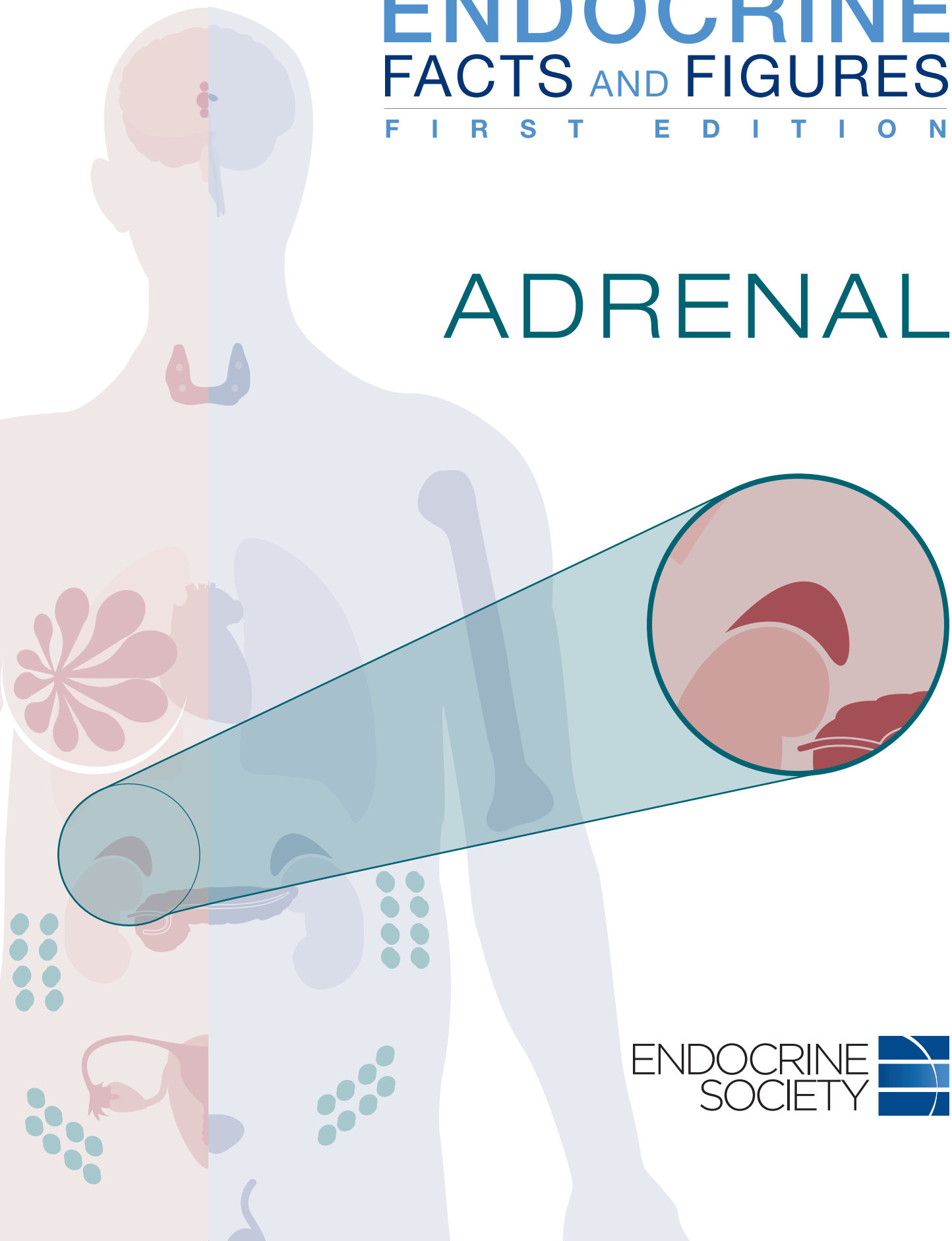
ENDOCRINE FACTS AND FIGURES

FIRST EDITION

ADRENAL



ENDOCRINE SOCIETY

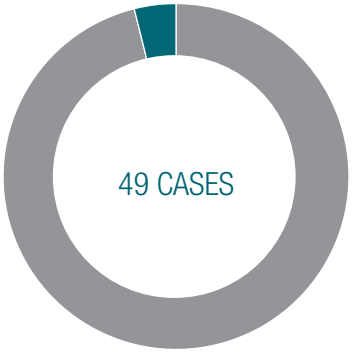
PREVALENCE AND INCIDENCE

PRIMARY ADRENAL INSUFFICIENCY

PER 1,000,000 IN THE US[1,2]

CUSHING'S SYNDROME

INCIDENCE PER 1,000,000 ADULTS <65 IN THE US[3]



CUSHING'S DISEASE

INCIDENCE PER 1,000,000 ADULTS <65 IN THE US[3]

COST BURDEN

$4,957
DISEASE-RELATED COSTS

$9,353
TREATMENT COSTS

SEX DIFFERENCES

CUSHING'S DISEASE

CASES PER 1,000,000 PER YEAR IN THE US[3]

Source:

1 Betterle C., Morlin L. Autoimmune Addison's Disease. *Endocr Dev*. 2011;20:161-172.

2 National Institute of Diabetes and Digestive Kidney Diseases (NIDDK). Adrenal Insufficiency and Addison's Disease. Bethesda, MD: NIH; 2014:1-16.

3 Broder M.S., Neary M.P., Chang E., Cherepanov D., Ludlam W.H. Incidence of Cushing's syndrome and Cushing's disease in commercially-insured patients <65 years old in the United States. *Pituitary*. 2014.

4 Broder M.S., Neary M.P., Chang E., Cherepanov D., Ludlam W.H. Burden of Illness, annual healthcare utilization, and costs associated with commercially insured patients with Cushing Disease in the United States. *Endocr Pract*. 2015;21(1):77-86.

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Mission Statement of the Endocrine Society

The mission of the Endocrine Society is to advance excellence in endocrinology and promote its essential and integrative role in scientific discovery, medical practice, and human health.

About Endocrine Facts and Figures

Endocrine Facts and Figures is a compendium of epidemiological data and trends related to a spectrum of endocrine diseases. The data is organized into nine chapters covering the breadth of endocrinology: Adrenal, Bone and Mineral, Cancers and Neoplasias, Cardiovascular and Lipids, Diabetes, Hypothalamic-Pituitary, Obesity, Thyroid, and Reproduction and Development.

