference Network on Rare Endocrine Conditions (Endo-ERN), which are endorsed specifically for the diagnosis and treatment of CS, thus allowing mapping of the current clinical practice for thromboprophylaxis management in patients with CS.

RESULTS

Response rates

Forty-three out of 54 RCs completed the primary survey, of which one RC was excluded because the RC did not treat patients with CS resulting in a final response rate of 78% (n = 42). The secondary survey was sent to the 42 responding RCs of the primary survey, and was completed by 27 RCs of which one RC was excluded due to the lack of both new and chronic patients in their center in the past 2 years. This resulted in a response rate of 62% (n = 26). One response was partial (up to and including the section 'Treatment of CS', see Supplemental file 5). Figure 1 shows an overview of the geographical distribution of RCs per country. Notably, no information on the Cushing population and available treatment modalities due to non-response or exclusion from analysis of both surveys was available for The Czech Republic and Latvia. Slovakia was included for analysis of only the primary survey, and thus, information was partly available.

Figure 1. European Landscape of RCs participating in MTG Pituitary and/or MTG Adrenal of Endo-ERN and responder status. Completion of both primary and secondary survey (green icons). Completion of only the primary survey or was included for analysis of only the primary survey (blue icons). Non-responder to the surveys or exclusion from analysis of both surveys (red icons). Endo-ERN The European Reference Network on Rare Endocrine Conditions, MTG main thematic group, RC reference center.

Primary survey

The results of the primary survey are summarized in Table 1. The majority of the RCs reported to treat patients with CD (n = 40/42), and benign adrenal CS (n = 39/42). More than half of the RCs (n = 27/42) reported treating the entire spectrum of CS at their center including benign adrenal CS, malignant adrenal CS, CD, and ectopic CS. These RCs were heterogeneously spread across Europe. Additionally, the majority of the RCs (n = 36/42) provided all treatment modalities regarding CS, including surgery, medical treatment, and radiotherapy and administered combination therapy (i.e. combination of surgery and ≥1 of the other treatment modalities). The geographical distribution of the RCs, that provided all treatment modalities for patients with CS, showed almost complete coverage of the countries with the exception of Slovakia and Cyprus that have no RC providing all treatment modalities. An overview of the RC's countries that treated the whole spectrum of CS and provided all treatment modalities is shown in Figures 4A and 4B included in an supplemental file (see Supplemental file 1).

Sixteen of 42 RCs routinely provided preoperative medical treatment, and nearly three-quarters of RCs (n = 31) routinely provided thromboprophylaxis to patients with CS, of which the majority (n = 25) gave thromboprophylaxis only in the inpatient setting, while six RCs also prescribed thromboprophylaxis in the ambulatory setting. Eleven of 42 RCs reported to have a dedicated thromboprophylaxis protocol/policy available at their center. Twenty-four of 42 RCs systematically registered TE events, of which the majority (n = 17) specifically registered PE, DVT, and arterial thrombosis (AT), while seven RCs only registered PE, and DVT specifically. Eighteen RCs systematically registered bleeding complications, and twenty-two RCs documented the severity and outcome of the bleeding.

Secondary survey

Definitions

The section on definitions was completed by 26 RCs. First, the definitions of new and chronic patients being used by RCs varied greatly. The majority of the RCs used the following definitions: (a) new patients were defined as patients not previously seen by their center (n = 8), or as treatment naive patients, in addition to any patient not previously seen by their center (n = 8), and (b) chronic patients were defined as patients under active treatment (n = 7). An overview of all used definitions of new and chronic patients by the different RCs is presented in Table 4 enclosed in an supplemental file (see Supplemental file 2).

Epidemiology

Twenty-six RCs were included in the analysis for the section on epidemiology. Complete estimated numbers of new and chronic patients under local care, and numbers of performed transsphenoidal surgeries and adrenalectomies in 2019 and 2020 were provided (Table 5; see Supplemental file 3). Among the participating RCs, the number of new patients with CS ranged from 0 to 45 in 2019, and from 0 to 56 in 2020. The number of patients with CS under chronic care ranged from 1 to 196 in 2019, and from 0 to 215 in 2020. The highest number of both new and chronic patients with CS was

Table 1. Results of the primary survey.

Characteristics	Total number of RCs (N = 42)
Etiology of CS treated at RC[a]	
Benign adrenal CS	39 (93%)
Malignant adrenal CS	31 (74%)
Cushing's disease	40 (95%)
Ectopic CS	33 (79%)
Whole spectrum of CS (i.e. benign adrenal CS, malignant adrenal CS, CD and ectopic CS) treated at RC	27 (64%)
Treatment modalities for CS available at RC	
Surgery + medical treatment	3 (7%)
Surgery + medical treatment + combination therapy[b]	2 (5%)
Surgery + medical treatment + combination therapy[b] + radiotherapy	36 (86%)
Combination therapy[b]	1 (2%)
Preoperative medical treatment routinely provided at RC, yes (%)	16 (38%)
Thromboprophylaxis routinely provided at RC, yes (%)	31 (74%)
If yes, setting[a]	
In the inpatient setting	25/31 (81%)
In the ambulatory setting	6/31 (19%)
Presence of a thromboprophylaxis protocol for patients with CS, yes (%)	11 (26%)
Registration of bleeding complication, yes (%)	18 (43%)
Documentation of severity and outcome of bleeding, yes (%)	22 (52%)
Registration of TE events, yes (%)	24 (57%)
If yes, specific registration of	
PE + DVT	7/24 (29%)
PE + DVT + AT	17/24 (71%)

AT arterial thrombosis, CS Cushing's syndrome, CD Cushing's disease, DVT deep vein thrombosis, PE pulmonary embolism, RC reference center, TE thromboembolic

[a] Not mutually exclusive

[b] Combination therapy was defined as combination of surgery and ≥ 1 of the other treatment modalities

reported by France and the Netherlands, respectively. The number of transsphenoidal surgeries that were performed in 2019 and 2020 ranged from 0 to 16, and 0 to 20, respectively. The number of adrenalectomies in 2019 and 2020 ranged from 0 to 21, and 0 to 20, respectively. The highest numbers of performed transsphenoidal surgeries and adrenalectomies were reported by French RCs. Since only the number of CS patients per RC and the number of patients operated on within 1 year were requested in the survey, the number of newly diagnosed patients and patients operated on may not be the same in a single RC due to the fact that patients diagnosed in 1 year, may have had their surgery in another year.

Thromboprophylaxis in Cushing's syndrome

The section on thromboprophylaxis in CS was completed by 25 RCs. Ten RCs answered that thromboprophylaxis was routinely provided to all patients with CS. Thirteen centers provided

thromboprophylaxis only in selected and/or severe cases with or without risk factors for venous thromboembolism. Two centers never provided thromboprophylaxis to patients with CS.

