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REVIEW

5th International ACC Symposium: Old Syndromes with New Biomarkers and New Therapies with Old Medications

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Abstract Adrenocortical carcinoma (ACC) is a rare endocrine malignancy with variable but often aggressive clinical course. Hormonal overproduction can be seen in about half of all ACC cases. When present, the hormonal excess leads to a wide range of metabolic, musculoskeletal, cardiovascular, and infectious complications and adds multiple layers of complexity to the management of ACC. To improve the outcome of patients with hormonally functioning ACC, an effective approach should include parallel efforts to achieve oncologic and hormonal control. An experienced multidisciplinary team is crucial to deliver and coordinate care to manage the specific aspects of this condition. In this review, we summarized the clinical features and management of hormonally functioning ACCs to assist practicing physicians in addressing the complex medical issues that can be seen in the context of this clinical entity.

Epidemiology

ACC is a rare endocrine malignancy with an estimated prevalence of about 1–2 cases per million population each year [1–3]. It is generally believed that over half of ACCs are associated with excessive hormonal production, but these estimates vary between different reports, ranging from 42 to 76 % [4–10]. Considering the retrospective nature of data to estimate the prevalence of hormonal overproduction in ACC, it is expected to see this wide range of estimates because of the referral and selection biases as well as variation in methodology to detect hormonal production between different series. Cortisol overproduction (Cushing syndrome) is the most clinical apparent syndrome in hormonally functioning ACC. In a report of 524 ACC patients who had complete surgical resection, 249 patients (47.5 %) had hormonally silent ACCs while 275 patients (52.5 %) had hormonally active disease. Excessive production of cortisol was seen in 150 patients (28.7 %), androgens in 58 patients (11.1 %), estrogen in 9 patients (1.7 %), mineralocorticoids in 7 patients (1.3 %), and more than one hormone (often cortisol with sex steroids) in nearly 10 % [9]. This distribution of hormonal production is relatively close to other estimates in other published series [5, 10].

Laboratory Assessment

In patients with adrenal tumors suspected to be ACC, a battery of tests is often ordered, including fasting blood glucose, serum potassium, bicarbonate, cortisol, adrenocorticotropic hormone (ACTH), 24-h urinary free cortisol, serum cortisol at 8 AM following a 1-mg dose of dexamethasone at midnight, renin and aldosterone levels (in patients with hypertension), adrenal androgens (dehydroepiandrosterone-sulfate (DHEA-S), androstenedione, testosterone), 17-OH progesterone, and serum estradiol (in men and postmenopausal women). It is also important to exclude pheochromocytoma by checking either plasma-free metanephrines or 24-h urinary metanephrines and catecholamines [11]. Various clinical syndromes of hormonal excess can be associated with ACC (Table 1). While clinical presentation can guide laboratory testing in most cases, many patients do not have pathognomonic symptoms but may still have asymptomatic

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Table 1 Clinical syndromes of hormonal excess in ACC with laboratory findings

Clinical presentation	Laboratory features
Cushing syndrome	↑ Glucose, ↑ HCO3, ↑ cortisol (urine, serum, or salivary) or after dexamethasone ↓ potassium, ↓ ACTH
Hyperandrogenism	↑ Testosterone, ↑ DHEA-S
Hyperaldosteronism	↑ HCO3, ↑ plasma aldosterone concentration ↓ potassium, ↓ plasma renin activity
Feminization	↑ Estradiol

pheochromocytoma or subclinical Cushing syndrome. Thus, all patients must have enough work-up to rule out pheochromocytoma and cortisol excess prior to surgical resection in order to prevent perioperative complications.

Urinary Steroid Biomarkers in ACC

Adrenal steroids are secreted from the adrenal cortex and usually follow a daily circadian secretion pattern. This circadian rhythm is usually lost in hormonally active ACCs. Thus, measuring 24-h urinary excretion of steroids and their metabolites is superior to single time point measurement of plasma/serum steroids to accurately assess adrenal steroid production. Gas chromatography with mass spectrometry has been used for almost five decades to measure steroid profiles and has been proposed as a useful tool to characterize adrenal tumors [12, 13].