All data is sourced from peer-reviewed publications, with an additional round of review by a group of world-renowned experts in the field. Additional oversight from the Endocrine Facts and Figures Advisory Panel ensured fair and balanced coverage of data across the therapeutic areas.

The first edition of **Endocrine Facts and Figures** emphasizes data on the United States. Future updates to the report will include additional data for other countries.

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For More Information

For more information, updates, and the online version of this report, visit: www.endocrinefacts.org

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Disclaimer

This publication summarizes current scientific information about epidemiology and trends data related to a spectrum of endocrine diseases. It is not a practice guideline or systematic review. Except when specified, this publication does not represent the official policy of the Endocrine Society.

I OVERVIEW

In 1849, Thomas Addison identified adrenal insufficiency (AI) and named it Addison's disease (AD). He termed it a "remarkable form of anemia" and attributed it to dysfunctions of the "supra-renal capsules."[1] Each of these human adrenal glands is located on top of one of the kidneys, and can release four types of hormones in response to physiological stimuli: glucocorticoids (e.g., cortisol) that control inflammation; mineralocorticoids that regulate kidney and cardiovascular functions; catecholamines (e.g., adrenaline, noradrenaline, and dopamine) that regulate heart rate, blood pressure, and other functions; and adrenal androgens (e.g., dehydroepiandrosterone [DHEA]) that are precursors to testosterone and estrogen.[2]

The adrenal glands commonly are studied in the context of the hypothalamic-pituitary-adrenal axis because these glands collectively produce hormones that affect each other and regulate a variety of physiological processes: For example, the hypothalamus signals the pituitary to release adrenocorticotropic hormone (ACTH), which in turn affects the production and secretion of hormones from the adrenal cortex. Furthermore, increased cortisol levels from the adrenal glands can signal the pituitary to reduce ACTH production, which in turn reduces the production of cortisol.[2,3] Cushing's syndrome (CS) is caused by excess cortisol and may follow over-administration of prednisone, dexamethasone, or prednisolone.[4] Cushing's disease (CD) is a form of CS that causes overproduction of ACTH.[5]

Three types of AI are generally recognized: primary, secondary, and tertiary; Table 1 lists common characteristics of AI.

1.1 EPIDEMIOLOGY

1.1.1 Overall Prevalence and Incidence of Adrenal Insufficiency

In 2002, researchers reported the prevalence of primary AI as 40-100 cases/million and the incidence as 6 cases/million/year.[2,6] Recent data from Europe indicate that the prevalence of chronic primary AI rose from 47-70 cases/million in the 1960s to 93-144 cases/million by the end of the past century, and the current estimated incidence is 4.4-6.0 new cases/million/year.[7] The European data also suggest that genetic causes of primary AI are more common among children than in the adult population. In one group of children with primary AI, autoimmune disease appeared in only 13% of cases, but congenital adrenal hyperplasia and other genetic causes accounted for 78% of cases.[7]

Table 1

Common characteristics of adrenal insufficiency.

TYPE	FEATURES	CAUSES	REFERENCE
Primary (AD)	ACTH independent Greater than 90% loss of adrenal tissue Increased ACTH production Possible hyperpigmentation Lifetime therapy required	Autoimmune in 70-90% of US cases Polyglandular deficiency Infection (e.g., present in 30% of advanced HIV cases) Cancer Acute Addisonian crisis following infection, stress, hemorrhage, or shock	Betterle et al. 2011[6]; NIDDK, 2014[2]
Secondary	ACTH dependent Loss of glucocorticoid function Intact mineralocorticoid function Often hypoglycemic	Decreased or absent ACTH Pituitary depression or dysfunction Tumor or postpartum complication	Betterle et al. 2011[6]; NIDDK, 2014[2]
Tertiary	Caused by hypothalamic or pituitary depression or absence	Iatrogenic corticosteroid therapy with suppression of the hypothalamic-pituitary-adrenal axis Hypothalamic failure or dysfunction	Betterle et al. 2011[6]; NIDDK, 2014[2]

Abbreviations: ACTH, adrenocorticotropic hormone; HIV, human immunodeficiency virus; US, United States; AD, Addison's disease

1.2
COST BURDEN OF DISEASE

1.2.1
Cost of Adrenal Insufficiencies

Many studies of the burdens associated with adrenal insufficiencies have focused on patients' quality of life (QOL) (Table 2), but few reports estimated direct costs.

A United Kingdom (UK) study[15] calculated the direct and indirect cost of illness associated with AI over a 1-year period. AI patients do not produce cortisol and require glucocorticoid replacement therapy to survive, which is predominantly immediate-release hydrocortisone in the UK. With current therapy, AI patients have increased morbidity, premature mortality, and reduced QOL. Costs include the cost of glucocorticoid replacement therapy, primary and secondary care costs (general practitioner and outpatient appointments, admissions for adrenal crises, diagnosis and management of AI), and costs associated with reduced productivity (absenteeism). The costs associated with premature mortality, the treatment and management of co-morbidities, and the burden associated with reduced QOL were not included due to lack of data.

There are ~20,000 AI patients in the UK. The estimated cost of illness (in 2016 dollars) associated with AI is ~$4,768 per patient or ~$95 million over 1 year: replacement therapy, ~$52 million; general practitioner appointments, ~$4.3 million; secondary care, ~$10.6 million; and reduced productivity, ~$28 million.[15]

The high health care and social costs associated with AI highlight the clinical and economic need to improve glucocorticoid replacement therapy. Indeed, as some consequences of the disease were not included in the calculations, ~$95 million is likely a considerable underestimate of the true burden of disease.[15]

Researchers in New Zealand and Ireland reported that follow-up of incidentally detected adrenal masses identified few (< 1% of patients) functional carcinomas, and during follow-up, the false positive rates for