Treatment duration of thromboprophylaxis

From the twenty-three RCs that provided thromboprophylaxis routinely, or only in selected/severe cases, the majority (n = 11) started thromboprophylaxis from diagnosis onwards. Six centers started thromboprophylaxis on the day of the surgery, or 1 day prior. Four centers started thromboprophylaxis preoperatively, of which three centers provided specifics regarding the moment of thromboprophylaxis initiation; namely at an average of 7, 14 and 18 days preoperatively. Furthermore, three RCs started thromboprophylaxis postoperatively, of which two RCs started at an average of 1 day, and one RC at an average of 3 days postoperatively. Two RCs reported that the start of thromboprophylaxis for patients with CS varied, and depended on presentation. Having started thromboprophylaxis in patients with CS, the time at which thromboprophylaxis was abrogated was standardized in approximately one-third of the RCs (n = 8/23), and individualized in two-thirds (n = 15/23), as shown in Table 2. The standardized discontinuation of thromboprophylaxis varied greatly between the RCs. One out of eight RCs stopped somewhere between 1 week before to 2 weeks after surgery, one RC stopped between 5 and 6 days postoperatively and two RCs between two to 4 weeks postoperatively. Furthermore, three RCs stopped at 1 month postoperatively and one RC at 3 months postoperatively. The individualized discontinuation of thromboprophylaxis, on the other hand, depended most frequently on the mobility (n = 9/15), and to a lesser extent on remission according to normalization of cortisol production (n = 6/15). One RC used crosslinked fibrin (XDP), prothrombin time (PT), aPTT and fibrinogen to make an individualized decision on the duration of thromboprophylaxis. Four out of 15 RCs reported that treatment duration varied according to the status of the patient, improvement of clinical parameters (e.g. hypertension, hyperglycemia and hypercortisolism) and/or current risk factors.

Factors influencing the initiation of thromboprophylaxis

The three most frequently selected factors influencing the start of thromboprophylaxis were 'previous VTE' (n = 15/23), 'severity of hypercortisolism' (n = 15/23), and 'limitation of mobility' (n = 13/23), as depicted in Figure 2. Risk factors for VTE—other than positive history—including older age, cancer and current smoking influenced the start of thromboprophylaxis at ten out of 23 centers. Eight centers started thromboprophylaxis in all patients with CS regardless of the presence of risk factors. Known hereditary thrombophilia (e.g. factor V Leiden/Prothrombin 2021a), and vWF promoter polymorphism haplotype 1 were reported to be used in the decision to start thromboprophylaxis by seven, and three centers, respectively, while non-0 blood group (BG) was not considered by any center. Four centers considered the subtype of CS in the decision of starting thromboprophylaxis (Figure 2). The prothrombotic considered subtypes of CS most frequently named by these centers were ectopic ACTH/CRH syndrome (n = 3/4) and malignant adrenal CS (n = 3/4), and, to a lesser extent, CD (n = 1/4).

Table 2. Time for initiation and time for abrogation of thromboprophylaxis in patients with Cushing's syndrome.

Characteristic	Total number of RCs (N = 23)
Time for initiation of thrombo-prophylaxis[a]	
From diagnosis onwards	11 (48%)
X days preoperatively (mean):	4 (17%)
X = 7	1/4 (25%)
X = 14	1/4 (25%)
X = 18	1/4 (25%)
Not specified	1/4 (25%)
Start on the day before/of the surgery	6 (26%)
X days postoperatively (mean):	3 (13%)
X = 1	2/3 (67%)
X = 3	1/3 (33%)
Other: varies, depends on presentation	2 (9%)
Time for abrogation of thrombo-prophylaxis	
Standardized	8 (35%)
Stop 1 week before until 2 weeks after surgery	1/8 (13%)
Stop between 4 and 6 days postoperatively	1/8 (13%)
Stop between 2 and 4 weeks postoperatively	2/8 (25%)
Stop at 1 month postoperatively	3/8 (38%)
Stop at 3 months postoperatively	1/8 (13%)
Individualized[a]	15 (65%)
Stop upon achieving remission according to normalization of cortisol production	6/15 (40%)
As soon as the patient is no longer immobile	9/15 (60%)
Based upon hemostatic parameters	1/15 (7%)
Other: Varies, depends on patient status, improvement of clinical parameters and/or risk factors	4/15 (27%)

RC reference center

[a] Not mutually exclusive

Anticoagulant treatment and hereditary screening for thrombophilia in Cushing's syndrome

All twenty-three RCs that routinely provided thromboprophylaxis, or only in selected/severe cases reported low-molecular-weight-heparin (LMWH) as the first-choice anticoagulant drug for thromboprophylaxis in patients with CS. Direct oral anticoagulants including apixaban, rivaroxaban, dabigatran and edoxaban were not reported. A thromboprophylaxis protocol for patients with CS was provided by only one of 23 centers. All 25 RCs including the centers that never provided thromboprophylaxis answered the question whether they routinely screened for hereditary thrombophilia during diagnostic work up. One RC reported to perform this screening test routinely.

Role of venous thromboembolism in preoperative medical treatment of CS

Twenty-five RCs completed the section on preoperative medical treatment in CS. Twenty-three RCs answered that preoperative medical treatment was provided to patients with CS (routinely to all

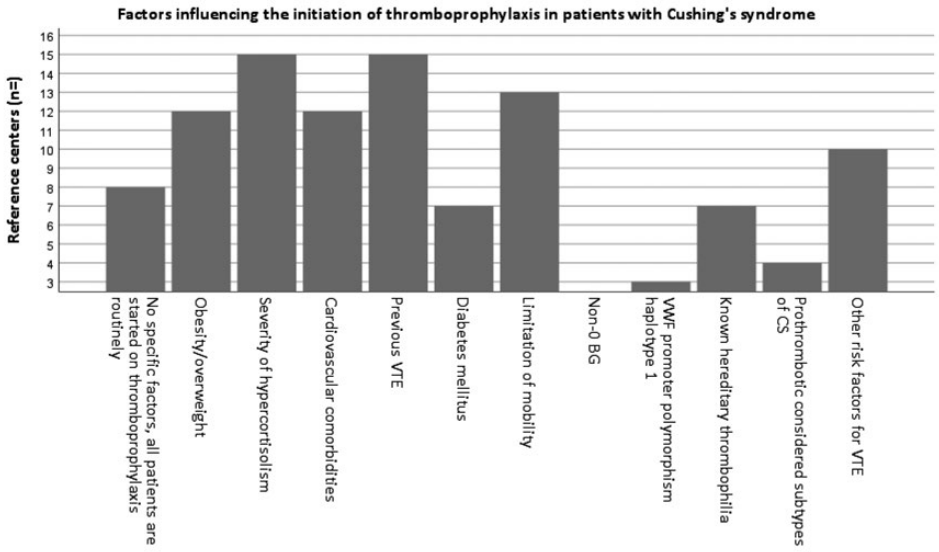

Figure 2. Proportion of responses including each factor influencing initiation of thromboprophylaxis in patients with Cushing's syndrome (not mutually exclusive).BG blood group, CD Cushing's disease, CS Cushing's syndrome, VTE venous thromboembolism, vWF von Willebrand Factor.

patients or only in selected and/or severe cases). About half of these RCs (n = 12/23) took a previous VTE into account when starting preoperative medical treatment, and about two-thirds (n = 15/23) included 'reduction of VTE' as a goal of treatment.