ACCs have distinct urinary steroid profiles compared to benign adenomas, and this profile has high sensitivity to predict the malignant potential of adrenal tumors [14–16]. ACCs have relative deficiency in some key enzymes of the steroid metabolic pathway that could explain the difference in steroid secretion between adenomas and ACCs [17]. In a study by Kikuchi et al., the urinary steroid profile of patients with aldosterone or cortisol-secreting adrenal adenomas had increased the metabolites of the respective end hormones and immediate precursors. In contrast, ACC patients had elevated metabolites of 11-deoxycortisol or 33-hydroxy-5-ene [18]. In a retrospective study of 147 patients (102 with adrenocortical adenomas and 45 with ACC) who underwent a detailed analysis of their urinary steroid metabolites, the ACC group had a different urinary steroid profile compared to the adrenocortical adenoma group. The ACC cohort had increased levels of androgen precursor metabolites (pregnenediol, prenenetriol, DHEA, and 16-α-OH-DHEA), active androgen metabolites (androsterone and etiocholanolone), certain mineralocorticoid precursors (tetrahydro-11-dexoycorticosterone and 5-α-tetrahydro-11-deoxycorticosterone), glucocorticoid precursors (pregnenediol, pregnenetriol, 17-hydroxyprogesterone, and tetrahydro-11-deoxycortisol), free cortisol, 6-βOH-cortisol, tetrahydrocortisol, and α-cortrol, when compared to the adrenocortical adenoma cohort [16]. An ongoing international prospective study (EURINE-ACT) is expected to report the utility of urinary steroids' profiling in patients with adrenocortical neoplasia (ACC vs. adenoma).

Clinical Features

Cortisol Excess: Cushing Syndrome

Cushing syndrome associated with ACC can lead to the classic symptoms of weight gain, central fat distribution, moon facies, purple striae, edema, and proximal muscle weakness. In advanced ACC, patients may experience paradoxical weight loss and wasting. In addition to the known morbidity related to hyperglycemia, bone loss, and hypertension, cortisol overproduction is associated with increased risk for infections and thromboembolic complications. Compared to non-functioning ACCs, cortisol-producing ACCs carry worse prognosis with shortened recurrence-free survival after complete surgical resection (hazard ratio of 1.3) and also worsened overall mortality (hazard ratio of 1.55). There is no confirmed relationship between hormonal status and markers of cellular proliferation (mitotic rate), but it is assumed that cortisol production leads to a state of immunosuppression early in the disease course that predisposes these patients to have micrometastases [9]. Low serum glucocorticoid kinase 1 (SGK1) expression in human ACC has recently been proposed as a negative prognostic factor, as it is inversely proportional to cortisol secretion [19].

Glucocorticosteroid-induced venous thromboembolism (VTE) was first reported in 1950 [20]. Patients with Cushing syndrome from any cause (mostly pituitary Cushing disease) have a risk of 1.9–2.5 % to develop unprovoked VTEs which is ten times higher than the risk of VTE in general population [21, 22], a remarkable finding when compared to postoperative VTE in orthopedic cases, which can range from 1.3 to 4.4 %. Patients with cortisol-producing ACCs are expected to carry an even higher risk for VTEs compared to patients with pituitary Cushing disease, by mechanical impairment of the venous return from the lower extremities, especially in tumors invading major vessels (inferior vena cava and renal veins).

Glucocorticosteroid-induced VTE has been attributed as a cause of death in up to 1.9 % of Cushing syndrome cases [23]. This hypercoagulable state is likely multifactorial, related to the overproduction of coagulation factors, and due to the activation of coagulation pathways as well as impaired fibrinolysis [24, 25]. Retrospective data showed that using anticoagulation postoperatively in patients with Cushing syndrome was associated with lower risk for VTE compared to patients who did not receive anticoagulation therapy [21]. The risk for VTE remained elevated for about a year after surgical cure of Cushing syndrome. There is no prospective data to validate the rule of prophylactic anticoagulation in patients with Cushing syndrome.