Table 2

Adrenal insufficiencies: burdens assessed by quality of life outcomes.		
POPULATION	QOL OUTCOMES	REFERENCE
Norway, N=79 AD patients	Patient with AI had impaired general health, vitality, social functioning, and emotional states.	Lovas et al. 2002[8]
Denmark, N=989 AI (primary or secondary) patients, N=124,854 osteoarthritis patients	Patient with AI had a 2.68 times greater rate of readmission for affective disorder and 2.12 greater rate of readmission for depressive disorder compared to those with osteoarthritis.	Thomsen et al. 2006[9]
Germany, N=256 AI patients	Patient with AI had impairment of subjective health status and greater depression; 18.3% were unemployed compared to 4.1% in the general population	Hahner et al. 2007[10]
Germany, N=216 primary or secondary AI patients	< 30% of women and < 50% of men were diagnosed within the first 6 months of symptom onset; > 67% consulted ≥ 3 physicians, and 68% were incorrectly diagnosed.	Bleicken et al. 2010[11]
International, N=1,245 primary or secondary AI patients (5% were unsure of diagnosis)	64% reported making changes to physical activity or social, work, or family life because of subjective health concerns; 40% missed school or work; 76% were concerned about long-term side effects of therapy.	Forss et al. 2012[12]
Netherlands, N=54 primary AI patients, N=54 matched controls	Maladaptive personality traits were positively associated with hydrocortisone dose, as were depression and impaired QOL.	Tiemensma et al. 2014[13]
A systematic literature search identifying 102 papers about QOL in pituitary adenoma patients	Surgical and pharmacological interventions improved but did not normalize QOL; psychosocial interventions possibly helped. Greater focus on QOL, better questionnaires, and more follow-up may lead to improvements.	Andela et al. 2015[14]

Abbreviations: AI, adrenal insufficiencies; QOL, quality of life; N, number; AD, Addison's disease

identifying adrenal carcinomas typically were 50 times greater than true positive rates.[16] Both the direct costs of treatment — including radiation exposure — and the indirect emotional costs to patients warrant a review of current guidelines.

1.2.2

Cost of Cushing's Disease

CD is a rare disorder resulting from ACTH-secreting pituitary tumors, in commercially insured patients in the United States (US).

A cost of illness study identified patients with CD in 2010 using the IMS Health PharMetrics and Truven Health Analytics MarketScan claims databases.[17] Because there is no diagnosis code for CD, patients were identified as having CD if they had a claim for CS plus either benign pituitary adenoma or hypophysectomy.

The study identified 685 CD patients (81% female; mean age, 41.7 years; mean Charlson comorbidity index, 1.6; mean number of chronic conditions, 4.2). Patients had a mean of 3.2 CD-related office visits per year, 26.9% had CD-related hospitalizations, 0.9% had CD-related emergency department visits, and 36.8% had CD treatments. Annual costs were $14,310 (CD treatment costs, $9,353; other CD-related costs, $4,957).[17]

The study also reported that CD patients have a high burden of illness. Among CD patients in this study, 30.5% had diabetes, 22.5% had psychiatric disturbances, 21% had infections, 8.6% had osteoporosis, 8% had cardiovascular disease/stroke, and 5.5% had kidney stones. Patients had 19.8 office visits per year, and > 34% of patients were hospitalized. Mean total cost of care was approximately $35,000 per year.[17]

II ADRENAL INSUFFICIENCIES

2.1

PREVALENCE AND INCIDENCE

Primary adrenal insufficiency (PAI) (also known as Addison's disease [AD]) is a rare health problem, which is associated with significant morbidity and an increased risk of mortality. Secondary adrenal insufficiency (SAI), which is due to disease in the pituitary or hypothalamus, is thought to be more common than PAI.[26] Table 3 summarizes available data for the prevalence and incidence of PAI and SAI.

Adrenal crisis (AC), which is an acute alteration in physiology due to adrenal hormone deficiency, is a life-threatening consequence of AI. It includes symptoms and signs such as vomiting, syncope, hypotension, and electrolyte abnormalities.[26]

Table 3

Prevalence and incidence of primary and secondary adrenal insufficiencies.

TYPE	POPULATION	PREVALENCE: CASES PER MILLION	INCIDENCE: CASES PER MILLION PER YEAR	REFERENCE
Primary	US	40-110	6	Betterle et al. 2011[6] NIDDK, 2014[2]
Primary	Norway	144	0.044	Erichsen et al, 2009[18]
Primary	European, white patients	93-140	4.7-6.2	Kong et al. 1994[19] Willis et al. 1997[20]
Primary	U.K	39	0.8	Mason et al. 1968[21]
Primary	Norway	140	0.62	Lovas et al. 2002[22]
Secondary AI	Germany, the UK and Sweden	150-280	N/A	Ekman et al. 2014[23]
Secondary AI	Sweden	6-11	N/A	Nilsson et al. 2000[24]
Secondary AI	Spain	2.9-4.5	N/A	Regal et al. 2001[25]

Abbreviations: ACTH, adrenocorticotropic hormone; HIV, human immunodeficiency virus; US, United States; UK, United Kingdom; AI, adrenal insufficiencies; N/A, not available

A recent meta-analysis of 74 studies (3,753 patients) found AI correlated with doses of corticosteroids and ranged from 2.4% among patients who received low doses to 21.5% among those who received high doses.[27] Among asthma patients who received corticosteroids, AD was associated with duration of administration and ranged from 1.4% for patients with a duration less than 28 days to 27.4% for patients with a duration greater than 1 year.[27]

The study concluded that AI after glucocorticoid discontinuation occurs frequently; there is no administration form, dosing, treatment duration, or underlying disease for which AI can be excluded with certainty, although higher dose and longer use give the highest risk; and the threshold to test corticosteroid users for adrenal insufficiency should be low in clinical practice, especially for those patients with nonspecific symptoms after cessation.[27]

2.2 DEMOGRAPHIC DIFFERENCES FOR ADRENAL INSUFFICIENCIES

Data indicates that both primary and secondary AI effect women more than men.[28,29] However, there have been no racial difference described in AI.[30]

An analysis of 140 families containing patients with AD without hypoparathyroidism, AD with hypoparathyroidism, and hypoparathyroidism alone showed significantly greater similarity of clinical and other attributes among affected persons within the families than among unrelated persons. This suggests that there are several categories distinct in origin and in characteristics. Some of these classes are apparently genetically determined and the distributions of affected persons are compatible with the autosomal recessive pattern. Other classes do not fit any Mendelian pattern, even while containing families with more than one affected person. This observation suggests additional heterogeneity.[28]

2.3 LIFE EXPECTANCY AND MORTALITY FOR ADRENAL INSUFFICIENCIES

Data on life expectancy and mortality data for AI are limited. Table 4 presents mortality data for AD.

2.4 KEY TRENDS AND HEALTH OUTCOMES FOR ADRENAL INSUFFICIENCIES

2.4.1 Diagnosis

AD results in glucocorticoid and mineralocorticoid deficiency. Orthostatic hypotension, fever, and hypoglycemia characterize acute AC; whereas chronic primary AI presents with a more insidious history of malaise, anorexia, diarrhea, weight loss, joint, and back pain. The cutaneous manifestations include darkening of the skin, especially in sun-exposed areas, and hyperpigmentation of palmar creases, frictional surfaces, vermilion borders, recent scars, genital skin, and oral mucosa. Measuring basal plasma cortisol is an insensitive screening test. Synthetic adrenocorticotropin 1-24 at a dose of 250 micrograms works well as a dynamic test.