Indications for the initiation of postoperative thromboprophylaxis

Twenty-five RCs completed the section on postoperative thromboprophylaxis (if not (routinely) provided preoperatively) and follow-up care in CS. Five RCs reported not to routinely prescribe thromboprophylaxis in the postoperative setting (Figure 3). The most frequently selected indication for postoperative thromboprophylaxis was 'severe immobilization' (n = 15/25); 'known thromboembolic risk' was reported by one center as shown in Figure 3.

Follow-up care

Six out of 25 centers included hemostatic parameters in routine postoperative laboratory testing. These hemostatic parameters are shown in Table 3. Nine out of 25 centers routinely provided graduated compression stockings to patients with CS after surgery. From this group of RCs the treatment duration was until hospital discharge at five centers and until complete mobilization at one center. The remaining three centers did not specify the treatment duration.

DISCUSSION

This study examined the current clinical practice for thromboprophylaxis management in patients with CS across Endo-ERN RCs. This study provides valuable insight into the large variety

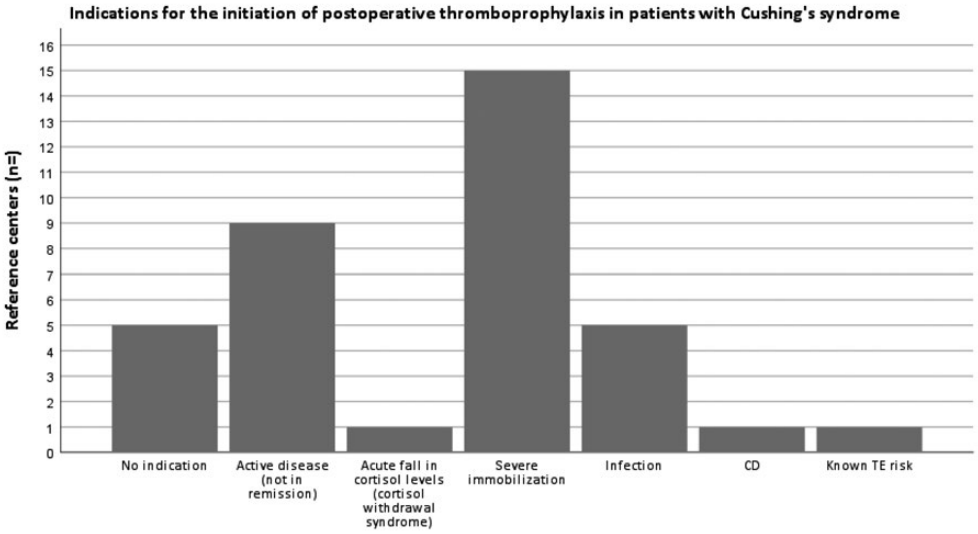

Figure 3. Proportion of responses from each indication for the initiation of postoperative thromboprophylaxis in patients with Cushing's syndrome (not mutually exclusive). CD Cushing's disease, TE thromboembolic.

of thromboprophylaxis strategies for patients with CS, and the limited availability of protocols on thromboprophylaxis even in the reference centers of Endo-ERN that have been endorsed as expert centers for the diagnosis and treatment of CS.

CS is associated with hypercoagulability and an increased risk of VTE (i.e. PE or DVT) both during the active phase of the disease, in postoperative setting, and even after biochemical remission [2]. There are currently no treatment studies on thromboprophylaxis of CS and no guidelines on the use of thromboprophylaxis for patients with CS, and therefore thromboprophylaxis management is committed to each center's clinical practice [5].

The in-depth assessment of thromboprophylaxis management showed that the majority of the RCs provided thromboprophylaxis routinely to all patients with CS or only in selected/severe cases (n = 23/25), however, a thromboprophylaxis protocol for patients with CS was unavailable in the vast majority of them (n = 22/23). Thromboprophylaxis was mostly started from diagnosis onwards, whereas the moment of stopping thromboprophylaxis was merely based on individual characteristics rather than standardized treatment duration. Because active CS is associated with a moderate to high risk on VTE [2,3,4] there is a rationale to start with thromboprophylaxis at diagnosis. On the other hand, treatment with anticoagulation is accompanied by an increased risk of major bleeding, which has been reported to be between 2.8 and 6 per 100 person years [3]. However, the bleeding tendency in CS may be only theoretical, as no increased bleeding complications were found in patients with CS undergoing laparoscopic adrenalectomy [9]. Although CS is associated with bruising and poor wound healing, these manifestations are thought to be the result of alterations in synthesis of skin components rather than specific coagulation disorders [10]. Future studies should assess additional risk factors to determine which patients are particularly at risk for VTE and would benefit from thromboprophylaxis. The individualized

Table 3. Characteristics of postoperative care.

Characteristic	Total number of RCs (N = 25)
Hemostatic blood testing as standard postoperative care	
Yes, namely:	6 (24%)
Thrombocytes + INR	1/6 (17%)
Platelet count + aPTT + PT + vWF + AT III + PS + PC	1/6 (17%)
aPTT + PT	1/6 (17%)
aPTT + INR + D-dimer + fibrinogen	1/6 (17%)
aPTT + PT + INR + D-dimer	1/6 (17%)
aPTT + PT + fibrinogen + XDP	1/6 (17%)
Graduated compression stockings as standard postoperative care	
Yes	9 (36%)

aPTT activated partial thromboplastin time, AT-III antithrombin III, PC protein C, PS protein S, PT prothrombin time, RC reference center, vWF von Willebrand Factor, XDP serum crosslinked fibrin.

decision to abrogate depended mostly on the mobility status of the patient. Risk factors that influenced the initiation of thromboprophylaxis in patients with CS were most frequently reported to be 'previous VTE' and 'severity of hypercortisolism', and LMWH was selected as the first-choice anticoagulant drug by all RCs. Furthermore, the majority of RCs reported 'severe immobilization' as an indication to start postoperative thromboprophylaxis in patients with CS if not (routinely) provided preoperatively, and lastly, did not provide standardized testing for hemostatic parameters in the postoperative care of CS.

A thromboprophylaxis protocol for patients with CS was provided by only one center. This center referred to a recently published article by Barbot et al [11]. In this article, perioperative multidisciplinary management of patients with sellar lesions submitted for transsphenoidal surgery was described and suggested. Specifically for patients with CD, the clinical practice included elastic compression stockings for every patient from the day of admission until full mobilization, treatment with enoxaparin 4000 U once daily, doubling the dose for patients with a body weight above 80 kg for 30 days, starting 24 h after the surgical procedure. However, this protocol did not compromise the whole spectrum of CS [11].