There is a concern about systemic opportunistic infections at chemotherapy induction or surgery without proper hormonal management. Elevated cortisol levels are associated with a variety of invasive fungal or opportunistic infections including *Pneumocystis carinii*, aspergillosis, candidiasis, and cryptococcus, in addition to the more common infections. It is estimated that one fifth of all cases of death in hypercortisolemic patients are attributed to infections [26, 27]. Appropriate suppression and treatment of the cortisol excess can reverse the immunocompromised state [28]. Despite the lack of prospective data about the benefit of hormonal control to reduce infectious complications, our standard practice is to achieve intensive control of cortisol overproduction prior to the start of chemotherapy or surgery with the assumption that this could reduce the risk of infectious and other complications.

Hyperandrogenism

Androgen oversecretion is seen in about 10 % of hormonally producing ACCs [9]. It manifests with hirsutism, menstrual abnormalities, infertility, and virilization in women (which would include alopecia, lower toned voice, and clitoral hypertrophy). The co-secretion of androgens and cortisol in patients with adrenal masses is highly suggestive of ACC.

Aldosterone Excess

Aldosterone hypersecretion is one of the least common syndromes of hormonal overproduction in ACC. It typically presents as uncontrolled or difficult to control hypertension with hypokalemia, and some patients may develop weight loss associated with tumor burden [29]. There have been unusual cases of aldosterone-producing ACC in the absence of hypertension [30]. In addition, these tumors may not show the large adrenal mass typical of ACC [29, 31].

Feminization

Estrogen-secreting tumors are rare, about 1–2 % of ACCs, and almost exclusively described in male patients presenting with gynecomastia [32–34]. Other symptoms seen may be related to low-androgen state, such as fatigue, decreased libido, and erectile dysfunction. Women may manifest symptoms of postmenopausal vaginal bleeding, with or without changes in libido [35].

Hormonal Management

Surgery remains the most important treatment of ACC, regardless of the hormonal excess in question [4, 36]. Complete surgical resection offers the best clinical outcomes and prolongs survival [37]. However, for unresectable tumors, the recurrence of tumor after surgery, or preoperatively, medical therapy is often required for hormonal control as shown in Table 2 [36]. Multiple medications can be used and they often target key enzymes within the steroidogenesis pathway (Fig. 1). A tailored approach is necessary when treating hormonal excess in ACC.

Mitotane

Mitotane has been in use to treat ACC for a few decades and can have particular benefit in hormonally active ACCs [9, 10]. Mitotane inhibits 11-β hydroxylase and cholesterol side-chain cleavage. In addition, mitotane has adrenolytic properties with direct cytotoxic action on the adrenal cortex [36, 38]. Mitotane's beneficial effects on cortisol production was seen with a median plasma level of 10 mg/L and with an average daily dose of 2.7 g, compared to the commonly targeted level of 14–20 mg/L and typical dose of 3–6 g for oncological purposes [39, 40]. The main side effects of mitotane include adrenal insufficiency (due to

Table 2 Most commonly used medications to control hormonal excess in ACC

Drug	Mechanism of action	Dose	Titration	Precautions	Cost
Mitotane	• Adrenolytic • cholesterol side-chain cleavage • inhibition of 11-βOHase	3–6 g	Tolerance and mitotane levels	Toxicity, drug interactions with CYP3A4 induction	+++
Metyrapone	• Inhibition of 11-βOHase	750–3000 mg	Tolerance and cortisol levels	Hypertension, hypokalemia, and androgen excess	+++
Ketoconazole	• Cholesterol side-chain cleavage • inhibition of 11-βOHase • C17-20 desmolase • inhibition of 18-OHase	400–1200 mg	Tolerance and cortisol levels	Liver toxicity (black box warning) CYP3A4 inhibition	+
Mifepristone	• Glucocorticoid receptor blocker	300–1200 mg	Clinical assessment	Hypertension and hypokalemia	+++
Etomidate	• Inhibition of 11-βOHase • Cholesterol side chain cleavage	3–5 mg loading dose followed by 0.03–0.10 mg/kg/h	Renal function and tolerance	Sedation	+++
Aldosterone antagonists (spironolactone)	• Mineralocorticoid receptor blocker	50–400 mg	Renal function and electrolytes	Hyperkalemia	+