Table 4

Addison disease standard mortality ratios.

STUDY PERIOD	POPULATION	SMR	REFERENCE
1964-2004	Sweden, N=3,299	Men: 2.5 Women: 2.9* **	Bergthorsdottir et al. 2006[31]
1987-2001	Sweden, N=1,675	Men: 2.19 Women: 2.86**	Bensing et al. 2008[32]
1943-2005	Norway, N=881	Woman: 1.18 Men: 1.10***	Erichsen et al. 2009[33]

Abbreviations: SMR, standard mortality ratio

Note: *, In these patients, the relative risk for death was approximately twice that of the general population and was associated with concomitant cardiovascular, malignant, and infectious diseases.[31]; **, A limitation of both Swedish studies was their use of high doses of glucocorticoids.[34,31]; ***, For both men and women, the mean ages at death (75.7 years and 64.8 years, respectively) were somewhat younger than estimated life expectancies (–3.2 years and –11.2 years, respectively).[33]

Elevated plasma levels of adrenocorticotropin and renin confirm the diagnosis.[35]

With the introduction of modern cortisol and ACTH assays, the interpretation of tests used for diagnosis and differential diagnosis has become more complex and requires local validation.[30]

Acute stress can aggravate symptoms. A simple strategy or diagnostic screening and early intervention with sodium chloride-containing fluids and hydrocortisone should be widely implemented for cases with suspected acute AI crisis. In contrast, the chronic replacement dosage for patients with AI should be as low as possible with clear instructions for dosage adjustments in case of stress or acute emergencies.[36]

In developed nations, autoimmune destruction of the adrenal cortex is a leading cause of AI.[37] The human leukocyte antigen genotype DR3/4-DQB1*0302 has been associated with type 1 diabetes and AI, and the allele frequency of the major histocompatibility complex gene, *MICA5.1*, was associated with patients who developed AI.[37] Even so, the authors noted that the current state of clinical knowledge does not warrant routine testing for these genetic factors.

2.4.2

Treatment for Adrenal Insufficiencies

Before synthetic glucocorticoid replacement therapies became available (e.g., mineralocorticoid desoxycorticosterone acetate in 1938 and hydrocortisone in 1948), AD was associated with > 80% 2-year mortality and an upper survival limit of approximately 5 years.[34,38]

Early daily doses of hydrocortisone typically were ≥ 30 mg, but later studies showed that healthy individuals physiologically produced 10-20 mg/d (based on body surface area), which led to clinicians prescribing correspondingly lower doses, that typically were administered in divided doses in order to mimic the circadian rhythm of cortisol production.[34]

Today, pharmaceutical approaches to treatment of AI involve 2- or 3-times daily administration of hydrocortisone, perhaps with once-daily fludrocortisone. However, emerging treatments focus on modified-release or continuous subcutaneous hydrocortisone infusion, as well as ACTH stimulation and immunomodulatory therapies.[39]

Despite improved outcomes following these changes, patients with AI continue to suffer from poor metabolic profiles, low quality of sleep, infertility, sexual dysfunction, and lower QOL.[40]

Tertiary AI often follows long-term exogenous glucocorticoids administration and the resultant extended suppression of the hypothalamic secretion of corticotropin-releasing hormone (CRH), arginine vasopressin, or both; thus treatment often involves glucocorticoid withdrawal at 9-12 months.[7,41]

Patients who are cured of CS may also develop tertiary AI, because persistently elevated serum cortisol levels suppress the hypothalamus-pituitary-adrenal axis in much the same manner as do elevated exogenous doses of glucocorticoids.[7]

Glucocorticoid signal transduction is impaired by drugs such as mifepristone, antipsychotics, and antidepressants, thereby contributing to tertiary AI.[7]

Other drug interactions have been suggested in the development of secondary AI. For example, researchers have reported six cases in which ritonavir and exogenous steroid medications required corticosteroid replacement therapy and hospitalization in two patients.[42]

Another group reported the development of secondary AI and CS after a patient received concomitant triamcinolone and ritonavir.[43] Others have pointed out that stopping, decreasing the dose, or changing the type of inhaled corticosteroids can result in secondary AI.[44]

DHEA-replacement therapy could help to restore QOL. However, glucocorticoid-replacement quality monitoring is hampered by lack of objective assessment methods, and is therefore largely based on clinical grounds.[29]

Treatment for AD has not significantly improved in 60 years, but current studies of modified-release hydrocortisone and subcutaneous infusion — although still in development — may contribute to improved patient health, satisfaction, and QOL.[39]

Long-term management in patients with AI remains a challenge, requiring an experienced specialist. However, all doctors should know how to diagnose and manage suspected acute adrenal failure.[29]

Table 5 presents available treatment options for AI.

2.5 ADRENAL INSUFFICIENCY CRISES

AC is a life-threatening event that can occur in AI patients receiving standard replacement therapy. Patient reports suggest that it is an underestimated and under-managed event.

In a postal survey in 2003 of 840 patients in with AD in four countries, UK (n=485), Canada (n=148), Australia (n=123), and New Zealand (n=85), about 8% of respondents needed hospital treatment for an AC annually

Exposure to gastric infection is the single most important factor predicting the likelihood of AC. Concomitant diabetes and/or asthma increase the frequency of ACs reported by patients.[51]

In another study of AC that prospectively followed up 423 patients with AI (PAI, n=221; SAI, n=202) for 2 years identified 64 ACs in 767.5 patient-years (8.3 crises per 100 patient-years). The precipitating causes were mainly gastrointestinal infection, fever, and emotional stress (20%, respectively). The study also documented the unexplained sudden onset of AC (7%) or other stressful events (e.g., major pain, surgery, strenuous physical

Table 5

Treatment options for adrenal insufficiencies.