As no studies have been conducted on thromboprophylaxis management in patients with CS, we compared our findings with currently available reports on closely related topics. First, in our study, multiple factors were reported that were taken into account in the decision of thromboprophylaxis initiation in patients with CS. Currently available studies reported multiple risk factors that may be associated with the hypercoagulable state of CS and to our knowledge, no evidence- based VTE risk assessment model for patients with CS has been published thus far [3, 12,13,14]. In our study, the severity of hypercortisolism was one of the most frequently reported factors that influenced the initiation of thromboprophylaxis. One study found that patients with CS developing VTE had significantly higher plasma cortisol concentrations, compared with CS patients without VTE [12]. However, this was a retrospective study with a very small sample size. Multiple studies found no correlations between

the severity of hypercortisolism, and coagulation and fibrinolysis indexes, which was confirmed by Wagner et al. in their recently published systematic meta-analysis [3, 15, 16].

Furthermore, in our study we found a limited role for the measurement of coagulation parameters in the thromboprophylaxis management of CS applied by the Endo-ERN expertise centers. Only one RC reported that the ending of thromboprophylaxis in patients with CS depended on the results of hemostatic variables, including XDP, PT, aPTT and fibrinogen. Additionally, only six RCs reported that hemostatic parameters were screened routinely during follow-up care after transsphenoidal surgery or adrenalectomy. Results of studies examining the hemostatic profiles in patients with CS and the effect of (successful) treatment on these profiles were diverse. A prospective study by Manetti et al. [16] showed an improvement of coagulations indices after successful surgery including vWF, thrombin-antithrombin, antithrombin III, PAI-1, alpha 2-antiplasmin and aPTT. Kastelan et al. [17] found extensive significant improvements of coagulation factors in patients with CS after remission and concluded that the risk of TE 6 months after successful treatment was not greater than the risk faced by healthy individuals. In contrast, a cohort study by Dekkers et al. [13] reported high risks of VTE during the first 3 months following surgery in patients with CS. Furthermore, a study by van der Pas et al. [15] showed no significant changes in aPTT and vWF:Ag in patients with CD after successful pharmaceutical treatment, and additionally showed persistent elevated levels of PAI-1 and alpha 2-antiplasmin. A reason for these contradicting findings may well be the differences in follow-up duration. A systematic meta-analysis by Wagner et al. [3] confirmed the association between CS and VTE, and changes in coagulation parameters including vWF, protein C, protein S, aPTT, fibrinogen and factor VIII, but found no relationship between coagulation parameters and number of thrombotic events. However, more evidence is needed to show whether screening for hemostatic parameters and (changes in) laboratory coagulation metrics can define timing, duration and intensity of (extended) thromboprophylaxis before implementation in daily clinical practice.

In our study we found that four out of 23 centers reported to consider the subtype of CS in the decision of initiation of thromboprophylaxis. The subtypes of CS that were deemed to be associated with an increased risk of TE by these RCs were CD, ectopic ACTH/CRH syndrome and/or malignant adrenal CS. Previous studies showed a higher VTE rate in patients with CD compared to adrenal CS [4, 6]. The reason for the differences in VTE incidence in patients with different etiologies of CS is not clear. Tirosh et al. [18] observed higher AT- III activity and vWF:Ag antigen in patients with CD compared to patients with primary adrenal CS, along with higher baseline mean cortisol levels, and proposed that higher cortisol levels could explain the differences in coagulation profile and increased risk for VTE. However, another study reported no significant differences in coagulation profile between ACTH- dependent and ACTH- independent CS [19]. As to patients with adrenal carcinoma and ectopic ACTH source, the presence of malignancy per se is considered a VTE risk factor, and therefore, these subtypes of CS can be considered prothrombotic in clinical practice, as seen in our study.

The association between preoperative medical treatment and reduction of VTE risk in patients with CS remains controversial. In our detailed assessment of the use of preoperative medical treatment at the different centers, we found that only about half of the responding RCs (n = 12/23) reported to take risk factors for VTE (e.g. older age, cancer and previous VTE) into account in

the decision of starting treatment in patients with CS. In addition, about two-thirds (n = 15/23) reported that reduction of the risk of VTE postoperatively was one of the goals of preoperative medical treatment. Preoperative medical treatment might have a role in reducing the likelihood of VTE by reducing the cortisol withdrawal syndrome (i.e. a rapid and large decrease in cortisol exposure after surgery) that can trigger a rebound inflammatory response by withdrawal of the anti-inflammatory effect of cortisol [3]. Stuijver et al. [4] reported a reduced risk ratio of VTE 3 months postoperatively in patients with CS who were medically pretreated before surgery, in comparison to patients who were not. In contrast, a study by Valassi et al., in which data on preoperative medical treatment from The European Registry on Cushing's syndrome (ERCUSYN) was analyzed, reported no differences in postsurgical morbidities including thromboembolism within 180 days of surgery between patients who received preoperative medical treatment compared to patients who underwent surgery directly. Furthermore, there was little evidence that preoperative medical treatment affected postsurgical outcome [20].

Important limitation of our study is that our findings may be biased due to non-responders and missing data. However, a minimum response rate of 60% was achieved, and the survey questions were mainly independent from each other. We tried to prevent ambiguity in our survey questions by making a clear distinction between start of thromboprophylaxis in an inpatient and/or ambulatory/out-patient setting, and by enquiring about the exact time of initiation of thromboprophylaxis. However, thromboprophylaxis management in general of patients who are not diagnosed with CS or of patients admitted to the RCs for surgery related to a condition other than CS was not surveyed.

CONCLUSIONS

Current clinical thromboprophylaxis management in patients with CS varies considerably across Endo-ERN reference centers. In the absence of prospective studies evaluating thromboprophylaxis on the occurrence of VTE in patients with CS, no evidence-based guidelines on thromboprophylaxis management for patients with CS exist. As the clinical practices have shown to be highly variable, randomized, controlled trials are needed to establish the optimal prophylactic anticoagulant regimen for patients with CS taking into account the increased risk of perioperative bleeding and the presence of additional risk factors for thrombosis.

METHODS

Aim of the study

The aim of this study was to map the current thromboprophylaxis regimens, (perioperative) treatment practices, and follow-up care after treatment for CS across the (inter)nationally endorsed RCs of the Endo-ERN.

Study setting

In March 2017, European Reference Networks for rare and complex diseases (ERNs) were installed. ERNs are virtual networks involving RCs across the EU and their primary aim is to enhance cross-border expert consultation and guide conformity for rare and/or complex diseases [21]. The Endo-ERN

includes 71 RCs in 19 EU member states. Each of the RCs has been endorsed both nationally and subsequently at the European level for specific expertise for CS, RCs participate in the main thematic disease groups of 'Adrenal' and 'Pituitary' [22].

Study design

This was a survey based study, with a primary and secondary survey which are included in Supplemental files 4 and 5, respectively.

The questionnaires included compulsory questions presented in open-ended and multiple choices and in yes/no-format. The surveys were developed using the EU Survey tool and RCs were approached by email which included a link to the survey. A reminder email was sent approximately 4 weeks after the initial mail-out. RCs that did not respond to the reminder email within 2 weeks after the reminder mail-out were considered non-respondents. Partial completions of the questionnaires were included in the study analysis due to the independent character of the survey questions. The exclusion criteria of the primary survey was the absence of patients with CS, and of the secondary survey was the lack of new and chronic patients with CS in their center in 2019 and 2020. A response rate of 60% was considered sufficient for analysis.