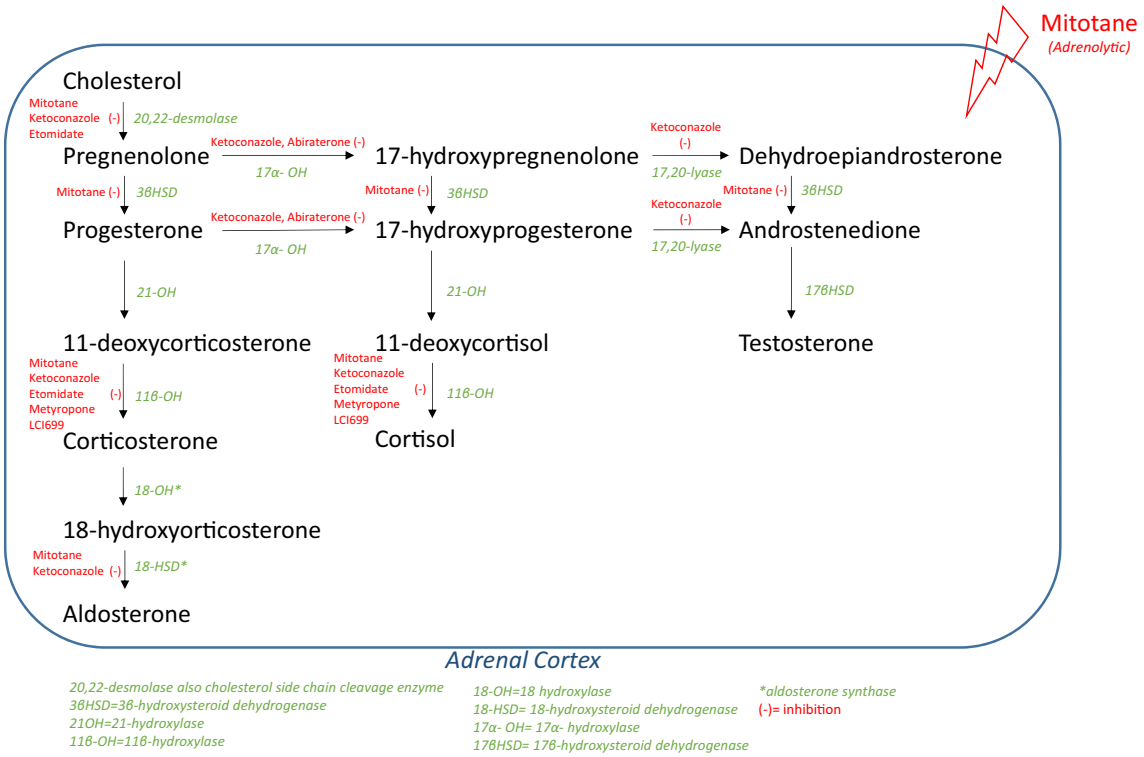

Fig. 1 Medication inhibition in steroidogenesis pathway

adrenolytic effect on the remaining adrenal gland and the activation of CYP3A4, leading to increased hydrocortisone inactivation), and, therefore, concurrent administration of higher than the average glucocorticoid replacement is necessary. Other adverse reactions include gastrointestinal symptoms (anorexia, nausea, and vomiting) and neurologic disturbances (such as ataxia, somnolence, and lethargy) [4, 36]. These side effects may be sustained due to the prolonged half-life and storage in adipose tissue, and its action of onset is delayed, often necessitating the use of other treatment for faster hormonal regulation [36, 41]. While few patients are intolerant to mitotane, many patients can be treated successfully with mitotane for prolonged periods of time by proper management of adverse effects.

Ketoconazole

Ketoconazole, an imidazole derivative and antimycotic, is a steroidogenesis inhibitor impairing P450-dependent enzymes in glucocorticoid and mineralocorticoid syntheses: 17,20-lyase, 11-β-hydroxylase, 17-hydroxylase, 18-hydroxylase, and cholesterol side-chain cleavage. Ketoconazole is orally administrated and the dose is usually between 400 and 1200 mg daily. Titration is based on cortisol level, side effect profile (which most prominently includes hepatotoxicity), and drug-drug interaction. On average, there is a greater than 50 % drop in cortisol levels, as well as improvements seen in other metabolic and electrolyte derangements of Cushing syndrome [42]. It has also been shown to control androgen excess in ACC, where the hormonal improvement in DHEA-S and testosterone were seen within 1 week of treatment [43, 44]. Overall, it is an inexpensive medication, making it very accessible.

Metyrapone

Metyrapone is another orally administered inhibitor of 11-β-hydroxylase in the steroidogenesis pathway, and the daily dose is between 750 and 3000 mg. However, given the short half-life of 2 h, multiple daily doses are required [45]. Side effects include hypertension, hypokalemia (both due to the accumulation of mineralocorticoid precursors), and can worsen hirsutism and acne (due to a shift towards androgen synthesis as shown in Fig. 1). Gastrointestinal disturbances are noted at the higher, therapeutic doses to control hypercortisolism.

Combination Therapy

Corcuff et al. reported the benefit of the combination therapy of metyrapone and ketoconazole with mitotane. Both metyrapone and ketoconazole have rapid onset of action and can work synergistically to inhibit various sites on the steroidogenesis pathway, thereby enabling a lower dose of each medication to avoid adverse effects. This combination was studied in eight patients with ACC, where urine-free cortisol markedly improved. In six out of eight of these patients, mitotane was also implemented

either at the onset or during the treatment for more long-term control of cortisol. The side effects of this combination therapy were similar to the individual drug adverse reactions, including mild gastrointestinal disturbance, and transaminitis seen in one case where ketoconazole was stopped in that patient [46].

Mifepristone

Mifepristone is a synthetic orally administered antiprogesterone drug when used in low doses, but it also blocks glucocorticoid receptor when given at higher doses. Mifepristone has higher affinity to competitively bind to the glucocorticoid receptor compared to cortisol [47]. Mifepristone has three active metabolites that can also antagonize glucocorticoid receptors [48]. Mifepristone is approved to control hyperglycemia in Cushing syndrome patients who are not surgical candidates or failed surgical intervention. Daily dose ranges from 300 to 1200 mg. Studies have shown improvement in glycemic control and mood stabilization [49, 50]. The reported experience with mifepristone in cortisol-producing ACC is limited to few reports. Castinetti et al. observed clinical improvement in 8/12 patients with ACC within the first month who were previously treated unsuccessfully with surgery, cytotoxic chemotherapy, and/or mitotane, or combinations of mitotane, ketoconazole, metyrapone, or etomidate [51]. Titration of mifepristone is based on clinical assessment, such as glucose levels and weight loss, as the cortisol level may not change with the initiation of treatment. Therefore, it may be considered difficult to monitor due to the lack of a laboratory marker. It is one of the more expensive regimens to treat hypercortisolemia compared to ketoconazole [50]. The most common side effect is hypokalemia, which can occur in 34 % of patients [49]. There is a potential for drug-drug interactions due to its metabolism via CYP3A4 and its long half-life (approximately 85 h) especially after multiple doses [48]. Therefore, drugs with a major effect on CYP3A4 should be avoided in patients receiving mifepristone. If used in combination with ketoconazole, which is also a CYP3A4 inhibitor, mifepristone levels can rise, and, therefore, the dose should be limited to 300 mg/day. The combination of mifepristone and metyrapone can worsen hypokalemia [48].

Etomidate

Etomidate, an imidazole derivative like ketoconazole, has been used as an anesthetic during surgery and has the advantage of rapid onset of sedation and favorable cardiovascular profiles [41, 52]. However, it is used less often now as an anesthetic due to the potential outcome of adrenal insufficiency leading to increased postoperative mortality. It inhibits 11-β-hydroxylase and cholesterol side-chain cleavage with immediate reduction in cortisol levels, with effects persisting hours after surgery [53]. As an intravenous medication, its potential is seen in those who have excessive cortisol levels and unable to take oral medications, especially in emergency cases with acute symptoms of hypercortisolemia, or as a bridge to surgery [52]. Patients receiving etomidate should be monitored in the intensive care unit, and cortisol levels should be checked every 4–6 h.

LCI699 (Osilodrostat)

LCI699 is a potent inhibitor of 11-β-hydroxylase and currently under investigation for the treatment of Cushing disease [41, 54]. It has been shown at higher doses to inhibit 11-β-hydroxylase, with half-life of 4 h [41, 55]. The evidence of aldosterone reduction and control of hypertension was also seen [55]. The inhibition of 11-β-hydroxylase is similar to that of metyrapone; however, it is more potent and has a rapid onset of action. In a study of 12 patients with Cushing disease, 11 of them saw the normalization of their urine-free cortisol at the end of the 10-week treatment period. The adverse reactions appeared to be similar to metyrapone, with fatigue and gastrointestinal intolerance as the most common complaints. Testosterone level also increased in women compared to baseline; though due to the short study period, hirsutism was not observed [55]. In patients with hyperaldosteronism, one study demonstrated a 70–80 % reduction in urine and plasma aldosterone, and correction in hypokalemia within the first week of treatment [54]. Though this has not been studied directly in ACC, it has the potential of reducing both aldosterone and cortisol levels with more rapid onset time.

Abiraterone Acetate

Abiraterone acetate is an androgen synthesis inhibitor that blocks steroidogenesis at multiple levels leading to androgen and cortisol reduction. It is approved in the treatment of castration-resistant prostate cancer. It potently and irreversibly blocks 17-α-hydroxylase and is ten times more potent than ketoconazole [56].

Aldosterone Antagonists

Mineralocorticoid receptor blockade with spironolactone and eplerenone has effects of normalizing potassium and blood pressure. The starting dose of spironolactone is 12.5–25 mg daily with food and titrated per response. Eplerenone is started at 25 mg twice a day and titrated up for blood pressure and potassium. In a randomized clinical trial comparing spironolactone and eplerenone in primary hyperaldosteronism, there was greater reduction in diastolic blood pressure in spironolactone compared to eplerenone, however, with a 21 versus 4.5 % development of gynecomastia in men, respectively [57]. Alternatively, for those intolerant to the above, amiloride and triamterene can also be implemented and are potassium-sparing diuretics that block aldosterone sodium

channels in the collecting tubules. In aldosterone-producing ACCs, high doses of spironolactone are often needed approaching 300–400 mg daily to help with hypokalemia and hypertension.

Aromatase Inhibitors/SERMs

Rarely, ACC patients can have estrogen production leading to gynecomastia or abnormal vaginal bleeding in postmenopausal women. Aromatase inhibitors or antiestrogens could be used in estrogen-producing ACC though there is no published literature about their efficacy in this clinical situation.

Conclusion

In the absence of prospective data, the control of hormonal excess syndromes in ACC (cortisol overproduction in particular) remains a clinically prudent measure to improve the performance status of these patients and potentially reduce the complications associated with hormonal overproduction.

The medical treatment targeting hormonal excess can be divided into two major categories: enzyme blockade in steroidogenesis and attempts to block steroids action at the receptor level. The success of such treatment will depend on coordinated multidisciplinary effort that combines cytoreductive strategy (surgery or chemotherapy) with effective medical treatment to address the hormonal overproduction.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

References

1. Else T et al (2014) Adrenocortical carcinoma. Endocr Rev 35(2): 282–326
2. Kebebew E et al (2006) Extent of disease at presentation and outcome for adrenocortical carcinoma: have we made progress? World J Surg 30(5):872–8
3. Kerkhofs TM et al (2013) Adrenocortical carcinoma: a population-based study on incidence and survival in the Netherlands since 1993. Eur J Cancer 49(11):2579–86
4. Luton JP et al (1990) Clinical features of adrenocortical carcinoma, prognostic factors, and the effect of mitotane therapy. N Engl J Med 322(17):1195–201
5. Ayala-Ramirez M et al (2013) Adrenocortical carcinoma: clinical outcomes and prognosis of 330 patients at a tertiary care center. Eur J Endocrinol 169(6):891–9
6. Crucitti F et al (1996) The Italian registry for adrenal cortical carcinoma: analysis of a multiinstitutional series of 129 patients. The ACC Italian registry study group. Surgery 119(2):161–70
7. Vassilopoulou-Sellin R, Schultz PN (2001) Adrenocortical carcinoma. Clinical outcome at the end of the 20th century. Cancer 92(5): 1113–21
8. Icard P et al (2001) Adrenocortical carcinomas: surgical trends and results of a 253-patient series from the French association of endocrine surgeons study group. World J Surg 25(7):891–7
9. Berruti A et al (2014) Prognostic role of overt hypercortisolism in completely operated patients with adrenocortical cancer. Eur Urol 65(4):832–8
10. Abiven G et al (2006) Clinical and biological features in the prognosis of adrenocortical cancer: poor outcome of cortisol-secreting tumors in a series of 202 consecutive patients. J Clin Endocrinol Metab 91(7):2650–5
11. Fassnacht M, Allolio B (2009) Clinical management of adrenocortical carcinoma. Best Pract Res Clin Endocrinol Metab 23(2):273–89
12. Sjovall K et al (1966) Estimation of dehydroepiandrosterone sulfate in human serum by gas–liquid chromatography. Anal Biochem 14(3):337–46
13. Horning EC, Brooks CJ, Vanden Heuvel WJ (1968) Gas phase analytical methods for the study of steroids. Adv Lipid Res 6:273–392
14. Grondal S et al (1990) Steroid profile in urine: a useful tool in the diagnosis and follow up of adrenocortical carcinoma. Acta Endocrinol (Copenh) 122(5):656–63
15. Shackleton CH (1993) Mass spectrometry in the diagnosis of steroid-related disorders and in hypertension research. J Steroid Biochem Mol Biol 45(1–3):127–40
16. Arlt W et al (2011) Urine steroid metabolomics as a biomarker tool for detecting malignancy in adrenal tumors. J Clin Endocrinol Metab 96(12):3775–84
17. Lipsett MB, Hertz R, Ross GT (1963) Clinical and pathophysiologic aspects of adrenocortical carcinoma. Am J Med 35:374–83
18. Kikuchi E et al (2000) Urinary steroid profile in adrenocortical tumors. Biomed Pharmacother 54(Suppl 1):194s–197s
19. Ronchi CL et al (2012) Low SGK1 expression in human adrenocortical tumors is associated with ACTH-independent glucocorticoid secretion and poor prognosis. J Clin Endocrinol Metab 97(12): E2251–60
20. Cosgriff SW, Diefenbach AF, Vogt W Jr (1950) Hypercoagulability of the blood associated with ACTH and cortisone therapy. Am J Med 9(6):752–6
21. Boscaro M et al (2002) Anticoagulant prophylaxis markedly reduces thromboembolic complications in Cushing's syndrome. J Clin Endocrinol Metab 87(8):3662–6
22. Rees DA et al (2002) Long-term follow-up results of transsphenoidal surgery for Cushing's disease in a single centre using strict criteria for remission. Clin Endocrinol (Oxf) 56(4): 541–51
23. Van Zaane B et al (2009) Hypercoagulable state in Cushing's syndrome: a systematic review. J Clin Endocrinol Metab 94(8):2743–50
24. Naess IA et al (2007) Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost 5(4):692–9
25. van der Pas R et al (2013) Hypercoagulability in Cushing's syndrome: prevalence, pathogenesis and treatment. Clin Endocrinol (Oxf) 78(4):481–8
26. Fareau GG, Vassilopoulou-Sellin R (2007) Hypercortisolemia and infection. Infect Dis Clin North Am 21(3):639–57, viii
27. Ntali G et al (2013) Mortality in Cushing's syndrome: systematic analysis of a large series with prolonged follow-up. Eur J Endocrinol 169(5):715–23
28. Wurzburger MI et al (1986) Cushing's syndrome—transitory immune deficiency state? Postgrad Med J 62(729):657–9
29. Seccia TM et al (2005) Aldosterone-producing adrenocortical carcinoma: an unusual cause of Conn's syndrome with an ominous clinical course. Endocr Relat Cancer 12(1):149–59
30. Song MS et al (2012) Aldosterone-producing adrenocortical carcinoma without hypertension. Korean J Intern Med 27(2):221–3

31. Hussain S et al (2015) Pure aldosterone-secreting adrenocortical carcinoma in a patient with refractory primary hyperaldosteronism. Endocrinol Diabetes Metab Case Rep 2015:150064
32. Moreno S et al (2006) Feminizing adreno-cortical carcinomas in male adults. A dire prognosis. Three cases in a series of 801 adrenalectomies and review of the literature. Ann Endocrinol (Paris) 67(1):32–8
33. Fancellu A, Pinna A, Porcu A (2014) Feminizing adrenocortical carcinoma with distant metastases: can surgery be considered? Clin Pract 4(2):651
34. Libe R et al (2014) A feminizing adrenocortical carcinoma in the context of a late onset 21-hydroxylase deficiency. J Clin Endocrinol Metab 99(6):1943–4
35. Barcelo B et al (1979) Feminizing adrenocortical carcinoma in a postmenopausal woman. Postgrad Med J 55(644):406–8
36. Nieman LK et al (2015) Treatment of Cushing's syndrome: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 100(8):2807–31
37. Berruti A et al (2012) Adrenal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 23(Suppl 7):vii131–8
38. Nelson AA, Woodard G (1949) Severe adrenal cortical atrophy (cytotoxic) and hepatic damage produced in dogs by feeding 2,2-bis(parachlorophenyl)-1,1-dichloroethane (DDD or TDE). Arch Pathol (Chic) 48(5):387–94
39. Baudry C et al (2012) Efficiency and tolerance of mitotane in Cushing's disease in 76 patients from a single center. Eur J Endocrinol 167(4):473–481
40. Terzolo M et al (2013) Mitotane levels predict the outcome of patients with adrenocortical carcinoma treated adjuvantly following radical resection. Eur J Endocrinol 169(3):263–70
41. Daniel E, Newell-Price JD (2015) Therapy of endocrine disease: steroidogenesis enzyme inhibitors in Cushing's syndrome. Eur J Endocrinol 172(6):R263–80
42. Castinetti F et al (2014) Ketoconazole in Cushing's disease: is it worth a try? J Clin Endocrinol Metab 99(5):1623–30
43. Verhelst JA et al (1989) Use of ketoconazole in the treatment of a virilizing adrenocortical carcinoma. Acta Endocrinol (Copenh) 121(2):229–34
44. Kruimel JW et al (1991) Favourable response of a virilizing adrenocortical carcinoma to preoperative treatment with ketoconazole and postoperative chemotherapy. Acta Endocrinol (Copenh) 124(4):492–6
45. Verhelst JA et al (1991) Short and long-term responses to metyrapone in the medical management of 91 patients with Cushing's syndrome. Clin Endocrinol (Oxf) 35(2):169–78
46. Corcuff JB et al (2015) Rapid control of severe neoplastic hypercortisolism with metyrapone and ketoconazole. Eur J Endocrinol 172(4):473–81
47. Johanssen S, Allolio B (2007) Mifepristone (RU 486) in Cushing's syndrome. Eur J Endocrinol 157(5):561–9
48. Morgan FH, Laufgraben MJ (2013) Mifepristone for management of Cushing's syndrome. Pharmacotherapy 33(3):319–29
49. Fleseriu M et al (2012) Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome. J Clin Endocrinol Metab 97(6):2039–49
50. Fleseriu M et al (2013) A new therapeutic approach in the medical treatment of Cushing's syndrome: glucocorticoid receptor blockade with mifepristone. Endocr Pract 19(2):313–26
51. Castinetti F et al (2009) Merits and pitfalls of mifepristone in Cushing's syndrome. Eur J Endocrinol 160(6):1003–10
52. Preda VA et al (2012) Etomidate in the management of hypercortisolaemia in Cushing's syndrome: a review. Eur J Endocrinol 167(2):137–43
53. Wagner RL et al (1984) Inhibition of adrenal steroidogenesis by the anesthetic etomidate. N Engl J Med 310(22):1415–21
54. Amar L et al (2010) Aldosterone synthase inhibition with LCI699: a proof-of-concept study in patients with primary aldosteronism. Hypertension 56(5):831–8
55. Bertagna X et al (2014) LCI699, a potent 11beta-hydroxylase inhibitor, normalizes urinary cortisol in patients with Cushing's disease: results from a multicenter, proof-of-concept study. J Clin Endocrinol Metab 99(4):1375–83
56. Potter GA et al (1995) Novel steroidal inhibitors of human cytochrome P45017 alpha (17 alpha-hydroxylase-C17,20-lyase): potential agents for the treatment of prostatic cancer. J Med Chem 38(13): 2463–71
57. Parthasarathy HK et al (2011) A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism. J Hypertens 29(5):980–90