TREATMENT	POPULATION	DESIGN	OUTCOMES	REFERENCE
DHEA replacement*	N/A	Review of studies on DHEA replacement	DHEA replacement produced moderate improvements in mood, sexuality, and subjective health status, but results were highly variable.	Lang et al. 2015[45]
CSHI versus OHC	Norway and Sweden N=25	An open, randomized, 2-period, 12-week crossover trial	CSHI re-established a circadian cortisol rhythm and normalized ACTH levels. CSHI produced a more stable nighttime glucose level compared with OHC without compromising insulin sensitivity.	Bjornsdottir et al. 2014[46]
Subcutaneous hydrocortisone infusion	Norway and Sweden N=33	Prospective crossover, randomized, multicenter clinical trial	Restored ACTH and cortisol levels to near normal circadian levels and improved patients' QOL.**	Oksnes et al. 2014[47]
4 weeks of CSHI and oral placebo versus subcutaneous placebo and OHC following a 2-week washout	Australia N=10	Multicenter, double-blind, placebo-controlled trial	Similar cortisol exposure during each treatment period, although a more circadian pattern was evident during CSHI. CSHI does not improve SHS in AD with good baseline SHS. This casts some doubt on the potential benefit of circadian cortisol delivery on SHS in AD.	Gagliardi et al. 2014[48]
Daily doses of a dual-release hydrocortisone formulation versus thrice-daily administration of a conventional dose	N=64	24-month trial	DR-HC is well tolerated in patients with primary AI during 24 consecutive months of therapy.	Nilsson et al. 2014[49]
Dual-release hydrocortisone formulation	N=30	Open, prospective trial at one endocrine center	Reduced body mass indexes and lowered HbA1c levels	Quinkler et al. 2015[50]

Abbreviations: OHC, orally administered hydrocortisone; CSHI, continuous subcutaneous hydrocortisone infusion; N, number; QOL, quality of life; ACTH, adrenocorticotropic hormone; SHS, subjective health status

Note: *, Treatments typically involve glucocorticoid replacement, the effectiveness of which is limited by the inability of conventional thrice daily dosing to mimic the body's diurnal cortisol profile.[45]; **, This delivery system may help patients who are poorly controlled by conventional therapy.[4]

activity, heat, pregnancy). Patients with a previous AC were at a higher risk of crisis.[52]

III CUSHING'S SYNDROME AND CUSHING'S DISEASE

CS refers to the clinical manifestations induced by chronic exposure to excess glucocorticoids and may have exogenous causes (e.g., excess glucocorticoid intake for the treatment of inflammatory conditions) or endogenous. There are three pathological conditions that can result in the chronic overproduction of endogenous cortisol. The most common condition is CD, where pituitary corticotroph adenoma overproduces ACTH. Secondly, and more rare, a non-pituitary tumor can produce ACTH in an "ectopic" manner. Finally, one or (rarely) both two adrenals that have tumors (benign or malignant) can directly over-secrete cortisol. Adrenocortical or exogenous adenomas and carcinomas cause primary hypercortisolism, which accounts for 20% of endogenous CS cases.[5,53,54] Chronic hyperproduction of ACTH causes secondary hypercortisolism, which accounts for roughly 80% of endogenous CS,[54] and ACTH-secreting pituitary or exogenous adenomas causes CD, which is the most common form of secondary hypercortisolism. CD accounts for 70% of CS cases.[55]

CS may follow over administration of prednisone, dexamethasone, or prednisolone. CS manifestations typically are nonspecific, which complicates the initial diagnosis.[4]

Commonly recommended initial testing are urinary free cortisol, late-night salivary cortisol, and 1-mg overnight dexamethasone suppression test (DST). Imaging is the key to diagnosis. CS continues to pose diagnostic and therapeutic challenges; life-long follow-up is mandatory.[56] Untreated, it has significant morbidity and mortality. The syndrome remains a challenge to diagnose and manage.[57,58]

3.1 PREVALENCE AND INCIDENCE FOR CUSHING'S SYNDROME

CS is a rare condition that, according to one estimate, affects fewer than five in 10,000 individuals.[59] Table 6 summarizes data on the prevalence and incidence of CS and CD.

3.2 DEMOGRAPHIC DIFFERENCES FOR CUSHING'S DISEASE

Initial diagnosis of CD typically is made in adults — mostly women — aged 30-50, and pediatric cases are rare.[63] Table 7 shows the age distribution among CD patients. Endogenous CS has been divided into corticotropin-dependent and corticotropin-independent types; the former may account for 80-85% of instances, of which an estimated 80% are caused by pituitary adenomas.[57]

3.3 LIFE EXPECTANCY AND MORTALITY FOR CUSHING'S SYNDROME AND CUSHING'S DISEASE

CS is rare and is associated with increased mortality in patients with no concurrent malignancy; also, the excess mortality usually occurs during the first year of disease. However, data on mortality associated with CD and CS are scarce, and the impaired quality of health in long-term survivors of CD is not fully explained.[61,64] Table 8 presents mortality data related to CD and CS.

3.4 KEY TRENDS AND HEALTH OUTCOMES FOR CUSHING'S SYNDROME AND CUSHING'S DISEASE

3.4.1 Diagnosis for Cushing's Syndrome and Cushing's Disease

Clinical presentation can be highly variable, and establishing the diagnosis can often be difficult.[58]

A positive diagnosis of CS requires that chronic hypercortisolism is unequivocally demonstrated biologically using tests such as the 24-hour urinary cortisol, late-evening plasma or salivary cortisol, diurnal cortisol test, midnight 1-mg, or the classic 48-hour-low-dose DST. All of which have essentially the same diagnosis potencies. The search for the responsible cause then relies on the assessment of corticotroph function and imaging. Suppressed ACTH plasma levels indicate adrenal CS, and the responsible unilateral adrenocortical tumor is always visible on computed tomography scans. However, its benign or malignant nature may be difficult to diagnose before surgery. Imaging can suspect bilateral adrenal CS, when the two adrenals are small, as in the

Table 6

The prevalence and incidence of Cushing's syndrome and Cushing's disease.				
POPULATION	DESIGN	PREVALENCE PER MILLION	INCIDENCE RATES: CASES PER MILLION PER YEAR	REFERENCE
US, aged ≤ 65 from 2007 to 2010*	Commercial database of patients	N/A	CS, 48.6 in 2009 and 39.5 in 2010.** CD, 7.6 in 2009 and 6.2 in 2010.***	Broder et al. 2014[60]
Medline database, 2000-2005	Systematic review	CS, 20,000-50,000 in patients with diabetes	0.7 to 2.4 (Researchers acknowledged that this estimate probably was too low.)	Newell et al. 2006[57]
166 Danish patients diagnosed with CS 1985-1995.	Data from the National Patient Register of the Danish National Board of Health	N/A	CD, 1.2-1.7; adrenal adenoma, 0.6; adrenal carcinoma, 0.2	Lindholm et al. 2001[61]
49 CD patients in Vizcaya (Spain) between 1975 and 1992	Epidemiological study	CD, 39.1	CD, 2.4 (15 times more frequent in women vs. men)	Extabe et al. 1994[62]

Abbreviations: N/A, not available; CS, Cushing's syndrome; CD, Cushing's disease; US, United States

Note: *, The authors defined CS as ≥ 2 claims of CS diagnosis in 1 year and defined CD as CS plus a diagnosis of benign pituitary adenoma or hypophysectomy during the same year.[60]; **, The authors noted that their estimates of US cases of CS and CD were somewhat higher than previous estimates from Europe. The lowest rates of CS were in ≤ 17-year-olds and highest rates were in 35- to 44-year-olds.[60]; ***, The lowest rates of CD were in ≤ 17-year-olds and highest rates were in 18- to 24-year-olds. The rates varied by sex (2.3-2.7 in males, 9.8-12.1 in females). In females, lowest rates ranged 2.5-4.0 in ≤ 17-year-olds and highest 16.7-27.2 in 18-24 year olds. In males, there were too few cases to report estimates by age.[60]

Table 7

Age distribution among United States Cushing's disease patients in 2010.		
≤ 17	29 (4.2)	REFERENCE
18–24	65 (9.5)	Broder et al. 2015[17]
25–34	108 (15.8)	
35–44	175 (25.5)	
45–54	186 (27.2)	
55–64	114 (16.6)	
≥ 65	8 (1.2)	

Table 8

Mortality associated with Cushing's disease and Cushing's syndrome.			
DATA SOURCE	NUMBER OF PATIENTS	SMR	REFERENCE
166 Danish patients diagnosed with CS from 1985-1995.	Data from the National Patient Register of the Danish National Board of Health	Of 139 patients with nonmalignant disease, SMR=3.68. In 45 patients with CD who had been cured through transsphenoidal neurosurgery, SMR=0.31. Of 20 patients with persistent hypercortisolism after initial neurosurgery, SMR=5.06. In patients with adrenal adenoma, SMR=3.95.	Lindholm et al. 2001[61]
N/A	Systematic review and meta-analysis of mortality studies in patients with CD and CS secondary to a benign adrenal adenoma	In patients with CD, SMR=1.84. In CD patients with persistent disease after initial surgery, SMR=3.73. In CD patients with initial remission, SMR=1.23. In patients with a benign adrenal adenoma, SMR=1.90.*	Graversen et al. 2012[64]
Spain, N=49 1975-1992	Epidemiological study	Overall, SMR=3.8. In patients with vascular disease, SMR=5.**	Extabe et al. 1994[62]
UK 1967-2009, Greece 1962-2009, N=418, all with endogenous CS (311 with CD, 74 with adrenal CS and 33 with ectopic CS)	A systematic analysis of a large series with prolonged follow-up	In CD overall, SMR=9.3. In adrenal CS, SMR=5.3.*** In ectopic CS, SMR=68.5.	Ntali et al. 2013[65]
N=33, CS patients	Columbia Presbyterian Medical Center Records, 1932-1951	5-year survival rate was 50%; life expectancy generally was limited by cardiovascular events, but over time mortality rates have decreased.	Plotz et al. 1952[66]
N=60, UK, 51 female, median age 36-46 years, median follow-up 15 years	SMR for 60 CD patients was compared with general UK. A meta-analysis of SMRs from seven studies (including this study) was performed for overall mortality in CD.	Overall, SMR=4.8 For vascular disease, SMR=13.8. For persistent disease (n=6), SMR=16 vs. remission (n=54) SMR=3.3. After adjustment for age and sex, relative risk of death for persistent disease was 10.7. Hypertension and diabetes mellitus were associated with significantly worse survival.	Clayton et al. 2011[67]
N=248 Dutch patients with pituitary adenomas treated by transsphenoidal surgery for NFMAs (n=174) and ACTH-producing adenomas (n=74).	Clinical study	For the entire cohort, SMR=1.41. For NFMA patients, SMR=1.24 vs. 2.39 in CD. In patients with CD vs. NFMAs, the age-adjusted mortality was significantly increased.	Clayton et al. 2011[67]

Abbreviations: N/A, not available; UK, United Kingdom; SMR, standard mortality ratio, CS, Cushing's syndrome; CD Cushing's disease; N, number; NFMA, nonfunctioning pituitary macroadenomas

Note: *, Age, sex and observation time did not significantly impact mortality.[64]; **, Higher age, persistence of hypertension and abnormalities of glucose metabolism after treatment, were independent predictors of mortality (multivariate analyses, $P < 0.01$).[62]; ***, SMR was high overall as well as in all subgroups of patients irrespective of their remission status. In CD, the probability of 10-year survival was 95.3% with 71.4% of the deaths attributed to cardiovascular causes or infection/sepsis. In adrenal CD, the probability of 10-year survival was 95.5%. Patients with ectopic CD had the worst outcome with 77.6% probability of 5-year survival.[65]

primary pigmented nodular adrenal dysplasia associated with Carney complex, or enlarged, as in the ACTH-independent macronodular adrenocortical hyperplasia (or primary macronodular adrenal hyperplasia). Measurable or increased ACTH plasma levels indicate either CD or the ectopic ACTH syndrome. When the dynamics of the corticotroph function (high-dose DST, the CRH test) are equivocal, and/or the imaging is non-contributive, it may be difficult to distinguish between the two. This is a situation where sampling ACTH plasma levels in the inferior petrosal sinus may be necessary.[53]

Biochemical diagnosis of CS is complicated by the cyclical nature of cortisol secretions. First-line biochemical tests include late-night salivary cortisol and urinary free cortisol tests.[57] Researchers have compared these two diagnostic approaches in a group of patients who presented with CS, CD, or obesity; each patient provided three samples for both tests.[69] The two approaches had similar variability, but late-night salivary cortisol testing demonstrated better diagnostic performance.[69]

Dexamethasone extinction testing is another approach to confirm a CS diagnosis, but it requires careful controls and may not provide sufficient diagnostic accuracy to be used alone.[57] Thus, a differential CS diagnosis often relies on biochemical assays.[70] The dexamethasone extinction test followed by the CRH extinction test[71,72] has provided a single measurement of cortisol from late-night serum or saliva samples. The desmopressin test may facilitate a rapid diagnosis of cyclical CD.[73] Researchers are studying tests and strategies that may enable more accurate and more convenient diagnosis of CS and CD.[74,75]

Imaging studies for the diagnosis of CS and CD have been challenging: MRI has been estimated to detect only 60-70% of CD adenomas.[76-78] Moreover, positive MRI results may be confounding because incidental pituitary adenomas may exist in 10% of the population.[79] Further, microadenomas may be difficult to image, and full-body scans have been used for differential diagnosis.[53]

Bilateral intrapetrosal sinus sampling may help physicians to distinguish between pituitary and ectopic sources of increased ACTH levels,[80,81] but the procedure has been termed invasive and elaborate.[77,78,81,82]

Authors of a later study suggested that because adrenal lesions are relatively common place and are easily detected by advanced imaging technologies, clinicians may be tempted to test all patients with such lesions for excess cortisol secretion that is indicative of CS.[83] However, since most such lesions rarely lead to frank disease, one author suggested that routine screening in unselected populations is clinically ineffective and potentially deleterious if unaffected patients undergo invasive surgery.[83]

One report suggested that the probability of finding an adrenal incidentaloma in a patient 20-29 years old was 0.2%, but the probability of such a finding in a patient > 70 years was 6.9%.[84]

Some authors suggested that CS should be included in the differential diagnoses of certain high-risk patient populations, including patients who present with diabetes mellitus, hypertension, and early-onset osteoporosis.[85]

3.4.2
Quality of Life for Cushing's Syndrome

CS of any etiology (adrenal, pituitary, or ectopic) impacts negatively on health-related QOL, especially in active hypercortisolism but also after an endocrine cure. Generic questionnaires (e.g., the short-form 36 health survey SF-36, the derived SF-12, and the Hospital Anxiety and Depression Scale), as well as disease-specific measures (e.g., the Cushing QOL and the Tuebingen CD-25 questionnaires) have provided information on the impact of CS on patients perceived health.[86] Patients may experience severe fatigue, physical changes, emotional instability, depression, and cognitive impairment.[87]

Treating CS improves patient-perceived QOL, but it often takes many months and often never normalizes. In addition to persistent decreased QOL in cured CS patients, brain and cerebellar volume are also reduced. Depression, anxiety, and cognitive dysfunction are common. Pediatric patients with CS also have worse QOL than normal children, and they have delayed growth and pubertal development and sub-normal body composition and psychological and cognitive maturation. Fluoxetine has been suggested as a neuroprotectant and antidepressant for patients with CS, although no prospective studies are yet available.[86]

The initial onset of CD is insidious and can involve nonspecific, highly variable, and often cyclical presentations of clinical signs (Table 9). Reports about the time required for CD diagnosis vary widely. A study that included 19 patients with ACTH-secreting tumors reported an average of 4.3 years from initial presentation to diagnosis.[88] A study that included 49 patients reported

an average time from symptom onset to diagnosis of 45.8 ± 2.7 months (range 6-144 months).[62] The European Registry on CS identified 481 CS patients (66% of whom presented with CD) and reported a median diagnostic delay of 2 years.[89]

3.4.3

Treatment for Cushing's Syndrome and Cushing's Disease

The therapeutic goal is to normalize tissue exposure to cortisol to reverse increased morbidity and mortality. Optimum treatment consisting of selective and complete resection of the causative tumor is necessary to allow eventual normalization of the hypothalamic-pituitary-adrenal axis, maintenance of pituitary function, and avoidance of tumor recurrence. The development of new drugs offers clinicians several choices to treat patients with residual cortisol excess. However, for patients affected by this challenging syndrome, the long-term effects and comorbidities associated with hypercortisolism require ongoing care.[90]

3.4.4

Surgery for Cushing's Syndrome and Cushing's Disease

Surgery (resection of the pituitary or ectopic source of ACTH, or unilateral or bilateral adrenalectomy) remains the optimal treatment in all forms of CS, but may not always lead to remission. Bilateral adrenalectomy is reserved for recurrent cases of CD and can be performed laparoscopically.[91]

The best treatment option of CD is total removal of the responsible corticotroph adenoma using a transsphenoidal approach, while preserving the normal anterior pituitary function. If this fails, all other options directed towards the pituitary (radiation therapies) or the adrenals (medications or surgery) have numerous side effects. There is at present no recognized efficient medical treatment for corticotroph adenomas.[53]

Medical therapy (steroidogenesis inhibitors, agents that decrease ACTH levels, or glucocorticoid receptor antagonists) and pituitary radiotherapy may be needed as an adjunct. A multidisciplinary approach, long-term follow-up, and treatment modalities customized to each individual are essential for controlling hypercortisolemia and managing comorbidities.[58]

A study that examined two US claims databases between 2008 and 2010 and reported that among 228 newly treated CD patients, 180 (78.9%) underwent surgery, 42 (18.4%) received pharmacotherapy, and 6 (2.6%) were administered radiotherapy.[92]

Table 10 presents outcomes data of surgical/radiation treatments for CD and CS.

3.4.5

Drug Therapies for Cushing's Syndrome and Cushing's Disease

Pharmaceutical therapies for CD can be divided into two groups: steroidogenesis inhibitors (drugs that act on the corticotrophic cells of the adenoma) and glucocorticoid receptor antagonists.[106]

Steroidogenesis inhibitors currently used for the treatment of CD include ketoconazole, metyrapone, mitotane, and etomidate.[106]

Ketoconazole and metyrapone are enzyme inhibitors that have a rapid onset but diminished control following corticotropin oversecretion in CD.[57] Both these agents are used off-label to treat CS.[107] The long-term use of ketoconazole may be limited by liver toxicity.[108,109] Mitotane has been used to treat relatively benign

Table 9

Comorbidities that may present with Cushing's syndrome.

SYMPTOM	PREVALENCE IN ALL CS PATIENTS	REFERENCE
Hypertension	58-85%	Feelders et al. 2012[87]
Obesity	32-41%	
Diabetes mellitus	50-81%	
Major depression	31-50%	
Osteoporosis	31-50%	
Dyslipidemia	38-71%	

CD, and etomidate, which is the only drug approved for intravenous treatment of CD, rapidly reduces cortisol levels.[108,110]

In 2012, the FDA approved pasireotide and mifepristone as pharmacological alternatives for treating CD patients who are not eligible for surgery.[106,111-113] Pasireotide targets the somatostatin receptor subtype 5, which is overexpressed in corticotrophic adenomas.[114] Ongoing phase III trials are further investigating pasireotide's safety and efficacy in new, persistent, or recurring cases of CD, and another clinical trial is evaluating an extended-release formulation of pasireotide for once-a-month dosing.[113] Pasireotide's safety profile is similar to that of other somatostatin analogs but has been associated with elevated incidences of hyperglycemia.[108,114]

Mifepristone is a glucorticoid receptor antagonist that reportedly improved glucose tolerance with patients and showed long-term safety.[115]

A proof-of-concept study is currently underway for the treatment of CD with LCI699, a potent 11β-hydroxylase inhibitor.[110,116,117] Table 11 summarizes outcome data on a variety of drug therapies for CD and CS.

3.4.6 Genetic Approaches for Cushing's Disease

Studies are examining genetics-based approaches for treating CD. One author reasoned that disruptions of cell signaling were associated with ACTH-producing adenomas and suggested investigating epithelial growth factor receptors, cyclins, and cyclin-dependent kinases.[124]

Table 10

Surgical/radiation treatments for Cushing's syndrome and Cushing's disease		
TREATMENT	OUTCOMES	REFERENCE
Transsphenoidal surgery	Remission rates were between 60-80% (< 15% for microadenomas), but relapse rates were as high as 20%.	Newell-Price et al. 2006[57]
	Remission rates were between 65-90% (65% for macroadenomas > 1 cm).	Aghi et al. 2008[93]
	Remission occurred in 60-90% of CD patients with microadenomas and slightly fewer (50-70%) in cases with macroadenomas.	Hofman et al. 2008[94] Hoybye et al. 2004[95] Shimon et al. 2002[96]
	Experienced neurosurgeons reportedly have achieved perioperative mortality rates between 0-1.5% with low overall complication rates.	Barker et al. 2003[97]
	Recurrence was as high as 25% at 45 months.	Patil et al. 2008[98]
	Recurrence occurred in 20-25% of patients.	Barbetta et al. 2001[99] Sonino et al. 1996[100] Patil et al. 2008[98]
Repeat transsphenoidal surgery	Treatment resulted in remission in 50-60% of patients, along with corresponding increases in the incidence of complications.	Biller et al. 2008[101] Tritos et al. 2011[102]
Laparoscopic surgery	Prognosis was good except for adrenocortical carcinomas.	Newell-Price et al. 2006[57]
Conventional fractionated radiotherapy	Treatment was effective but was associated with long-term hypopituitarism.	Newell-Price et al. 2006[57]
Proton stereotactic radiation therapy	Treatment led to remission in 17 cases (52%).	Petot et al. 2008[103]
Laparoscopic adrenalectomy	All patients resolved signs/symptoms of CS, maintained weight, improved glucose tolerance and blood pressure control, and had no residual cortisol secretion.	Vella et al. 2001[104]
Bilateral adrenalectomy	50% of patients experienced tumor progression within 3 years.	Assie et al. 2007[105]

Abbreviations: CD, Cushing's disease; CS, Cushing's syndrome

3.5

SUBCLINICAL CUSHING'S SYNDROME

Abstract clinically unapparent adrenal masses have become a common in everyday practice. These are usually incidentally detected, mostly due to the routine use of imaging techniques, such as ultrasound and computed tomography. A substantial percentage of these incidentalomas are hormonally active, with 5-20% of the tumors producing glucocorticoids. Autonomous glucocorticoid production without specific signs and symptoms of CS is termed subclinical CS.[125,126] With an estimated prevalence of 79 cases per 100,000 persons, subclinical CS is much more common than classic CS. Depending on the amounts of glucocorticoids secreted by the tumor, the clinical spectrum ranges from slightly attenuated diurnal cortisol rhythm to complete atrophy of the contralateral adrenal gland with lasting AI after unilateral adrenalectomy.[125]

Patients with subclinical CS lack the classical stigmata of hypercortisolism but have a high prevalence of obesity, hypertension, type 2 diabetes and cardiovascular complications. All patients with incidentally detected adrenal masses scheduled for surgery must undergo testing for subclinical CS to avoid postoperative adrenal crisis.[125]

The diagnosis of subclinical CS is based on biochemical evaluation; however, there is still no consensus regarding diagnostic criteria. Many experts agree that an abnormal 1mg DST initial screening test in combination with at least one other abnormal test of the hypothalamic-pituitary-adrenal axis is sufficient to diagnose subclinical CS. Although some recommend a higher dexamethasone dose (3 mg instead of 1 mg) to reduce false-positive results.[125]

The optimal management of patients with subclinical CS is not yet defined. The conservative approach of observation and medical treatment of morbidities is appropriate for the majority of these patients; however, the duration of follow-up and the frequency of periodical evaluation still remain open issues. Surgical resection may be beneficial for patients with hypertension, diabetes mellitus type 2, or abnormal glucose tolerance and obesity.[126] Some researchers also recommend surgery in patients < 50 years and those with suppressed plasma ACTH.[125]

Table 11

Studies on drug therapies for Cushing's syndrome and Cushing's disease.		
TREATMENT	OUTCOMES	REFERENCE
Mifepristone (Phase 3)	Treatment improved glycemic control in 60% and reduced hypertension in some subgroups; the overall clinical status of 87% of patients improved.	Fleseriu et al. 2012[118]
LCI699 (phase 2)	Treatment reduced plasma aldosterone and ACTH-stimulated cortisol response at all doses administered with no increased side effects compared with placebo.	Wang et al. 2015[119]
Ketoconazole	One study reported that 50% of patients taking ketoconazole achieved biochemical control and clinical improvement, but 20% of the patients discontinued the drug because of poor tolerability.	Fleseriu et al. 2015[110]
Cabergoline	Treatment has been reported to suppress cortisol production in 50-70% of patients over a 12-month period, but only 30-40% of patients remain in remission after 2 to 3 years.	Pivonello et al. 1999[120] Pivonello et al. 2009[121] Godbout et al. 2010[122]
	Treatment was well tolerated, but normalized cortisol levels in only one-third of patients.	Molitch et al. 2014[108]
Pasireotide	Treatment decreased cortisol levels in 88% of patients in a recent phase 3 study.	Colao et al. 2012[123]
	Treatment normalized cortisol levels in 25% of patients who received the drug and worsened glucose tolerance in most patients.	Molitch et al. 2014[108]

Abbreviation: CS, Cushing's syndrome; ACTH, adrenocorticotropic hormone

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