Study parameters

Primary survey

First, a primary survey was developed and send to 54 participating RCs of the Endo-ERN endorsed for the diagnosis and treatment of CS. The primary survey included eighteen questions which served as a screening tool to capture the first essential data for the development of the secondary survey. The questionnaire addressed current practices related to key performance indicators, treatment of CS, and cortisol-lowering treatment prior to surgery, i.e. preoperative medical treatment, prophylactic anticoagulation treatment, and monitoring for thromboembolic events (TE) and bleeding complications in patients with CS.

Secondary survey

Next, we developed a secondary survey based on the outcome of the primary survey questionnaire. The secondary survey included 35 questions and was sent to all responders of the primary survey. The section on thromboprophylaxis in CS in the secondary survey was fully completed by RCs that provided thromboprophylaxis to patients with CS. RCs that never provided thromboprophylaxis to patients with CS were requested to answer the questions on 'hereditary screening for thrombophilia in CS', 'indications for the initiation of postoperative thromboprophylaxis' and 'follow-up care'. Information on treatment duration of thromboprophylaxis in patients with CS was assessed with questions on the time for initiation of thromboprophylaxis, and the time at which thromboprophylaxis was abrogated. Furthermore, remission of CS was defined as normalization of cortisol production in the survey.

The main goal of the secondary survey was a more in-depth assessment of thromboprophylaxis management in daily clinical practice in patients with CS, protocols for thromboprophylaxis, if

any, and (perioperative) treatment practices and follow-up care after transsphenoidal surgery or adrenalectomy in patients with CS. Furthermore, the epidemiological distribution of new and chronic CS patients and performed surgeries were assessed. This was done for both 2019 and 2020 to avoid distortion of information as a result of the COVID-19 pandemic. Lastly, to prevent information bias definitions of new and chronic patients were surveyed too.

Statistical analyses

Descriptive statistics were used to present data, with categorical variables being presented as number (n), and continuous variables being described as means with ranges. Statistical analysis was performed using SPSS version 25.0.

ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
aPTT	Activated partial thromboplastin time
AT	Arterial thrombosis
CLT	Clot lysis time
CRH	Corticotropin-releasing hormone
CD	Cushing's disease
CS	Cushing's syndrome
DVT	Deep vein thrombosis
Endo-ERN	The European Reference Network on Rare Endocrine Conditions
ERN	European Reference Network
LMWH	Low-molecular-weight-heparin
PAI-1	Plasminogen activator inhibitor-1
PE	Pulmonary embolism
PT	Prothrombin time
RC	Reference center
TAFI	Thrombin activatable fibrinolysis inhibitor
TE	Thromboembolic
TSS	Transsphenoidal surgery
VTE	Venous thromboembolism
vWF	Von Willebrand Factor
XDP	Serum crosslinked fibrin

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APPENDIX

Supplemental file 1

Title: Characteristics of care for Cushing's syndrome patients at the reference centers

Description: Overviews of participating reference centers (RC's) per country that treated the complete spectrum of Cushing's syndrome (CS) and that provided the complete spectrum of treatment modalities for CS.

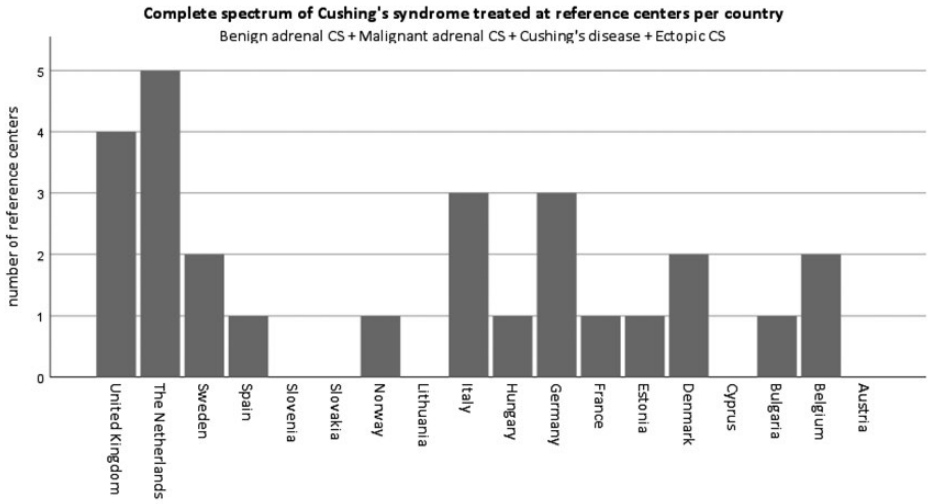

Figure 4A. Overview of the number of reference centers per country that treated the complete spectrum of Cushing's syndrome (CS).

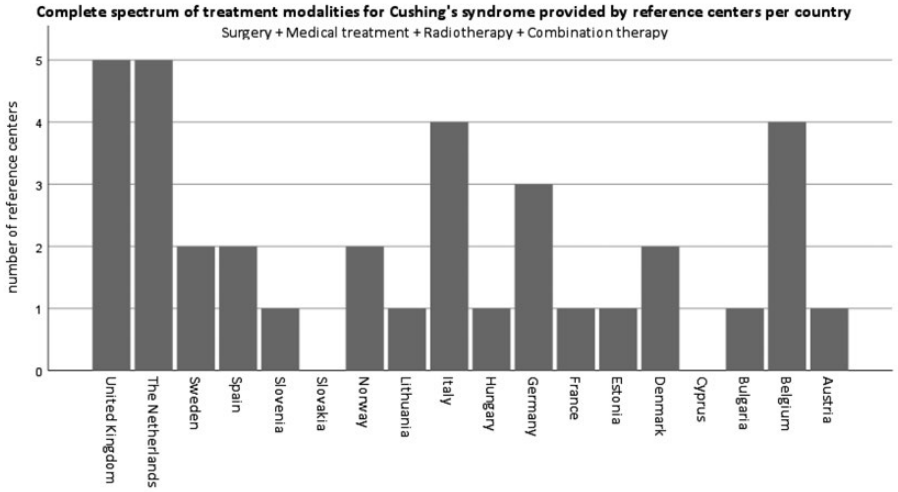

Figure 4B. Overview of the number of reference centers per country that provided the complete spectrum of treatment modalities for CS (n=36). CS, Cushing's syndrome.

Supplemental file 2

Title: Definitions used by the reference centers

Description: Overview of used definitions of new patients and patients under chronic care as reported by participating reference centers (RCs).

Table 4. Definition(s) of new patients and of patients under chronic care.

Definition(s) of new patients at RC	Total number of RCs (n=26)
Treatment naive patients	6 (23%)
Patients not previously seen by RC	8 (31%)
Treatment naive patients + Patients not previously seen by RC	8 (31%)
Patients not previously seen by RC + Patients with recurrent disease after initial remission	1 (4%)
Treatment naive patients + Patients not previously seen by RC + Patients with recurrent disease after initial remission	1 (4%)
Treatment naive patients + Patients not previously seen by RC + Patients with recurrent disease after initial remission + Any patient with an exceeding interval between the last and present consultation depending on the Health Record of the RC	2 (8%)
Definition(s) of patients under chronic care at RC	**Total number of RCs (n=26)**
Patients under active treatment at RC	7 (27%)
Patients with previous treatment at RC	4 (15%)
Patients with previous treatment currently under affiliated centers referred to RC for a single consultation only, diagnostic tests, or for specific procedure	2 (8%)
Patients under active treatment at RC + Patients with previous treatment at RC	6 (23%)
Patients under active treatment at RC + Patients with previous treatment currently under affiliated centers referred to RC for a single consultation only, diagnostic tests, or for specific procedure	2 (8%)
Patients under active treatment at RC + Patients with previous treatment at RC + Patients with previous treatment currently under affiliated centers referred to RC for a single consultation only, diagnostic tests, or for specific procedure	5 (19%)

Supplemental file 3

Title: Epidemiological data of Cushing's syndrome patient population across the Endo-ERN

Description: Numbers of patients newly diagnosed with CS, patients with CS under chronic care, performed transsphenoidal surgeries (TSSs) and adrenalectomies in 2019 and 2020 at participating reference centers (RCs).

Table 5. Numbers of patients newly diagnosed with CS, patients with CS under chronic care, performed TSS and adrenalectomies in 2019 and 2020 at RCs. Missing values are shown as X. CD, Cushing's disease; CS, Cushing's syndrome; RC, reference center; TSS, transsphenoidal surgery.

	Total new CS patients (n=)		Total chronic CS patients (n=)		TSSs (n=)		Adrenalectomies (n=)	
Name RC	**2019**	**2020**	**2019**	**2020**	**2019**	**2020**	**2019**	**2020**
Aarhus University Hospital	14	13	81	86	7	7	X	X
Assistance Publique - Hôpitaux de Marseille	45	56	148	171	15	20	20	20
Assistance Publique-Hopitaux de Paris -Consortium Hôpitaux Cochin, Robert Debré, Necker, St Antoine, La Pitié Salpétrière	44	37	92	101	16	10	21	18
Hospital-University of Padova	15	17	168	184	7	5	5	11
Azienda Ospedaliera Universitaria "Federico II", Napoli	7	1	67	74	3	1	6	2
Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino	5	4	2	1	2	1	3	2
UCL Cliniques Universitaires Saint-Luc	9	8	77	78	3	4	6	5
Erasmus MC: University Medical Center Rotterdam	22	17	196	215	7	5	7	6
Fundacio de Gestio Sanitaria Hospital de la Santa Creu i Sant Pau	11	12	42	43	5	6	3	3
Great Ormond Street Hospital - NHS Foundation Trust	2	5	4	4	0	3	2	2
Lithuanian University of Health Sciences	5	7	22	22	3	3	4	3
IRCCS Ospedale Policlinico San Martino – Genova – Italy	6	3	24	26	2	2	1	1
IRCCS Istituto Auxologico Italiano and BIOMETRA	21	18	29	19	2	2	10	10
Karolinska University Hospital	9	7	99	105	4	4	2	2
Leiden University Medical Center	15	14	52	51	15	15	3	2
Oslo University Hospital HF	11	12	33	36	5	5	5	5
Scientific Institute San Raffaele	2	0	10	10	0	0	1	0

Table 5. continued.

	Total new CS patients (n=)		Total chronic CS patients (n=)		TSSs (n=)		Adrenalectomies (n=)	
Name RC	**2019**	**2020**	**2019**	**2020**	**2019**	**2020**	**2019**	**2020**
Radboud University Nijmegen Medical Centre - including Amalia's children Hospital	29	20	113	113	11	10	8	4
Sahlgrenska University Hospital	6	6	84	87	3	5	2	1
Tartu University Hospital	4	3	13	12	2	2	1	1
The Cyprus Institute of Neurology and Genetics	1	1	1	0	0	0	0	1
University Hospital Southampton - NHS Foundation Trust	9	8	26	35	4	5	2	1
University Hospital Würzburg	X	X	X	X	X	X	X	X
University Hospitals Birmingham - NHS Foundation Trust	X	X	X	X	5	5	X	X
University Medical Centre Groningen	8	5	73	81	4	2	3	2
University Medical Centre Ljubljana	0	0	1	1	0	0	0	0

Supplemental file 4

Title: Primary survey

Description: The primary survey includes 18 questions serving as a screening tool to capture the first essential data for the development of the secondary survey. The questionnaire addressed current practices related to key performance indicators, treatment of Cushing's syndrome (CS) and pre-treatment prior to surgery, i.e. preoperative medical treatment (PMT), prophylactic anticoagulation treatment, and monitoring for thrombo-embolic (TE) events and bleeding complications in patients with CS.

1. Please select for which Main Thematic Group(s) your HCP participate in? (multiple options possible)
   a. MTG- Pituitary
   b. MTG- Adrenal

2. Would you be interested in participating in studies on the topic of Thromboprophylaxis in patients with Cushing's syndrome? (multiple options possible)
   a. Yes I would like to participate in retrospective chart study
   b. Yes I would like to participate in a RCT
   c. No

3. Does your center have a specific clinical trial unit? (yes/no)

4. Do you see patients with Cushing's syndrome? (yes/no)

5. Number of new patients per year:
   a. 0-5
   b. 5- 10
   c. 10- 20
   d. >20

6. Total number of patients under chronic care:
   a. 0-10
   b. 10-50
   c. 50-100
   d. >100

7. Please select the appropriate boxes for underlying cause of Cushing Syndrome: (multiple options possible)
   a. Adrenal CS, benign
   b. Adrenal CS, malignant
   c. Cushing's disease
   d. Ectopic- CS

8. Do you collect clinical data of your patient cohort in a specific database? (yes/no)
   If yes: Have (any part of) these data been published? (yes/no)
   If yes, provide reference

9. Are the following treatment modalities provided at your center? (multiple options possible)
   a. Surgery
   b. Medical treatment
   c. Radiotherapy
   d. Combination therapy (e.g. surgery and 1 of the treatment modalities)

10. Please select which medical treatment to you provide treat cortisol excess? (multiple options possible)
    a. Ketoconazole
    b. Metyrapone
    c. Pasireotide
    d. Other
       If other, please specify

11. Do you routinely pre-treat prior surgery? (yes/no)
    If yes, which medical agent? Please briefly specify protocol regarding duration and dose:

12. Do patients at your center routinely receive thromboprophylaxis? (multiple options possible)
    a. Yes, in the inpatient setting
    b. Yes, in the ambulatory setting
    c. No, only selected and/or severe cases with or without risk factors
    d. No

    If yes, please specify:
    a. All patients
    b. Only severe cases with or without other risk factors

13. Which kind of thromboprophylaxis? (multiple options possible)
    a. Low molecular weight heparin
    b. NOAC
    c. Other

    If other, please specify
14. Do you have a specific protocol for thromboprophylaxis? (yes/no)
    If yes, please select the specific duration of treatment (multiple options possible)
    a. From diagnosis onwards
    b. Peri- operatively

c. 6 weeks after surgery
d. 12 weeks after surgery
e. During hospitalization for other reason than elective pituitary or adrenal surgery

15. Do you specifically register bleeding complications? (yes/no)

16. Do you document the severity and outcome of the bleeding complications? (yes/no)

17. Do you specifically register thrombo-embolic events? (yes/no)
    If yes, do you register separately (multiple options possible)
    a. Pulmonary embolism
    b. Deep vein thrombosis
    c. Arterial thrombosis

18. Remarks/comments

Supplemental file 5

Title: Secondary survey

Description: The secondary survey includes 35 questions. The main goal of the secondary survey was a more in- depth assessment of thromboprophylaxis (TP) management in daily clinical practice in patients with Cushing's syndrome (CS), protocols for TP, if any, and (perioperative) treatment practices and follow-up care after transsphenoidal surgery (TSS) or adrenalectomy in patients with CS. Furthermore, the epidemiological distribution of new and chronic CS patients and performed surgeries were assessed for both 2019 and 2020, and definitions of new and chronic patients were surveyed too

Section 1: Definitions & Epidemiology

1. How do you define a new patient? (multiple options possible)
   a. Treatment naive patients
   b. Patients not previously seen by the reference center
   c. Any patient with an exceeding interval between the last and present consultation depending on the Health Record of the reference center (for instance more than 12 months)
   d. Patients with recurrent disease after initial remission
   e. Other, namely:

2. How do you define a patient under chronic care? (multiple options possible)
   a. Patients under active treatment at the reference center
   b. Patients with previous treatment at the reference center (e.g. patients in complete remission after treatment)
   c. Patients with previous treatment currently under affiliated centers referred to the reference center for a single consultation only, diagnostic tests, or for specific procedure
   d. Other, namely:

3. Do you have a specific database containing clinical characteristics of patients with Cushing's syndrome? (yes/no)
   » If yes, what kind of database? (for example Excel sheets or files of Electronic Health Record Software)
   » If no, are you interested in clinical data collection? (yes/no)

4. What is the number of patients newly diagnosed with the following subtypes of Cushing's syndrome (CS) in your center in 2019 and 2020?

CS subtype	Number of new diagnoses (2019)	Number of new diagnoses (2020)
Cushing's disease		
Ectopic ACTH		
Benign adrenal CS		
Malignant adrenal CS		

5. What is the number of patients under chronic care with the following subtypes of Cushing's syndrome (CS) in your center in 2019 and 2020?

CS subtype	Number of patients under chronic care (2019)	Number of patients under chronic care (2020)
Cushing's disease		
Ectopic ACTH/CRH syndrome		
Benign adrenal CS		
Malignant adrenal CS		

6.1 Does discharge of follow- up depend on etiology of Cushing's syndrome? (yes/no)
» If yes; please specify:

6.2 Is discharge of follow- up related to remission status in patients with Cushing's syndrome? Please specify (multiple options possible)
a. Discharge upon remission
b. Discharge X months/years in remission
» Please specify:
c. Not related to remission status; lifelong follow- up
d. Not related to remission status; patients are discharged of follow- up when...
» Please specify:

7. What is the frequency of transsphenoidal surgeries for Cushing's disease (CD) performed in 2019 and 2020?

Year	Number of transsphenoidal surgeries for CD
2019	
2020	

8. What is the frequency of adrenalectomies for Cushing's syndrome (CS) performed in 2019 and 2020?

Year	Number of adrenalectomies for CS
2019	
2020	

Section 2: Treatment of CS

The first- line treatment of all forms of Cushing's syndrome (CS) is surgery. If surgical resection of the primary tumour is not successful or not an option, second- line treatment includes medical treatment. Potential indications for medical therapy of CS include: 1) persistent or recurrent Cushing's syndrome after transsphenoidal or adrenal surgery; 2) non- feasibility for surgery; 3) acute complications of severe hypercortisolism; 4) pretreatment before surgery.

The following questions are about the first-choice medical therapy in the treatment of the different subtypes of CS, and about pretreatment before surgery (i.e. Preoperative Medical Treatment; PMT).

9. Which medical drug is first-choice in the treatment of Cushing's disease? (multiple options possible)
   - » Ketoconazole (x), metyrapone (x), mitotane (x), etomidate (x), osilodrostat (x), levoketoconazole (x), cabergoline (x), pasireotide (x), lanreotide (x), octreotide (x)
   - » Other, namely:
   - » Please specify in case of multiple options:

10. Which medical drug is first-choice in the treatment of ectopic ACTH/CRH syndrome? (multiple options possible)
    - » Ketoconazole (x), metyrapone (x), mitotane (x), etomidate (x), osilodrostat (x), levoketoconazole (x), cabergoline (x), pasireotide (x), lanreotide (x), octreotide (x)
    - » Other, namely:
    - » Please specify in case of multiple options:

11. Which medical drug is first-choice in the treatment of benign adrenal CS? (multiple options possible)
    - » Ketoconazole (x), metyrapone (x), mitotane (x), etomidate (x), osilodrostat (x), levoketoconazole (x), cabergoline (x), pasireotide (x), lanreotide (x), octreotide (x)
    - » Other, namely:
    - » Please specify in case of multiple options:
12. Which medical drug is first-choice in the treatment of malignant adrenal CS? (multiple options possible)

» Ketoconazole (x), metyrapone (x), mitotane (x), etomidate (x), osilodrostat (x), levoketoconazole (x), cabergoline (x), pasireotide (x), lanreotide (x), octreotide (x)
» Other, namely:
» Please specify in case of multiple options:

13. Do you provide combination medical therapy (e.g. combination of 2 or more cortisol lowering agents) in patients with severe hypercortisolism?
    a. No
    b. Yes, routinely
    c. Yes, sometimes depending on the case
    » If yes, which medical drugs does the first-choice combination therapy consist of?

Section 3: Preoperative medical treatment (PMT)

14. In the primary survey you indicated that your reference center provides PMT routinely to patients with Cushing's syndrome. Is this still applicable? Please specify.
    a. Yes, PMT is provided to all patients *Continue with question 16*
    b. Only in selected and/or severe cases with or without risk factors *Continue with question 16*
    c. No, PMT is never provided *Continue to part 4: Thromboprophylaxis*

15. In the primary survey you indicated that your reference center does not provide PMT routinely to patients with Cushing's syndrome. Is this still applicable? Please specify.
    a. Yes, PMT is never provided *Continue to part 4: Thromboprophylaxis*
    b. Only in selected and/or severe cases with or without risk factors *Continue with question 16*
    c. No, PMT is provided to all patients *Continue with question 16*

16. Providing PMT (routinely) to patients with Cushing's syndrome, do you take into account the following factors? (multiple options possible)
    a. No specific factors, all patients are medically pretreated before operation
    b. Severity of clinical syndrome as reflected by:
    1. Difficult-to-treat hypertension
    2. Uncontrolled diabetes mellitus or progressive glucose intolerance
    3. Biochemical severe cortisol excess
    4. Clinical severe syndrome/symptoms
    5. Severe psychotic decompensation
    6. Other, namely
    c. Risk factors for VTE (e.g. older age, cancer, current smoking, previous VTE)
    d. Active malignancy with/without treatment

17. What is/are your goals of PMT in patients with Cushing's syndrome? (multiple options possible)

a. Decrease of cortisol excess
b. Complete normalization of cortisol production
c. Improved regulation of hypertension and/or diabetes mellitus
d. Reduction of VTE risk
e. Prevention of cortisol withdrawal syndrome
f. Reduction of infectious complications
g. Reduction of other surgery- related complications (e.g. bleeding)
h. Reduction of psychopathology
i. Other, namely:

18. Which medical drug is first-choice in the preoperative medical treatment of the following subtypes of Cushing's syndrome (CS)? (multiple options possible)
    1. Pituitary CS: Ketoconazole (x), metyrapone (x), mitotane (x), etomidate (x), osilodrostat (x), levoketoconazole (x), cabergoline (x), pasireotide (x), lanreotide (x), octreotide (x)
    » Other, namely:
    » Please specify in case of multiple options:

    2. Benign adrenal CS: Ketoconazole (x), metyrapone (x), mitotane (x), etomidate (x), osilodrostat (x), levoketoconazole (x), cabergoline (x), pasireotide (x), lanreotide (x), octreotide (x)
    » Other, namely:
    » Please specify in case of multiple options:

    3. Malignant adrenal CS: Ketoconazole (x), metyrapone (x), mitotane (x), etomidate (x), osilodrostat (x), levoketoconazole (x), cabergoline (x), pasireotide (x), lanreotide (x), octreotide (x)
    » Other, namely:
    » Please specify in case of multiple options:

19. Do you provide combination preoperative medical treatment therapy (e.g. combination of two or more cortisol lowering agents) in Cushing's syndrome?
    a. No
    b. Yes, routinely
    c. Yes, sometimes depending on the case
    » If yes, which medical drugs does the combination therapy usually consist of?

20. When do you start PMT in patients with Cushing's syndrome?
    a. From diagnosis onwards
    b. ***X*** days preoperatively
    c. X days postoperatively
    d. Other, namely:

21. When do you stop PMT in patients with Cushing's syndrome?
    a. **X** days preoperatively
    b. **X** days postoperatively
    c. Other, namely:

Section 4: Thromboprophylaxis in CS

22. In the primary survey you indicated that your reference center provides thromboprophylaxis routinely to patients with Cushing's syndrome. Is this still applicable? Please specify.
    a. Yes, thromboprophylaxis is provided to all patients *Continue with question 25*
    b. Only in selected and/or severe cases with or without risk factors *Continue with question 25*
    c. No, thromboprophylaxis is never provided *Continue with question 30*

23. In the primary survey you indicated that your reference center provides thromboprophylaxis only in selected and/or severe cases of Cushing's syndrome with or without risk factors. Is this still applicable?
    a. Yes, only in selected and/or severe cases with or without risk factors. *Continue with question 25*
    b. No, thromboprophylaxis is provided to all patients *Continue with question 25*
    c. No, thromboprophylaxis is never provided *Continue with question 30*

24. In the primary survey you indicated that your reference center does not provide thromboprophylaxis to patients with Cushing's syndrome. Is this still applicable?
    a. Yes, thromboprophylaxis is never provided *Continue with question 30*
    b. Only in selected and/or severe cases with or without risk factors *Continue with question 25*
    c. No, thromboprophylaxis is provided to all patients *Continue with question 25*

25. Providing thromboprophylaxis routinely or only in selected and/or severe cases, when do you start thromboprophylaxis in patients with Cushing's syndrome?
    a. From diagnosis onwards
    b. X days preoperatively
    c. Start on the day before/of the surgery
    d. X days postoperatively
    e. Other, namely:

26. In starting (perioperative) thromboprophylaxis do you take into account the following factors? (multiple options possible)
    a. No specific factors, all patients are started on thromboprophylaxis routinely
    b. Obesity/overweight
    c. Severity of hypercortisolism
    d. Cardiovascular comorbidities

e. Previous VTE
f. Diabetes mellitus
g. Limitation of mobility
h. Non- 0 bloodgroup
i. von Willebrand Factor (VWF) promoter polymorphism haplotype 1
j. Known hereditary thrombophilia (e.g. factor V Leiden/Prothrombin 2021a)
k. Subtype of CS
» If yes: Which subtype(s) of CS is/are considered as a prothrombotic factor? (multiple options possible)
  • Cushing's disease
  • Ectopic ACTH/CRH syndrome
  • Adrenal CS, benign
  • Adrenal CS, malignant
l. Other risk factors for VTE (e.g. older age, cancer, current smoking)

27. Which anticoagulant drug is first-choice for (perioperative) thromboprophylaxis in patients with Cushing's syndrome? (multiple options possible)
  a. Low molecular weight heparin
  b. Unfractionated heparin via continuous iv infusion
  c. Apixaban
  d. Edoxaban
  e. Rivaroxaban
  f. Dabigatran
  g. Other, namely:
  h. Please specify in case of multiple options:

28. Having started (perioperative) thromboprophylaxis in patients with Cushing's syndrome, is the treatment duration standardized or individualized?
  a. Standardized
    » Continuation X days/weeks postoperatively.
  b. Individualized (multiple options possible)
  1. Stop upon achieving remission according to normalization of cortisol production.
  2. As soon as the patient is no longer immobile
  3. Based upon hemostatic parameters
    » If yes, which hemostatic parameters?
  4. Other, namely:

29. Can you please share the thromboprophylaxis protocol for patients with Cushing's syndrome (English version)? (yes/no)

30. If thromboprophylaxis is not (routinely) given (perioperatively), is there an indication for starting in the postoperative setting?
    1. No indication
    2. Active disease (not in remission)
    3. Acute fall in cortisol levels (cortisol withdrawal syndrome)
    4. Severe immobilization
    5. Infection
    6. Other, namely:

31. Do you routinely check for hereditary thrombophilia in patients diagnosed with Cushing's syndrome (for example Factor 5 Leiden, PT2021a)? (yes/no)

32. What is the frequency of clinical follow- up visits after surgery in case of uncomplicated surgery and post-operative course ?

33. What is the testing frequency of cortisol levels after surgery?

34. Does the postoperative laboratory testing include hemostatic parameters? (yes/no)
    - » If yes; which hemostatic parameters?

35. Do you routinely provide graduated compression stockings to patients with Cushing's syndrome after surgery? (yes/no)
    - » If yes, what is the duration of treatment?
      - » Not specified
      - » Until hospital discharge
      - » Continuously for *X* weeks postoperatively
      - » Other, namely: