REVIEW ARTICLE

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Corticosteroid-Induced Adverse Events in Adults

Frequency, Screening and Prevention

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Abstract

Corticosteroids represent the most important and frequently used class of anti-inflammatory drugs and are the reference therapy for numerous neoplastic, immunological and allergic diseases. However, their substantial efficacy is often counter-balanced by multiple adverse events. These corticosteroid-induced adverse events represent a broad clinical and biological spectrum from mild irritability to severe and life-threatening adrenal insufficiency or cardiovascular events.

The purpose of this article is to provide an overview of the available data regarding the frequency, screening and prevention of the adverse events observed in adults during systemic corticosteroid therapy (topically administered cortico-

steroids are outside the remit of this review). These include clinical (i.e. adipose tissue redistribution, hypertension, cardiovascular risk, osteoporosis, myopathy, peptic ulcer, adrenal insufficiency, infections, mood disorders, ophthalmological disorders, skin disorders, menstrual disorders, aseptic necrosis, pancreatitis) and biological (i.e. electrolytes homeostasis, diabetogenesis, dyslipidaemia) events. Lastly, data about the prescription of corticosteroids during pregnancy are provided. This review underscores the absence of data on many of these adverse events (e.g. lipodystrophy, dyslipidaemia).

Our intent is to present to practitioners data that can be used in a practical way to both screen and prevent most of the adverse events observed during systemic corticosteroid therapy.

For many decades, corticosteroids have been the reference therapy for numerous neoplastic, immunological and allergic diseases. The prevalence of people receiving corticosteroids for at least 3 months in the general population has been estimated to range from 0.2% to 0.5%.[1,2] However, their substantial efficacy in many diseases is often counter-balanced by multiple adverse events. These are well known by physicians, but are also known by patients who often associate corticosteroids with moon face, weight gain and a restriction of their diet. If physicians carefully survey adverse events that they consider as serious (e.g. metabolic disorders, osteoporosis, infections), the experience shows that patients feel more concerned by 'visible' (e.g. lipodystrophy, acne) or 'disturbing' (e.g. mood disorders, insomnia, hyperphagia) events. These adverse events, which are considered to be invalidating by patients, may limit the compliance to corticosteroids. On the one hand, medical research has allowed a better knowledge of physiopathological mechanisms of action, indications and the optimal method of administering corticosteroids. On the other hand, few publications have focused on frequency, prevention, screening and treatment of many corticosteroid-induced adverse events. Moreover, although some papers mention an extreme incidence of adverse events, others point out that many problems classically attributed to corticosteroids occur in increased incidence in the diseases being treated with corticosteroids. Peptic ulcer, for example, does not seem to occur more frequently in corticosteroid-treated patients with cirrhosis or asthma when compared with controls with the same disease.[3,4]

The aim of this literature review is to put forward certainties and uncertainties concerning adverse events due to systemic (i.e. oral, intravenous or intra-muscular) corticosteroid therapy and to present data that can be used by practitioners in a practical way to both screen and prevent most of these adverse events. Although topically administered corticosteroids are absorbed and can produce systemic adverse effects, they are outside the remit of this review as is budesonide, an oral corticosteroid with a low-systemic bioavailability.[5]

1. Literature Search Methodology

To identify studies reporting the frequency of corticosteroid-induced adverse events, we searched the electronic database MEDLINE from 1966 to October 2005 as well as the Cochrane Controlled trials registration for the following medical subject headings (MeSH) and text words: ('prednisone' OR 'prednisolone' OR 'methylprednisone' OR 'dexamethasone') AND ('adverse events' OR 'adverse effects' OR 'side effects') AND ('controlled trial' OR 'clinical trial' OR 'meta-analysis' [publication type]) AND ('English' OR 'French' [language]). We also compiled citations from the reference lists of original and review articles.

A total of 244 were identified as being potentially suitable for the study. After excluding irrelevant articles, 52 publications were full-text reviewed, 19 of which described in detail the observed adverse events (tables I and II).

Between October 2005 and October 2006, we performed a MEDLINE and Cochrane Controlled trials registration search to identify studies focusing on each of these corticosteroid-induced adverse

Table I. Studies reporting the spectrum of corticosteroid-induced adverse events

Year of publication	Type of study	No. of patients	Mean age (y)	Mean daily dosage of prednisone equivalent (mg)	Corticosteroid(s)	Mean duration of therapy (y)	Reference
2001	Randomised, placebo-controlled	42	78	NA	Prednisone	2	6
2002	Randomised, placebo-controlled	81	62	<10	Prednisone	2	7
2005	Randomised, placebo-controlled	192	51	<10	Prednisolone	2	8
2004	Randomised, placebo-controlled	72	72	≤25	Prednisone	<76wk	9
1997	Randomised	178	36	<40	Prednisolone	12wk	10
1998	Randomised	201	33	<40	Prednisone	8wk	11
1968	Case-control	550 cases, 499 controls	NA	NA	NA	NA	3
1972	Case-control	50 cases, 50 controls	45	<10	Prednisone	57mo	12
1984	Case-control	100 cases, 100 controls	77	<10	Prednisolone	4.8	13
1994	Case-control	112 cases, 112 controls	52	<10	Prednisone	5	14
2001	Case-control	367 cases, 734 controls	69	NA	Prednisolone	5.5	15
1997	Prospective cohort	72	40	13	Prednisone/deflazacort	37mo	16
2005	Prospective cohort	146	49	600	Methylprednisolone	3d	17
2007	Prospective cohort	80	59	42	Prednisone	3mo	18
1965	Retrospective cohort	47	NA	4–12	Triamcinolone	5–8	19
1997	Retrospective cohort	175	73	<10	NA	2.4	20
1997	Retrospective cohort	115	67	NA	Multiple corticosteroids	NA	21
2000	Retrospective cohort	163	14	15	NA	>7	22
2003	Retrospective cohort	120	75	14	Multiple corticosteroids	26mo	23
1994	Meta-analysis						24
2002	Review study						25

NA = data not available.

Table II. Clinical adverse events reported in these studies[a]

Reference	Lipodystrophy	Hypertension	Osteoporosis	Myopathy	Peptic ulcer	Infection	Mood disorders	Ophthalmological disorders	Skin disorders	Menstrual disorders
Jover et al.[6]	✓	✓	✓	✓	✓	✓	✓	✓		
Van Everdingen et al.[7]		✓	✓		✓	✓	✓	✓	✓	
Wassenberg et al.[8]	✓	✓	✓		✓			✓	✓	
Caporali et al.[9]		✓	✓	✓	✓	✓	✓	✓		
Campieri et al.[10]	✓								✓	
Bar-Meir et al.[11]	✓			✓	✓		✓		✓	
Smyllie and Connolly[3]		✓	✓		✓	✓	✓			
Lieberman et al.[12]		✓			✓		✓	✓		
Thomas[13]		✓	✓		✓			✓		
Saag et al.[14]			✓		✓	✓		✓		
Walsh et al.[15]	✓		✓	✓				✓	✓	
Rizzato et al.[16]	✓	✓	✓		✓	✓	✓	✓	✓	✓
Chibane et al.[17]		✓			✓		✓		✓	
Fardet et al.[18]	✓	✓		✓	✓	✓	✓		✓	✓
Shubin[19]	✓	✓	✓		✓	✓	✓		✓	
Gabriel et al.[20]		✓	✓	✓	✓	✓		✓		
Akerkar et al.[21]		✓				✓	✓			
Covar et al.[22]	✓	✓	✓	✓				✓	✓	
Proven et al.[23]		✓	✓		✓	✓		✓		
Conn and Poynard[24]		✓	✓		✓	✓	✓		✓	
Schacke et al.[25]		✓	✓	✓	✓	✓	✓	✓	✓	

a Adrenal insufficiency, pancreatitis and aseptic necrosis were not reported in these studies.

✓ indicates adverse event reported.

events. The search strategy included terms for systemic corticosteroids ('prednisone' OR 'prednisolone' OR 'methylprednisone' OR 'dexamethasone') and terms for adverse events (e.g. 'myopathy', 'aseptic necrosis'). Clinical trials and meta-analyses written in English or French language were screened with regard to the data on the frequency, screening and prevention of each adverse event. Since many of corticosteroid-induced adverse events depend on dose and duration of treatment, incidence/prevalence is related to a particular population of patients. Thus, when available, we chose to report the relative risk (RR)/odds ratio (OR) rather than prevalence/incidence data.

Because a complete literature review about the mechanisms involved in the adverse events of corticosteroids has been already published,[25] we chose not to focus on this topic in this review.

2. Clinical Adverse Events

2.1 Adipose Tissue Redistribution

Morphological changes that create a 'Cushingoid' aspect are often observed during long-term systemic therapy with corticosteroids. Clinically, adipose tissue accumulates in the facial ('moon face'), dorsocervical ('buffalo hump') and abdominal regions, whereas subcutaneous fat thickness is reduced in the limbs. Abdominal visceral fat accumulation is suspected. We prefer to use the term 'corticosteroid-induced lipodystrophy' to refer to these morphological changes.

While corticosteroid-induced lipodystrophy is considered by patients as the most distressing adverse event induced by corticosteroids,[18] few studies have focused on these morphological changes. The prevalence of corticosteroid-induced lipodystrophy widely varied in the literature. Shubin[19] found that 7 of 47 (15%) patients had 'moon face' after short-term (<3 months) therapy with 10–30 mg/day of a prednisone equivalent. More recently, others[10,11] have reported incidence rates of 33–40% after 8–12 weeks of treatment (mean prednisone dosage: 23 mg/day).

Long term corticosteroid-therapy (≥3 months) was linked to 'moon face', 'cushingoid appearance' or 'cushingoid faces' rates of 32–83%.[6,19,22] Most of these studies are retrospective and the lack of precise diagnostic criteria and/or an agreed-upon method to diagnose corticosteroid-induced lipodystrophy may explain these differences, as lipodystrophy is still exclusively diagnosed in a subjective and observer-dependent manner. In a prospective study, we recently found a cumulative incidence rate of corticosteroid-induced lipodystrophy after 3, 6, 9 and 12 months of prednisone therapy of 61%, 65%, 68% and 69%, respectively.[26]

Data on potential risk factors for corticosteroid-induced lipodystrophy are surprisingly sparse. To our knowledge, no data are available regarding the daily corticosteroid dosage (15–30 mg/day?[27]) and/or the duration of therapy inducing lipodystrophy. Wassenberg et al.[8] found that even a very low dose of prednisolone (5 mg/day) induced 'Cushing's syndrome'.

In the 1980s, two teams showed that high-residual secretion of hydrocortisone or decreased clearance of prednisolone may be risks factors for corticosteroid-induced lipodystrophy.[28,29] More recently, we showed that the risk of lipodystrophy after 3 months of therapy was higher in women (OR 10.87; 95% CI 2.43, 58.82), patients aged <50 years (OR 11.11; 95% CI 2.19, 37.89), patients with a high initial body mass index (OR 1.56; 95% CI 1.21, 2.03, per increment of 1 kg/m^2) and patients with high calorie intake (OR 6.11; 95% CI 1.35, 27.75, when >30 kcal/d/kg).[26] Lipodystrophy is usually reversible when prednisone equivalent daily dosage is <10 mg/day.[30] A low-calorie diet may then be prescribed for corticosteroid-treated patients to limit the risk of corticosteroid-induced lipodystrophy. Because lipodystrophy is associated with features of the metabolic syndrome, such as insulin resistance, dyslipidaemia and high blood pressure,[31] it should not be considered by physicians to be only an aesthetic challenge.

The frequency and clinical implications of adipose tissue redistribution are listed in table III.

2.2 Hypertension

Hypertension is a well known adverse event of corticosteroid therapy. Its frequency varies in the literature and depends on the duration and the daily dosage of corticosteroids and of the studied popula-

Table III. Frequency and clinical implications of corticosteroid-induced clinical adverse effects

Adverse clinical event	Frequency	Clinical implications
Adipose tissue distribution	61%, 65%, 68% and 69% after 3, 6, 9 and 12 months of high-dose prednisone therapy, respectively	Inform the patient about the high frequency and reversibility of corticosteroid-induced lipodystrophy A low-calorie diet may be useful in the prevention of corticosteroid-induced lipodystrophy Systematic screening of metabolic disorders associated with corticosteroid-induced lipodystrophy
Hypertension	OR 2.2 (95% CI 1.4, 3.8)	Systematic screening of corticosteroid-induced hypertension, in particular during the first months of therapy and in patients with corticosteroid-induced lipodystrophy Low-salt diet probably ineffective for the prevention of corticosteroid-induced hypertension
Cardiovascular risk	OR 1.25 (95% CI 1.21, 1.29) to 2.56 (95% CI 2.18, 2.99)	Inform the patient about the symptoms and the need to consult his/her physician if they occur
Osteoporosis	OR 4.2 (95% CI 1.4, 12.9)	Measurement of the bone mass density before initiation of a long-term systemic corticosteroid therapy at a baseline daily dosage ≥7.5mg Annual examination thereafter Calcium/vitamin D and/or bisphosphonates when necessary Exclusion or prevention of the other concomitant osteoporosis risk factors
Myopathy	OR 6.7 (95% CI 4.8, 9.3)	Systematic clinical screening of corticosteroid-induced myopathy Systematic recommendation of physical training
Peptic ulcer	OR 1.2 (95% CI 0.8, 2.1) to 2.3 (95% CI 1.4, 3.7)	A systematic prevention is not justified Avoid the association of corticosteroids and NSAIDs
Adrenal insufficiency	Undetermined	Inform the patient about symptoms
Infections	RR 1.6 (95% CI 1.3, 1.9) for infectious events; OR 1.2 (95% CI 1.0, 1.6) for bacterial sepsis	Systematic prevention of tuberculosis for patients starting long-term systemic corticosteroid and with a positive tuberculin skin test? Inform patients to avoid people with chickenpox and to report this to their doctor if they are in inadvertent contact When appropriate, prevention of strongyloidiasis When possible, recommend vaccinations before starting corticosteroids
Mood disorders	OR 1.3 (95% CI 0.8, 2.1) for psychosis; frequency of irritability or anxiety: 5–40%; frequency of insomnia: approximately 50%	Inform patients (and possibly their families) of the high frequency of mood disorders
Ophthalmological disorders	OR 1.41 (95% CI 1.22, 1.63) for ocular hypertension; prevalence of posterior subcapsular cataract: about 10%	Regular ophthalmological examination (the optimal schedule is unknown)
Skin disorders	Prevalence of trophic disorders: 2–73%; hirsutism: 2–26%; acne: 0–29%	Prescription of emollients?
Menstrual disorders	Prevalence: 16–39%	Inform patients
Aseptic necrosis	Prevalence: 1–16%	
Pancreatitis	Undetermined	Consider pancreatitis in corticosteroid-treated patients who report newly developed digestive symptoms such as abdominal pain or nausea

OR = odds ratio; **RR** = relative risk.

tions. In a meta-analysis of randomised, double-blind, controlled trials, an OR of 2.2 (95% CI 1.4, 3.8) for developing hypertension in corticosteroid-treated patients versus controls was demonstrated.[24] Risk factors for corticosteroid-induced hypertension are unknown. Some authors report that the risk of corticosteroid-induced hypertension is dose dependant.[32,33] In the study by Sato et al.,[32] corticosteroid-induced hypertension was diagnosed only in patients receiving >20 mg/day of prednisone equivalent. In patients >65 years, low calcaemia or a past history of familial hypertension seemed to be risks factors for corticosteroid-induced hypertension.[32] Hypertension seems to appear early after the

initiation of corticosteroids.[18,32,33] Nevertheless, because an increased mean blood pressure may be observed in patients who develop corticosteroid-induced lipodystrophy,[31] patients must be carefully screened for hypertension for the duration of therapy. The pathophysiological mechanisms of corticosteroid-induced hypertension are still uncertain.[34,35]

Compared with Cushing disease, it is easy to consider hypertension to be secondary to the mineralocorticoid effects of corticosteroids and to sodium/water retention. Nevertheless, the mineralocorticoid activity of synthetic molecules is lower than that of cortisol. When this activity is equal to 1 for cortisol, it is <0.5 for prednisone and prednisolone, and near 0 for methylprednisolone and dexamethasone.[36,37] Moreover, some authors have shown that hypertension is probably not linked with the potential mineralocorticoid activity of corticosteroids.[33,36,38,39] First, administration of spironolactone (or mineralocorticoid-antagonists that inhibit water and sodium retention), did not prevent or control corticosteroid-induced hypertension.[33,39] Secondly, dexamethasone and prednisolone induced hypertension despite their natriuretic effects.[36] Thirdly, in patients treated with 1 mg/day of corticotropin for 5 days, mean blood pressure increased by 12mm Hg in spite of a very low-sodium diet (<1g of sodium per day).[38] Pathophysiological mechanisms of corticosteroid-induced hypertension may then involve an increase of myocardial contractility.[25]

The frequency and clinical implications of corticosteroid-induced hypertension are listed in table III.

2.3 Cardiovascular Risk

Two studies are available in the literature regarding cardiovascular risk in corticosteroid-treated patients. In the first study,[40] which included 50 656 patients aged >50 years and diagnosed with ischaemic stroke, myocardial infarction or cardiac insufficiency and 50 656 controls, present or past systemic corticosteroid therapy was associated with an increased risk of a cardiovascular or cerebrovascular event (OR 1.25; 95% CI 1.21, 1.29). This risk was significant for cardiac insufficiency (OR 2.66; 95% CI 2.46, 2.87) and cardiac ischaemia (OR 1.20; 95% CI 1.11, 1.29), but was not significant for ischaemic stroke (OR 0.95; 95% CI 0.89, 1.01). The risk was higher for patients receiving corticosteroids at the time of the cardiovascular event and a dose-effect relationship was evidenced. Risk slowly decreased with time after corticosteroid treatment stopped.

In the second study[41] of 68 781 patients exposed to corticosteroids and 82 202 controls, multivariate analysis showed that patients exposed to ≥7.5 mg/day of systemic predsnisolone equivalent had a higher risk of cardiovascular events compared with non-exposed controls (OR 2.56; 95% CI 2.18, 2.99). This risk was significant for heart failure (OR 3.72; 95% CI 2.71, 5.12), myocardial infarction (OR 3.26; 95% CI 2.60, 4.09) and ischaemic stroke (OR 1.73; 95% CI 1.22, 2.44).

Sudden death is an exceptional event in corticosteroid-treated patients. Rare cases of cardiac arrhythmia have been reported after a pulse of corticosteroids. In 1989, an exhaustive review of severe cardiovascular complications of pulses gathered 18 events including 12 sudden deaths related to arrhythmia or myocardial infarction.[42] The relationship between these episodes and dyskalaemia is not clear; some authors have reported normokalaemia at the time of cardiac arrhythmia.[43-45] However, intracellular potassium depletion can not be excluded. Direct alteration of myocardial conduction by corticosteroids has been hypothesised.[46]

The frequency and clinical implications of cardiovascular risk in patients receiving corticosteroid therapy are listed in table III.

2.4 Osteoporosis

Patients who are subjected to long-term corticosteroid therapy develop an increased risk of osteoporosis, which is associated with a high risk of bone fracture. Corticosteroid-treated postmenopausal women have a 4-fold risk of osteoporosis compared with controls (OR 4.2; 95% CI 1.4, 12.9).[47] The bone loss depends on corticosteroid dosage[48,49] and is observed when dosage is >5 mg/day of prednisone equivalent.[50-52] Bone loss is major during the first 6 months of therapy (about 10%) and decreases thereafter (about 2–5% per year).[25,53,54]

Compared with control subjects, the risk of hip and vertebral fractures is 2- to 6-fold higher in

corticosteroid-treated patients.[48,49,55-57] Fracture risk increases not only with the dosage and treatment duration of corticosteroids, but also with female sex, older age and lower bodyweight.[58,59]

A measurement of the bone mass density is recommended before initiation of systemic corticosteroid therapy at a baseline daily dosage of ≥7.5mg and planned to last >1 or 3 months.[48,60] An annual examination is thereafter recommended.[48] Although most physicians are aware of the risk of osteoporosis, >50% of patients on significant doses of corticosteroids are not investigated for this adverse event.[61]

Three meta-analyses showed that calcium and vitamin D were effective in the prevention of corticosteroid-induced osteoporosis,[62] and that biphosphonates were effective for its prevention and treatment.[63,64] Guidelines for the prevention of corticosteroid-induced bone loss have been published,[65] but in spite of these consensual recommendations, >50% of patients do not receive adequate prevention.[66-68] Women are more likely than men to receive intervention (OR 4.41; 95% CI 2.17, 9.10), and rheumatologists perform better than internists, pulmonologists or other physicians.[66] After discontinuation of corticosteroid therapy, osteoporosis seems to be (partially) reversible.[54]

Both cross-sectional and longitudinal studies demonstrated significantly stronger losses of trabecular than of cortical bone.[69] Corticosteroids are responsible for both quantitative and qualitative deleterious effects on bone through their effects on bone cells, mainly osteoblasts (corticosteroid-induced bone loss results from stimulation of osteoclast-mediated bone resorption and reduction of osteoblast-mediated bone formation). Corticosteroids directly affect the osteoprotegerin (OPG)/receptor activator of nuclear kappa-B (RANK)/RANK ligand (RANKL) cytokine system.[70] The soluble cytokine RANKL is produced by the osteoblast under hormonal and cytokine control and is essential for osteoclastogenesis and bone resorption. Interacting with its receptor RANK, RANKL stimulates bone resorption. OPG, a decoy receptor of RANKL produced by osteoblastic cells, binds to RANKL and prevents its binding to RANK.[71] Therefore, the relative production of RANKL and OPG by osteoblastic cells dictates the rate of osteoclastic bone resorption.[72] Corticosteroids concurrently upregulate RANKL and suppress OPG in osteoblastic cells *in vitro*, and are among the most powerful drugs to suppress OPG serum levels *in vivo*.[73] Corticosteroids also exert direct effects on calcium metabolism and sex hormones.[25,48]

The frequency and clinical implications of corticosteroid-induced osteoporosis are listed in table III.

2.5 Myopathy

In a case-control study,[15] muscle weakness was 6.7 (95% CI 4.8, 9.3) times more frequent in corticosteroid-treated patients (n = 367) than in control subjects (n = 734) [unadjusted OR]. In this study, there was a highly significant dose relationship between corticosteroid dosage and muscle weakness (OR = 1.5; 95% CI 0.8, 3.0, for a mean prednisolone equivalent dosage = 11.7 mg/day vs 5.1 mg/day; OR = 2.5; 95% CI 1.2, 5.0, for a mean prednisolone equivalent dosage = 23.6 mg/day vs 5.1 mg/day and OR = 3.3; 95% CI 1.5, 7.0, for a mean prednisolone equivalent dosage = 60.6 mg/day vs 5.1 mg/day).

Biologically, muscle enzymes are usually normal,[74,75] even if Naim and Reed[76] found that 5 of 9 children receiving long-term high-dose corticosteroids with electromyogram findings consistent with corticosteroid-induced myopathy had muscle enzyme elevation (all of these children received corticosteroids for juvenile dermatomyositis). Urinary creatine excretion may be increased.[75,77] Physical training prevents and improves corticosteroid-induced myopathy,[78-80] which regresses after corticosteroid withdrawal within a few days to several months.[81,82] Corticosteroids affect skeletal muscle directly by interference with oxidative phosphorylation, inhibition of protein synthesis and impairment of muscle membrane excitability.[83,84] Type II fibre atrophy is the most common abnormality with reduced type II mean fibre areas.[74,81]

The frequency and clinical implications of corticosteroid-induced myopathy are listed in table III.

2.6 Peptic Ulcer

The higher risk of upper gastrointestinal complications induced by corticosteroids is still debated. Two large meta-analyses are available and their results are discordant. In the first one published in

1983,[85] the association between corticosteroids and subsequent peptic ulceration or gastrointestinal haemorrhage was examined by pooling data from 71 controlled clinical trials in which patients were randomised to systemic corticosteroid or to nonsteroid therapy. Of 3064 corticosteroid-treated patients evaluated for peptic ulcers, 55 (1.8%) had ulcers compared with 23 of 2897 controls (0.8%) [RR 2.3; 95% CI 1.4, 3.7]. Of 3135 corticosteroid-treated patients evaluated for gastrointestinal haemorrhage, 78 (2.5%) had bleeding compared with 48 of 2976 controls (1.6%) [RR 1.5; 95% CI 1.1, 2.2]. When separate analyses were performed for studies that were double-blind, using only oral or parenteral corticosteroids, or if patients with a history of ulcer were excluded, the trend did not always reach statistical significance. However, authors concluded that corticosteroids increase the risk of peptic ulcers and gastrointestinal haemorrhage. In the second study published in 1994, Conn and Poynard[24] pooled 93 randomised, double-blind, controlled trials in which corticosteroid-treated patients and the control group had been treated in the same manner except for the administration of corticosteroids (the concomitant administration of antacids agents was taken into account). In their analysis, 9 of 3267 (0.3%) patients in the control group versus 13 of 3335 (0.4%) patients in the corticosteroid group were reported to develop a peptic ulcer (OR 1.3; 95% CI 0.8, 2.1). Moreover, the risk of haemorrhage from ulcer (OR 1.2; 95% CI 0.7, 2.2), perforation of ulcer (OR 1.0; 95% CI 0.5, 1.9) or death from ulcer (OR 1.0; 95% CI 0.5, 1.9) was not different between the two groups. Symptoms compatible with peptic ulcer were reported more frequently in the corticosteroid group (26 vs 7 patients, OR 1.9; 95% CI 1.1, 3.0). The incidence of peptic ulcer tended to increase directly with the dosage and the duration of therapy.[24,85] The risk is also four to seven times higher in patients concomitantly receiving NSAIDs.[86,87]

The frequency and clinical implications of corticosteroid-induced peptic ulcer are listed in table III.

2.7 Adrenal Insufficiency

Administration of exogenous corticosteroids produces a negative feedback effect on the hypothalamic-pituitary-adrenal (HPA) axis with resulting suppression of normal cortisol production. There is no disagreement in the literature that systemic corticosteroids suppress pituitary and adrenal function as measured by body-fluid levels of adrenal corticosteroids and their metabolites.[88-90] Moreover, autopsies of patients have demonstrated that patients receiving corticosteroids for ≥5 days within 20 days of death had significant atrophic changes of the adrenal glands in comparison with control subjects.[91] Since there is considerable patient-to-patient variability, it is difficult to determine the smallest dosage or duration of therapy that will suppress the HPA axis. High-dose (15–50 mg/day) prednisone therapy results in a significantly depressed adrenal suppression in 45–100% of exposed patients even if the duration of therapy is short (i.e. <30 days)[92-95] and the HPA axis may remain suppressed for several weeks.[19,93] In the same way, a low dosage (0.09–0.15 mg/kg/day of prednisone equivalent) therapy may induce adrenal insufficiency when prescribed for >1 year[96] and recovery may take several months.[88]

Some synthetic corticosteroids (e.g. betamethasone) potentially induce a more profound adrenocortical suppression than others (e.g. prednisolone).[90] A Short Synacthen test (SST) using corticotropin 250μg is usually performed to evidence adrenal insufficiency, but it is not the only way to evaluate the HPA axis. Measurement of circulating cortisol under basal conditions, 24-hour cortisoluria and insulin tolerance tests have been used but they seem less reliable than SST using 250μg of corticotropin.[97] The value of the test using 1μg of corticotropin remains controversial[98-101] and, to date, it cannot be recommended for routine clinical use.[97] More recently, determination of salivary cortisol levels by enzyme immunoassay has been proposed, but this test is not routinely available.[102,103]

The incidence of clinical corticosteroid-induced adrenal insufficiency remains unknown and seems definitively lower than indicated by biological data. Available data were obtained from surgeons who showed that perioperative adrenal insufficiency in corticosteroid-treated patients was rare (<0.1%).[104] Thus, after an exhaustive literature review, Salem et al.[105] argued that "clinical and experimental evidence support the concept that the current amount of

perioperative glucocorticoid coverage is excessive and has been based on anecdotal information."

The optimal schedule of corticosteroid tapering is unknown. Adjunction of hydrocortisone during the last weeks of corticosteroid withdrawal or replacing prednisone with hydrocortisone[106] has been proposed to lower the risk of corticosteroid withdrawal; it is hypothesised that the use of this natural hormone is responsible for less HPA-axis suppression. However, this has been neither tested clinically nor demonstrated to be superior to simpler procedures. For all these reasons, we think that the best preventive measure of adrenal insufficiency is the information given to the patient: during the corticosteroid withdrawal period, the patient must be proactive in identifying subtle symptoms and bringing them to the physician's attention.

The frequency and clinical implications of adrenal insufficiency are listed in table III.

2.8 Infections

An obvious complication when using corticosteroids for immunosuppression is the patient's decreased resistance to infections. The basis for this is decreased inflammatory response due to decreased production, function and migration of inflammatory cells and decreased antibody production.[25,107] Studies showing an increased infectious risk in corticosteroid-treated patients[14,108,109] are difficult to interpret. First, small studies reporting rare infectious events are difficult to extrapolate to a general corticosteroid-treated population. Second, most of the patients are also immunosuppressed by their underlying disease or by other immunosuppressive drugs and the causal relationship between corticosteroids and the infectious event is difficult to assess.

However, a meta-analysis of 71 pooled controlled clinical trials[110] showed a RR of 1.6 (95% CI 1.3, 1.9) for infectious events in corticosteroid-treated patients (n = 2111) versus controls (n = 2087). When the daily dosage of prednisone equivalent ranged from 20mg to 40mg, the RR of infections was 2.1 (95% CI 1.3, 3.6) in corticosteroid-treated patients compared with controls. The rate was not increased in patients given a daily dose of <10mg or a cumulative dose of <700mg of prednisone. The risk of infection was particularly high in patients with neurological diseases (RR 2.8; 95% CI 1.9, 4.3).

The frequency and clinical implications of infections associated with corticosteroid therapy are listed in table III.

2.8.1 Bacterial Infections

Potentially, all the pyogenic bacteria can be involved and physicians must be aware that corticosteroids can mask the effects of infections, which can then present at an advanced stage. In the meta-analysis by Conn and Poynard,[24] bacterial sepsis was evidenced in 6.5% of 2868 corticosteroid-treated patients compared with 4.8% of 2776 patients in the placebo group (OR 1.2; 95% CI 1.0, 1.6). The relationship between corticosteroids and reactivation of latent tuberculosis is more debated,[111-113] but in a large case-control study (497 cases and 1966 controls),[114] the adjusted OR of tuberculosis for current use of corticosteroids compared with no use was 4.9 (95% CI 2.9, 8.3). The adjusted ORs for use of <15mg and ≥15mg of prednisone or its equivalent daily dose were 2.8 (95% CI 1.0, 7.9) and 7.7 (95% CI 2.8, 21.4), respectively.

As proposed in 2000 by the American Thoracic Society, "because prednisone (or its equivalent) given >15 mg/d for 2–4 weeks suppresses tuberculin reactivity and because lower doses or those given intermittently are not associated with tuberculosis, this dose is likely the lower limit that could predispose persons to develop tuberculosis."[115] The American Thoracic Society recommended systematic prevention with isoniazid for patients starting long-term systemic corticosteroid therapy and with a positive tuberculin skin test (i.e. ≥5mm).[115,116] To date, few studies have assessed the performances of new biological tests (i.e. *ex vivo* interferon-γ release assays) for the diagnosis of tuberculosis in immunocompromised patients. Nevertheless, in three studies with direct comparison, the prevalence of positive results on biological test was substantially higher than that of positive results on the tuberculin skin test, particularly in patients with greater immune suppression.[117]

Corticosteroids diminish the immune response to pneumococcal vaccine.[118,119]

2.8.2 Viral Infections

Some case-control studies have focused on the risk of severe varicella in corticosteroid-treated paediatric populations with contradictory results (e.g. OR 1.6 [95% CI 0.2, 16.9] in the study by Patel et al.[120] compared with OR 178 [95% CI 59, 541] in the study by Dowell and Bresee[121]). To our knowledge, no such data are available in adult populations but several cases of severe varicella in corticosteroid-treated adults have been reported.[122,123]

In 1996, the Department of Health in the UK defined immunosupressed adults at risk of severe varicella as "adults who have received prednisolone 40 mg/day for more than 1 week in the previous 3 months or patients on lower doses of corticosteroids (…) if they are given in combination with cytotoxic drugs."[124] An exposure to chickenpox was defined as "(1) contact with a person with chickenpox or exposed herpes zoster (2) during the period 48 hours before the rash until it crusts (3) for more than 15 minutes in the same room or face to face." It was proposed that an adult who fulfilled these criteria required zoster immunoglobulin by intramuscular injection.[124] Another alternative to zoster immunoglobulin is the use of prophylactic aciclovir. Moreover, patients who have no antibodies to chickenpox should be instructed to avoid chickenpox and if they are in inadvertent contact they should report this to their doctor immediately. In the UK, a corticosteroid card is given to patients and provides clear instructions to contact their doctor in such circumstances.[125]

Therapy with corticosteroids is associated with reactivation of replication of hepatitis B and C viruses.[126,127] Apart from their immunosuppressive effects, corticosteroids directly stimulate hepatitis B virus replication *in vitro*.[128] Lamivudine, an inhibitor of reverse transcriptase, has been used to prevent hepatitis B reactivation in patients receiving chemotherapy with or without corticosteroids.[129] Corticosteroids may also diminish the immune response to influenza vaccine.[130]

2.8.3 Fungal Infections

Corticosteroids have long been recognised to predispose patients to invasive fungal infections.[131] Invasive aspergillosis is the most common invasive mould infection associated with corticosteroids.[131] In an analysis of 331 recipients of allogeneic bone marrow transplants, the use of high-dose prednisone for graft-versus-host-disease prophylaxis was the most important risk factor for invasive fungal infection, including invasive aspergillosis; high-dose prednisone (0.5–1.0 mg/kg/day) increased such infections 6-fold compared with regimens with low-dose prednisone (0.25 mg/kg/day).[132]

Marr et al.[133] showed that corticosteroids administered in the late post-bone-marrow-transplant period increase the risk of aspergillosis dose dependently. Specifically, doses of <1.9 mg/kg/day, 1.9–3.0 mg/kg/day and >3 mg/kg/day were associated with risks of 5%, 10% and 14%, respectively. Invasive aspergillosis is a common cause of infectious death in patients with systemic lupus erythematosus, accounting for 15% of deaths in a Brazilian autopsy study.[134] Corticosteroids are also a risk factor for candidaemia and invasive candidiasis.[131,135] This increased risk has been shown for *Candida albicans* and non-albicans *Candida* species.[136,137]

Corticosteroid-treated patients more frequently developed pneumocystosis (PCP) than controls.[131] Yale and Limper[138] showed that 90% of patients with various conditions who had PCP had received corticosteroids the month before PCP diagnosis. In this study, a daily prednisone-equivalent dose of 30mg administered for a median of 12 weeks was further associated with worse PCP outcome.[138] Therefore, prophylaxis with cotrimoxazole (trimethoprim/sulfamethoxazole) should be considered for patients receiving a long course of corticosteroids, especially at high doses and when CD4+ lymphocyte counts drop below 200/μL.[139]

Finally, corticosteroids are associated with an increased risk of strongyloidiasis (RR 2.29 to 3.30).[140,141] A prevention of symptomatic strongyloidiasis should be envisaged for patients who have travelled in endemic areas, even several years before the introduction of corticosteroids.[142] In 2000, the US Centers for Disease Control and Prevention, the Infectious Disease Society of America and the American Society of Blood and Marrow Transplantation recommended oral ivermectin 200 μg/kg daily for 2 consecutive days (alternative: oral albendazole 400mg daily for 3 days or tiabendazole 25 mg/kg twice daily for 2 days) for the prevention

of strongyloidiasis in immunosuppressed patients.[143]

2.9 Mood Disorders

The effects of cortisol on human mental functioning are well known.[144] In a meta-analysis,[24] psychosis occurred 2-fold more frequently in corticosteroid-treated patients than in controls. Severe psychiatric disorders such as psychosis, depression or manic episode are reported in 5–34% of patients.[18,145,146] The risk of psychosis seemed higher within the first days or weeks of therapy[147,148] and psychiatric symptoms may be more common in women.[18,25] A prospective study evaluated 50 ophthalmological patients, of whom 26–34% experienced a hypomanic syndrome and 10–12% a depressive syndrome within the first 8 days of therapy.[145]

In retrospective or uncontrolled studies, frequency of minor mood disorders such as irritability or anxiety varied between <5%[3,17] and >40%,[6,18,149,150] probably depending on the definition of mood disorder used ('mental changes', 'neuropsychiatric disorders', 'emotional disturbance' or 'mental disturbance'). Insomnia was reported by approximately 50% of the patients after pulse[17,18] or oral[18] corticosteroid therapy.

The investigation of the Boston Collaborative Drug Surveillance Program showed a striking relationship between neuropsychiatric disorders and corticosteroid dosage, i.e. 1.3% of 463 patients who received <40 mg/day of prednisone, 4.6% of 175 patients who received 40–80 mg/day and 18.4% of 38 patients who received >80 mg/day.[151]

Corticosteroid withdrawal may also be associated with depression, irritability, apathy, insomnia, anorexia and memory loss, possibly lasting for several weeks after discontinuation.[152] Mania and delirium have also been described.[153,154] The mechanism by which corticosteroids produce psychiatric symptoms is probably multifactorial, including both direct and indirect effects on the brain.[25,155]

The frequency and clinical implications of corticosteroid-induced mood disorders are listed in table III.

2.10 Ophthalmological Disorders

An increased risk for the development of a cataract is well known in corticosteroid-treated patients. This cataract is posterior and subcapsular, which is relatively rare in patients not taking corticosteroids. In a study reviewing nine previous studies of asthmatic patients (n = 343) treated with systemic corticosteroids, the prevalence of a posterior subcapsular cataract was found to range from 0 to 54% with an average of 9%.[156] The risk increases with the daily cumulative dosage of corticosteroids and the duration of therapy. The risk is also influenced by the age and ethnic origin of patients.[156,157] This risk also exists with low dosage (<10 mg/day) corticosteroids.[14,158] Investigations in a model of cataract formation in chick embryos show that vitamin C may have a preventive role.[159,160] To date, there are no corresponding human data.

Systemic corticosteroid therapy is also associated with an increased risk of ocular hypertension. In a retrospective epidemiological study of elderly patients receiving oral corticosteroids, an overall OR of 1.41 (95% CI 1.22, 1.63) with regard to glaucoma induction was observed.[157] The OR showed a dose-relation increase: 1.26 (95% CI 1.01, 1.56) for hydrocortisone <40 mg/day, 1.37 (95% CI 1.06, 1.76) for 40–79 mg/day and 1.88 (95% CI 1.40, 2.53) for >80 mg/day. The OR also increased with the duration of treatment over the first 11 months of exposure.[157] Patients >40 years of age, those with diabetes mellitus or myopia and those with a family history of glaucoma appear to be at increased risk.[161] Typically, intraocular pressure returns to normal within a few weeks after the discontinuation of corticosteroids,[161,162] although irreversible intraocular pressure elevation has been reported.[163]

The frequency and clinical implications of ophthalmological complications associated with corticosteroid therapy are listed in table III.

2.11 Skin Disorders

Systemic corticosteroids can induce numerous cutaneous adverse events. The most frequent include trophic disorders such as atrophy of the epidermis and the dermis, spontaneous bruising and disturbed wound healing and other adverse events such as hirsutism, acne or perioral dermatitis. The

frequency of these events varies in the literature between 2% and 73%.[7,18-20] Their risk increases with age and with female sex.[18,164] No preventive therapy is available. Xerosis is also frequently reported by patients (32% in a series)[18] and, in our personal experience, emollients may be useful.

In men and women treated with systemic corticosteroids, the prevalence of hirsutism varies between 2.5% and 13%.[10,11,19] The incidence rate in women after 3 months of therapy increases to 26%.[18] No risk factor is evidenced in the literature. Hirustism is usually reversible and disappears after cessation of therapy.

Corticosteroid-induced acne is reported by 0–29% of corticosteroid-treated patients.[10,11,19] The mechanisms whereby corticosteroids produce an acneiform eruption are not elucidated whereas those of trophic disorders are well known. On the one hand, suppressive effects on cutaneous cell proliferation and protein synthesis are responsible for skin atrophy.[25] On the other hand, corticosteroids reduce the proliferative activity of keratinocytes and fibroblasts and their protein synthesis.[25]

The frequency and clinical implications of skin disorders are listed in table III.

2.12 Menstrual Disorders

Corticosteroid-induced menstrual disorders are frequent, but few data are available in the literature. In the study by Rizzato et al.,[16] 3 of 19 (16%) women reported amenorrhoea, dismenorrhoea or menorrhagia. We recently reported that 9 of 23 women (39%) starting a high dosage (≥20 mg/day) prednisone therapy reported menstrual disorders.[18] Women who start corticosteroid therapy must be informed of this potential problem.

The frequency and clinical implications of corticosteroid-induced menstrual disorders are listed in table III.

2.13 Aseptic Necrosis

Corticosteroids can cause aseptic necrosis that usually involves the femoral head (figure 1) but that may also occur in the knee and humeral head.[165,166] Aseptic necrosis of bone is unpredictable and may occur during the first weeks of therapy.[165,167] Its prevalence ranges from 1.1% in patients treated for acute leukaemia (6 of 551 patients)[168] to 16.3% in patients with systemic lupus erythematosus (28 of 172 patients).[169] In renal transplant populations, some studies have shown that 5.3% (29 of 546 patients)[170] to 11.7% (52 of 444 patients)[171] of patients developed bone necrosis. In the study by Proven et al.,[23] 3 of 103 (2.9%) patients with giant cell arteritis developed avascular necrosis of the hip during their follow-up. Black patients tended to be at higher risk of bone osteonecrosis.[171] The daily corticosteroids dosage seems to correlate with the risk of aseptic necrosis (a higher dosage being associated with a higher risk)[171] as well as the use of bolus injection.[170]

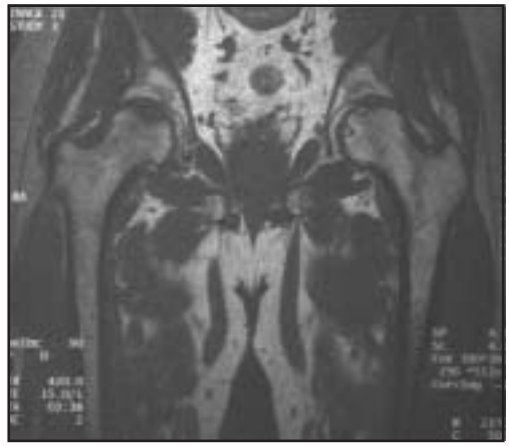

Fig. 1. Bilateral aseptic necrosis.

The frequency of corticosteroid-induced aseptic necrosis is listed in table III.

2.14 Pancreatitis

Symptomatic and asymptomatic pancreatitis have been observed after corticosteroid therapy and fatal cases have been reported.[172-174] However, at least some of these cases could possibly be related to the underlying disease (e.g. lymphoma, vasculitis) rather than the corticosteroids. In a paediatric series, Oppenheimer and Boitnott[175] reviewed the autopsy prevalence of pancreatitis in 102 patients with haematological/solid malignancies or nephrosis and found that 40% of nephritic patients who received corticosteroids had pancreatic lesions compared with 15% of control patients. No relationship to dose or duration of treatment could be determined. The

mechanisms by which corticosteroids induced pancreatitis are unknown.

The frequency and clinical implications of corticosteroid-induced pancreatitis are listed in table III.

3. Biological Adverse Events

3.1 Effects on Electrolyte Homeostasis

The main effects of natural corticosteroids on electrolyte homeostasis are classically fluid and sodium retention and potassium depletion. They exert these effects in a number of ways, the most important is exerted upon renal function.[176] Natural corticosteroids cause Na^+ retention by increasing the inherent tendency of the renal tubules to reabsorb Na^+ from the glomerular filtrate by means of a cation-exchange process in which K^+ and H^+ are secreted into the tubular urine.[176,177] Therefore, in general, natural corticosteroids that induce Na^+ retention also increase K^+ excretion.

When prednisone and prednisolone were first introduced, it was quickly recognised that, although they were more potent than cortisol as anti-inflammatory agents, they had less of an effect on fluid and electrolyte balance. Studies performed in the 1950s have confirmed that the tendency of synthetic corticosteroids to promote Na^+ retention and K^+ excretion is much lower than that of natural corticosteroids.[176,178,179] Concerning Na^+ excretion, prednisolone may induce an increase in the glomerular filtration rate and slight Na^+ diuresis in humans.[180] Aldosterone-like action is only observed with large dosages resulting in a mild retention of Na^+ with or without clinical symptoms.[12,181] In a prospective study, clinical fluid retention (i.e. swollen ankles) was observed in 10% of patients treated with high-dose prednisone.[18]

Making a parallel with natural corticosteroids, K^+ depletion may be hypothesised but in adrenalectomised dogs, it has been shown that potassium loss was approximately 30 times lower with prednisolone than with natural corticosteroids.[176] Moreover, well documented cases of hypokalaemia in corticosteroid-treated patients are rare.[182,183] For most other cases, patients had causes other than corticosteroids for K^+ depletion (e.g. Crohn's disease, diuretics).[21,184-186] In a literature review, Gennari[187] wrote that when given in the long-term, prednisone and hydrocortisone reduce serum potassium only slightly (by 0.2–0.4 mmol/L). However, the risk of hypokalaemia may be higher during short-term high-dose therapy, when the patient is ill and less able to achieve the electrolyte homeostasis.

The frequency and clinical implications of electrolyte homeostasis disturbances are listed in table IV.

3.2 Diabetogenesis

Corticosteroids are a well-known cause of insulin resistance. Corticosteroid-treated patients are at higher risk than controls to develop hyperglycaemia and diabetes. In a randomised, double-blind, place-

Table IV. Frequency and clinical implications of corticosteroid-induced biological adverse effects

Adverse clinical event	Frequency	Clinical implications
Electrolyte homeostasis	Frequency of hypokalaemia is undetermined but seems low	Clinical screening of fluid retention (and prescription of a low-salt diet when it happens?) Biological screening of hypokalaemia in particular during high-dose therapy
Diabetogenesis	RR for hyperglycaemia requiring hypoglycaemic therapy after oral glucocorticoid use: 2.23 (95% CI 1.92, 2.59); RR 1.7 (95% CI 1.1, 2.6) for diabetes	Systematic dosage of glycaemia before initiation of corticosteroids Systematic biological screening of hyperglycaemia and diabetes (the optimal schedule of screening remains to be determined) Screening and treatment of a worsening of glycaemic control in patients with known diabetes
Dyslipidaemia	Frequency of hypercholesterolemia and/or hypertriglyceridaemia is undetermined	Systematic evaluation of lipid profile before initiation of corticosteroids Screening of hyperlipidaemia in long-term corticosteroid-treated patients (the optimal schedule of screening remains to be determined)

RR = relative risk.

bo-controlled study,[7] glycaemia rose significantly (from 5.1 ± 0.6 mmol/L to 5.9 ± 1.9 mmol/L) in 41 rheumatic patients treated with prednisone 10 mg/day, whereas it was stable in controls. In a large (11 855 cases, 11 855 controls) case-control study,[188] the RR of developing hyperglycaemia requiring hypoglycaemic therapy after oral glucocorticoid use was 2.23 (95% CI 1.92, 2.59). In a meta-analysis,[24] diabetes was reported four times more frequently in the corticosteroid-treated group than in the placebo group. An enhanced incidence for gestational diabetes was also demonstrated in women receiving corticosteroids for threatened preterm delivery (23.8% in treated women vs 4% in controls; p = 0.001).[189]

Corticosteroids also induced a worsening of glycaemic control in patients with known diabetes. In a study,[190] 51 of 80 (64%) patients with diabetes required rapid insulin to control an increase of blood glucose after a pulse of methylprednisolone prescribed for ophthalmological diseases. A strong association between the cumulated prednisone dose and the development of diabetes has been shown. In a case-control study,[188] the risk of developing hyperglycaemia requiring hypoglycaemic therapy after oral corticosteroid use was 1.77 for patients receiving 1–10 mg/day of a prednisone equivalent, 3.02 for 10–20 mg/day, 5.82 for 20–30 mg/day and 10.34 for >30 mg/day. In another study,[191] the cumulative prednisone dosage was significantly higher in patients who developed diabetes versus those who did not (26.6g ± 28g vs 11.6g ± 11g; p < 0.02).

The mechanisms by which the pharmacological use of synthetic corticosteroids induces insulin resistance has been well demonstrated in animals and humans.[25,192] They decrease β-cell insulin production and reduce the effectiveness of insulin to suppress hepatic glucose production and to increase glucose uptake in muscle and fatty tissue.[193] Moreover, corticosteroids induce an increase in the synthesis of glucose. They restore carbohydrates from amino acids by stimulating gluconeogenesis enzymes in the liver, by mobilisation and degradation of proteins and by support of glycogen deposition in the liver.[25]

The frequency and clinical implications of diabetogenesis are listed in table IV.

3.3 Dyslipidaemia

Corticosteroids are supposed to induce hyperlipidaemia. However, few data are available and most studies focused on transplanted patients with potential confounding factors (e.g. other immunosuppressive therapies). In 70 long-term stable renal and liver transplant patients, the prednisone daily dosage was found to be the only independent variable predicting increased post-transplant serum cholesterol levels.[194] In a retrospective study of 92 cardiac transplant patients, cumulative prednisone exposure was the strongest predictor of both total and low-density lipoprotein cholesterol levels (p = 0.0001), independent of cumulative ciclosporin exposure and other clinical variables.[195] Lastly, several authors have shown an improvement in lipid profiles after corticosteroid withdrawal in adult or paediatric transplant populations.[196-198]

In non-transplant patients, data on the relationship between corticosteroids and hyperlipidaemia are conflicting. Compared with healthy people, a significant elevation in total cholesterol and a large decrease in high-density lipoprotein cholesterol (HDL-C) levels have been demonstrated in women (but not in men) receiving long-term corticosteroids therapy (mean duration of therapy: 3.1 years) for connective tissue disease or asthma.[199] In an older study that assessed 100 women with asthma receiving prednisone 5–15 mg/day for 4–13 years, only an increase in the triglycerides level (1.76 ± 0.61 mmol/L vs 1.29 ± 0.31 mmol/L for control subjects; p < 0.05) was demonstrated.[200] More recently, Picado et al.[201] did not find any differences in plasma levels of cholesterol, HDL-C, low-density lipoprotein-cholesterol (LDL-C) or free fatty acids between asthmatic patients not receiving corticosteroids (n = 30) and those receiving inhaled (n = 24) or oral (n = 24) corticosteroids. Nevertheless, a tendency towards an increase in the total cholesterol (197 mg/L, 212 mg/L and 233 mg/L, respectively), LDL-C (respectively 121 mg/L, 138 mg/L, 153 mg/L) and free fatty acid (87 mg/L, 90 mg/L, 102 mg/L, respectively) levels can be observed when the results are accurately analysed.

Lastly, an improvement of the atherogenic index (total cholesterol/HDL-C) was demonstrated in rheumatic patients receiving aggressive anti-rheu-

matic treatment including corticosteroids versus patients only treated with sulfasalazine.[202] Because of the design of the trial, the authors were unable to determine whether this was the result of better disease suppression or therapeutic components. However, their results suggest that changes in total cholesterol levels were the result of effective rheumatoid arthritis treatment, but changes in HDL levels were more specific to glucocorticoid treatment.

Pravastatin is effective at decreasing total cholesterol and LDL-C in heart transplant patients treated with a corticosteroid.[203] To our knowledge, no data are available regarding the effect of a systematic lipid-controlled diet for long-term corticosteroid-treated patients.

The frequency and clinical implications of dyslipidaemia are listed in table IV.

4. Corticosteroids and Pregnancy

In a population-based case-control study,[204] corticosteroid therapy during pregnancy does not appear to noticeably increase the risk of congenital abnormalities in humans (corticosteroid exposure during pregnancy occurred in 1.55% of 20 830 malformed cases and 1.41% of 35 727 healthy control births; $p = 0.2$). However, corticosteroids prescribed during the first trimester of pregnancy may be associated with a higher risk of cleft lip (OR 4.3 [95% CI 1.1, 17.2] to 6.55 [95% CI 1.44, 29.76])[205,206] or cleft palate (OR 5.3; 95% CI 1.1, 26.5)[206,207] in the newborn. Moreover, corticosteroids and indometacin have a synergistic effect on the frequency and severity of fetal ductus arteriosus constriction.[208] Women with uncomplicated pregnancies do not appear to be at greater risk for corticosteroid-induced adverse events than non-gravid women, except possibly in the cases of endometritis and gestational diabetes.[209-212] Hence, corticosteroids may be prescribed safely during pregnancy.

5. Conclusion

This review study evidences the lack of reliable data on many of the corticosteroid-induced adverse events, whether they are rare (e.g. pancreatitis, aseptic necrosis) or frequent (e.g. lipodystrophy, skin disorders). This is regrettable for several reasons. First, about 0.5% of the 1.2 billion people in industrialised countries[213] are treated with prolonged systemic corticosteroid therapy and they cannot be properly informed of some frequent and debilitating adverse events, such as lipodystrophy or neuropsychiatric disorders. Secondly, adverse events that physicians generally consider as 'minor' may nonetheless alter patients' quality of life and affect their adherence and willingness to continue therapy.[214] Thirdly, some of these complications may be overestimated or, on the contrary, underestimated with potential financial[215,216] and epidemiological consequences.

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References

1. Walsh LJ, Wong CA, Pringle M, et al. Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: a cross sectional study. BMJ 1996 Aug 10; 313 (7053): 344-6
2. van Staa TP, Leufkens HG, Abenhaim L, et al. Use of oral corticosteroids in the United Kingdom. QJM 2000 Feb; 93 (2): 105-11
3. Smyllie HC, Connolly CK. Incidence of serious complications of corticosteroid therapy in respiratory disease: a retrospective survey of patients in the Brompton hospital. Thorax 1968 Nov; 23 (6): 571-81
4. Quaade F. Undesirable effects of glucocorticoids. Acta Med Scand Suppl 1969; 500: 77-80
5. McKeage K, Goa KL. Budesonide (Entocort EC Capsules): a review of its therapeutic use in the management of active Crohn's disease in adults. Drugs 2002; 62 (15): 2263-82
6. Jover JA, Hernandez-Garcia C, Morado IC, et al. Combined treatment of giant-cell arteritis with methotrexate and prednisone. a randomized, double-blind, placebo-controlled trial. Ann Intern Med 2001 Jan 16; 134 (2): 106-14
7. van Everdingen AA, Jacobs JW, Siewertsz Van Reesema DR, et al. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. Ann Intern Med 2002 Jan 1; 136 (1): 1-12
8. Wassenberg S, Rau R, Steinfeld P, et al. Very low-dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years: a multicenter, double-blind, placebo-controlled trial. Arthritis Rheum 2005 Nov; 52 (11): 3371-80
9. Caporali R, Cimmino MA, Ferraccioli G, et al. Prednisone plus methotrexate for polymyalgia rheumatica: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 2004 Oct 5; 141 (7): 493-500
10. Campieri M, Ferguson A, Doe W, et al. Oral budesonide is as effective as oral prednisolone in active Crohn's disease. The Global Budesonide Study Group. Gut 1997 Aug; 41 (2): 209-14
11. Bar-Meir S, Chowers Y, Lavy A, et al. Budesonide versus prednisone in the treatment of active Crohn's disease. The

Israeli Budesonide Study Group. Gastroenterology 1998 Oct; 115 (4): 835-40
12. Lieberman P, Patterson R, Kunske R. Complications of long-term steroid therapy for asthma. J Allergy Clin Immunol 1972 Jun; 49 (6): 329-36
13. Thomas TP. The complications of systemic corticosteroid therapy in the elderly: a retrospective study. Gerontology 1984; 30 (1): 60-5
14. Saag KG, Koehnke R, Caldwell JR, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. Am J Med 1994 Feb; 96 (2): 115-23
15. Walsh LJ, Wong CA, Oborne J, et al. Adverse effects of oral corticosteroids in relation to dose in patients with lung disease. Thorax 2001 Apr; 56 (4): 279-84
16. Rizzato G, Riboldi A, Imbimbo B, et al. The long-term efficacy and safety of two different corticosteroids in chronic sarcoidosis. Respir Med 1997 Sep; 91 (8): 449-60
17. Chibane S, Feldman-Billard S, Rossignol I, et al. Short-term tolerance of three days pulse methyprednisolone therapy: a prospective study in 146 patients [in French]. Rev Med Interne 2005 Jan; 26 (1): 20-6
18. Fardet L, Flahault A, Kettaneh A, et al. Corticosteroid-induced clinical adverse events: frequency, risk factors and patient's opinion. Br J Dermatol 2007; 157 (1): 142-8
19. Shubin H. Long term (five or more years) administration of corticosteroids in pulmonary diseases. Dis Chest 1965 Sep; 48 (3): 287-90
20. Gabriel SE, Sunku J, Salvarani C, et al. Adverse outcomes of antiinflammatory therapy among patients with polymyalgia rheumatica. Arthritis Rheum 1997 Oct; 40 (10): 1873-8
21. Akerkar GA, Peppercorn MA, Hamel MB, et al. Corticosteroid-associated complications in elderly Crohn's disease patients. Am J Gastroenterol 1997 Mar; 92 (3): 461-4
22. Covar RA, Leung DY, McCormick D, et al. Risk factors associated with glucocorticoid-induced adverse effects in children with severe asthma. J Allergy Clin Immunol 2000 Oct; 106 (4): 651-9
23. Proven A, Gabriel SE, Orces C, et al. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. Arthritis Rheum 2003 Oct 15; 49 (5): 703-8
24. Conn HO, Poynard T. Corticosteroids and peptic ulcer: meta-analysis of adverse events during steroid therapy. J Intern Med 1994 Dec; 236 (6): 619-32
25. Schacke H, Docke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. Pharmacol Ther 2002 Oct; 96 (1): 23-43
26. Fardet L, Cabane J, Lebbé C, et al. Incidence and risk factors for corticosteroid-induced lipodystrophy: a prospective study. J Am Acad Dermatol. Epub 2007 Jun 18
27. Stanbury RM, Graham EM. Systemic corticosteroid therapy: side effects and their management. Br J Ophthalmol 1998 Jun; 82 (6): 704-8
28. Benet LZ, Frey FJ, Amend Jr WJ, et al. Endogenous and exogenous glucocorticoids in cushingoid patients. Drug Intell Clin Pharm 1982 Nov; 16 (11): 863-8
29. Bergrem H, Jervell J, Flatmark A. Prednisolone pharmacokinetics in cushingoid and non-cushingoid kidney transplant patients. Kidney Int 1985 Feb; 27 (2): 459-64
30. Fardet L, Flahault A, Tiev KP, et al. Natural history of corticosteroid-induced lipodystrophy: a prospective study in 37 patients. Rev Med Interne. In press
31. Fardet L, Cabane J, Kettaneh A, et al. Corticosteroid-induced lipodystrophy is associated with features of the metabolic syndrome. Rheumatology (Oxford) 2007 Jul; 46 (7): 1102-6
32. Sato A, Funder JW, Okubo M, et al. Glucocorticoid-induced hypertension in the elderly. Relation to serum calcium and family history of essential hypertension. Am J Hypertens 1995 Aug; 8 (8): 823-8
33. Williamson PM, Kelly JJ, Whitworth JA. Dose-response relationships and mineralocorticoid activity in cortisol-induced hypertension in humans. J Hypertens Suppl 1996 Dec; 14 (5): S37-41
34. Kelly JJ, Mangos G, Williamson PM, et al. Cortisol and hypertension. Clin Exp Pharmacol Physiol Suppl 1998 Nov; 25: S51-6
35. Whitworth JA, Schyvens CG, Zhang Y, et al. Glucocorticoid-induced hypertension: from mouse to man. Clin Exp Pharmacol Physiol 2001 Dec; 28 (12): 993-6
36. Whitworth JA, Gordon D, Andrews J, et al. The hypertensive effect of synthetic glucocorticoids in man: role of sodium and volume. J Hypertens 1989 Jul; 7 (7): 537-49
37. Truhan AP, Ahmed AR. Corticosteroids: a review with emphasis on complications of prolonged systemic therapy. Ann Allergy 1989 May; 62 (5): 375-91
38. Whitworth JA, Kelly JJ. Evidence that high dose cortisol-induced Na+ retention in man is not mediated by the mineralocorticoid receptor. J Endocrinol Invest 1995 Jul-Aug; 18 (7): 586-91
39. Montrella-Waybill M, Clore JN, Schoolwerth AC, et al. Evidence that high dose cortisol-induced Na+ retention in man is not mediated by the mineralocorticoid receptor. J Clin Endocrinol Metab 1991 May; 72 (5): 1060-6
40. Souverein PC, Berard A, Van Staa TP, et al. Use of oral glucocorticoids and risk of cardiovascular and cerebrovascular disease in a population based case-control study. Heart 2004 Aug; 90 (8): 859-65
41. Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. Ann Intern Med 2004 Nov 16; 141 (10): 764-70
42. Erstad BL. Severe cardiovascular adverse effects in association with acute, high-dose corticosteroid administration. DICP 1989 Dec; 23 (12): 1019-23
43. Tvede N, Nielsen LP, Andersen V. Bradycardia after high-dose intravenous methylprednisolone therapy. Scand J Rheumatol 1986; 15 (3): 302-4
44. Fujimoto S, Kondoh H, Yamamoto Y, et al. Holter electrocardiogram monitoring in nephrotic patients during methylprednisolone pulse therapy. Am J Nephrol 1990; 10 (3): 231-6
45. Bonnotte B, Chauffert B, Martin F, et al. Side-effects of high-dose intravenous (pulse) methylprednisolone therapy cured by potassium infusion [letter]. Br J Rheumatol 1998 Jan; 37 (1): 109
46. Gallant C, Kenny P. Oral glucocorticoids and their complications. A review. J Am Acad Dermatol 1986 Feb; 14 (2 Pt 1): 161-77
47. van der Voort DJ, Geusens PP, Dinant GJ. A cross-sectional study of postmenopausal women found an association between osteoporosis and past gastric surgery or oral corticosteroids. J Clin Epidemiol 2004 May; 57 (5): 533-8
48. Goldstein MF, Fallon Jr JJ, Harning R. Chronic glucocorticoid therapy-induced osteoporosis in patients with obstructive lung disease. Chest 1999 Dec; 116 (6): 1733-49
49. Van Staa TP, Laan RF, Barton IP, et al. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. Arthritis Rheum 2003 Nov; 48 (11): 3224-9
50. Hajiroussou VJ, Webley M. Prolonged low-dose corticosteroid therapy and osteoporosis in rheumatoid arthritis. Ann Rheum Dis 1984 Feb; 43 (1): 24-7
51. Michel BA, Bloch DA, Fries JF. Predictors of fractures in early rheumatoid arthritis. J Rheumatol 1991 Jun; 18 (6): 804-8
52. Pearce G, Ryan PF, Delmas PD, et al. The deleterious effects of low-dose corticosteroids on bone density in patients with

polymyalgia rheumatica. Br J Rheumatol 1998 Mar; 37 (3): 292-9
53. LoCascio V, Bonucci E, Imbimbo B, et al. Bone loss in response to long-term glucocorticoid therapy. Bone Miner 1990 Jan; 8 (1): 39-51
54. Laan RF, van Riel PL, van de Putte LB, et al. Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis: a randomized, controlled study. Ann Intern Med 1993 Nov 15; 119 (10): 963-8
55. Cooper C, Coupland C, Mitchell M. Rheumatoid arthritis, corticosteroid therapy and hip fracture. Ann Rheum Dis 1995 Jan; 54 (1): 49-52
56. McEvoy CE, Ensrud KE, Bender E, et al. Association between corticosteroid use and vertebral fractures in older men with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998 Mar; 157 (3 Pt 1): 704-9
57. Adinoff AD, Hollister JR. Steroid-induced fractures and bone loss in patients with asthma. N Engl J Med 1983 Aug 4; 309 (5): 265-8
58. Kaji H, Yamauchi M, Chihara K, et al. The threshold of bone mineral density for vertebral fracture in female patients with glucocorticoid-induced osteoporosis. Endocr J 2006 Feb; 53 (1): 27-34
59. Reid IR. Glucocorticoid-induced osteoporosis. Baillieres Best Pract Res Clin Endocrinol Metab 2000 Jun; 14 (2): 279-98
60. ANAES. L'ostéoporose chez les femmes ménopausées et chez les sujets traités par corticoides: méthodes diagnostiques et indications. avril 2001 [online]. Available from URL: http://www.unaformec.org/publications/kitunaf_01/recos/osteoporose.recos.pdf [Accessed 2007 Aug 28]
61. Bell R, Carr A, Thompson P. Managing corticosteroid induced osteoporosis in medical outpatients. J R Coll Physicians Lond 1997 Mar-Apr; 31 (2): 158-61
62. Homik J, Suarez-Almazor ME, Shea B, et al. Calcium and vitamin D for corticosteroid-induced osteoporosis. Cochrane Database Syst Rev 2000; (2): CD000952
63. Homik J, Cranney A, Shea B, et al. Bisphosphonates for steroid induced osteoporosis. Cochrane Database Syst Rev 2000; (2): CD001347
64. Amin S, Lavalley MP, Simms RW, et al. The comparative efficacy of drug therapies used for the management of corticosteroid-induced osteoporosis: a meta-regression. J Bone Miner Res 2002 Aug; 17 (8): 1512-26
65. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. Arthritis Rheum 2001 Jul; 44 (7): 1496-503
66. Yood RA, Harrold LR, Fish L, et al. Prevention of glucocorticoid-induced osteoporosis: experience in a managed care setting. Archives Intern Med 2001 May 28; 161 (10): 1322-7
67. Hougardy DM, Peterson GM, Bleasel MD, et al. Is enough attention being given to the adverse effects of corticosteroid therapy? J Clin Pharm Ther 2000 Jun; 25 (3): 227-34
68. Ettinger B, Chidambaran P, Pressman A. Prevalence and determinants of osteoporosis drug prescription among patients with high exposure to glucocorticoid drugs. Am J Manag Care 2001 Jun; 7 (6): 597-605
69. Lane NE, Lukert B. The science and therapy of glucocorticoid-induced bone loss. Endocrinol Metab Clin North Am 1998 Jun; 27 (2): 465-83
70. Humphrey EL, Williams JH, Davie MW, et al. Effects of dissociated glucocorticoids on OPG and RANKL in osteoblastic cells. Bone 2006 May; 38 (5): 652-61
71. Tsuda E, Goto M, Mochizuki S, et al. Isolation of a novel cytokine from human fibroblasts that specifically inhibits osteoclastogenesis. Biochemical and biophysical research communications. 1997 May 8; 234 (1): 137-42
72. Buckley KA, Fraser WD. Receptor activator for nuclear factor kappaB ligand and osteoprotegerin: regulators of bone physiology and immune responses/potential therapeutic agents and biochemical markers. Ann Clin Biochem 2002 Nov; 39 (Pt 6): 551-6
73. Hofbauer LC, Kuhne CA, Viereck V. The OPG/RANKL/RANK system in metabolic bone diseases. J Musculoskelet Neuronal Interact 2004 Sep; 4 (3): 268-75
74. Khaleeli AA, Edwards RH, Gohil K, et al. Corticosteroid myopathy: a clinical and pathological study. Clin Endocrinol (Oxf) 1983 Feb; 18 (2): 155-66
75. Askari A, Vignos PJ, Moskowitz RW. Steroid myopathy in connective tissue disease. Am J Med 1976 Oct; 61 (4): 485-92
76. Naim MY, Reed AM. Enzyme elevation in patients with juvenile dermatomyositis and steroid myopathy. J Rheumatol 2006 Jul; 33 (7): 1392-4
77. Decramer M, Stas KJ. Corticosteroid-induced myopathy involving respiratory muscles in patients with chronic obstructive pulmonary disease or asthma. Am Rev Respir Dis 1992 Sep; 146 (3): 800-2
78. Falduto MT, Czerwinski SM, Hickson RC. Glucocorticoid-induced muscle atrophy prevention by exercise in fast-twitch fibers. J Appl Physiol 1990 Sep; 69 (3): 1058-62
79. Falduto MT, Young AP, Hickson RC. Exercise interrupts ongoing glucocorticoid-induced muscle atrophy and glutamine synthetase induction. Am J Physiol 1992 Dec; 263 (6 Pt 1): E1157-63
80. Horber FF, Scheidegger JR, Grunig BE, et al. Evidence that prednisone-induced myopathy is reversed by physical training. J Clin Endocrinol Metab 1985 Jul; 61 (1): 83-8
81. Bielefeld P. Present status of cortisone myopathy [in French]. Rev Med Interne 1996; 17 (3): 255-61
82. Bowyer SL, LaMothe MP, Hollister JR. Steroid myopathy: incidence and detection in a population with asthma. J Allergy Clin Immunol 1985 Aug; 76 (2 Pt 1): 234-42
83. Hasselgren PO. Glucocorticoids and muscle catabolism. Curr Opin Clin Nutr Metab Care 1999 May; 2 (3): 201-5
84. Larsson L, Li X, Edstrom L, et al. Acute quadriplegia and loss of muscle myosin in patients treated with nondepolarizing neuromuscular blocking agents and corticosteroids: mechanisms at the cellular and molecular levels. Crit Care Med 2000 Jan; 28 (1): 34-45
85. Messer J, Reitman D, Sacks HS, et al. Association of adrenocorticosteroid therapy and peptic-ulcer disease. N Engl J Med 1983 Jul 7; 309 (1): 21-4
86. Hernandez-Diaz S, Rodriguez LA. Steroids and risk of upper gastrointestinal complications. Am J Epidemiol 2001 Jun 1; 153 (11): 1089-93
87. Piper JM, Ray WA, Daugherty JR, et al. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Ann Intern Med 1991 May 1; 114 (9): 735-40
88. Kos-Kudla B, Ciesielska-Kopacz N, Ostrowska Z, et al. Adrenal cortex function in asthmatic patients following the discontinuation of chronic therapy with systemic glucocorticosteroids. J Clin Pharm Ther 2003 Apr; 28 (2): 103-8
89. Pullar T, Sturrock RD. Adrenal response in rheumatoid arthritis treated with long-term steroids. Eur J Rheumatol Inflamm 1983; 6 (2): 187-91
90. Downie WW, Dixon JS, Lowe JR, et al. Adrenocortical suppression by synthetic corticosteroid drugs: a comparative study of prednisolone and betamethasone. Br J Clin Pharmacol 1978 Nov; 6 (5): 397-9
91. Salassa RM, Bennett WA, Keating Jr FR, et al. Postoperative adrenal cortical insufficiency; occurrence in patients previously treated with cortisone. JAMA 1953 Aug 15; 152 (16): 1509-15

92. Streck WF, Lockwood DH. Pituitary adrenal recovery following short-term suppression with corticosteroids. Am J Med 1979 Jun; 66 (6): 910-4
93. Henzen C, Suter A, Lerch E, et al. Suppression and recovery of adrenal response after short-term, high-dose glucocorticoid treatment. Lancet 2000 Feb 12; 355 (9203): 542-5
94. Claman HN. Glucocorticosteroids II: the clinical responses. Hosp Pract (Off Ed) 1983 Jul; 18 (7): 143-6, 149-51
95. Spiegel RJ, Vigersky RA, Oliff AI, et al. Adrenal suppression after short-term corticosteroid therapy. Lancet 1979 Mar 24; 1 (8117): 630-3
96. Hummel M, Warnecke H, Schuler S, et al. Risk of adrenal cortex insufficiency following heart transplantation [in German]. Klin Wochenschr 1991 Apr 4; 69 (6): 269-73
97. Walsh JP, Dayan CM. Role of biochemical assessment in management of corticosteroid withdrawal. Ann Clin Biochem 2000 May; 37 (Pt 3): 279-88
98. Tordjman K, Jaffe A, Trostanetsky Y, et al. Low-dose (1 microgram) adrenocorticotrophin (ACTH) stimulation as a screening test for impaired hypothalamo-pituitary-adrenal axis function: sensitivity, specificity and accuracy in comparison with the high-dose (250 microgram) test. Clin Endocrinol (Oxf) 2000 May; 52 (5): 633-40
99. Suliman AM, Smith TP, Labib M, et al. The low-dose ACTH test does not provide a useful assessment of the hypothalamic-pituitary-adrenal axis in secondary adrenal insufficiency. Clin Endocrinol (Oxf). 2002 Apr; 56 (4): 533-9
100. Rasmuson S, Olsson T, Hagg E. A low dose ACTH test to assess the function of the hypothalamic-pituitary-adrenal axis. Clin Endocrinol (Oxf). 1996 Feb; 44 (2): 151-6
101. Dorin RI, Qualls CR, Crapo LM. Diagnosis of adrenal insufficiency. Ann Intern Med 2003 Aug 5; 139 (3): 194-204
102. Jerjes WK, Cleare AJ, Wood PJ, et al. Assessment of subtle changes in glucocorticoid negative feedback using prednisolone: comparison of salivary free cortisol and urinary cortisol metabolites as endpoints. Clin Chim Acta 2006 Feb; 364 (1-2): 279-86
103. Gozansky WS, Lynn JS, Laudenslager ML, et al. Salivary cortisol determined by enzyme immunoassay is preferable to serum total cortisol for assessment of dynamic hypothalamic--pituitary--adrenal axis activity. Clin Endocrinol (Oxf) 2005 Sep; 63 (3): 336-41
104. Axelrod L. Perioperative management of patients treated with glucocorticoids. Endocrinol Metab Clin North Am 2003 Jun; 32 (2): 367-83
105. Salem M, Tainsh Jr RE, Bromberg J, et al. Perioperative glucocorticoid coverage: a reassessment 42 years after emergence of a problem. Ann Surg 1994 Apr; 219 (4): 416-25
106. Byyny RL. Withdrawal from glucocorticoid therapy. N Engl J Med 1976 Jul 1; 295 (1): 30-2
107. Baxter JD, Forsham PH. Tissue effects of glucocorticoids. Am J Med 1972 Nov; 53 (5): 573-89
108. Staples PJ, Gerding DN, Decker JL, et al. Incidence of infection in systemic lupus erythematosus. Arthritis Rheum 1974 Jan-Feb; 17 (1): 1-10
109. Myerowitz RL, Medeiros AA, O'Brien TF. Bacterial infection in renal homotransplant recipients: a study of fifty-three bacteremic episodes. Am J Med 1972 Sep; 53 (3): 308-14
110. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. Rev Infect Dis 1989 Nov-Dec; 11 (6): 954-63
111. Mok MY, Lo Y, Chan TM, et al. Tuberculosis in systemic lupus erythematosus in an endemic area and the role of isoniazid prophylaxis during corticosteroid therapy. J Rheumatol 2005 Apr; 32 (4): 609-15
112. Gaitonde S, Pathan E, Sule A, et al. Efficacy of isoniazid prophylaxis in patients with systemic lupus erythematosus receiving long term steroid treatment. Ann Rheum Dis 2002 Mar; 61 (3): 251-3
113. Hernandez-Cruz B, Ponce-de-Leon-Rosales S, Sifuentes-Osornio J, et al. Tuberculosis prophylaxis in patients with steroid treatment and systemic rheumatic diseases: a case-control study. Clin Exp Rheumatol 1999 Jan-Feb; 17 (1): 81-7
114. Jick SS, Lieberman ES, Rahman MU, et al. Glucocorticoid use, other associated factors, and the risk of tuberculosis. Arthritis Rheum 2006 Feb 15; 55 (1): 19-26
115. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. MMWR Recomm Rep 2000 Jun 9; 49 (RR-6): 1-51
116. American Thoracic Society. Medical Section of the American Lung Association: treatment of tuberculosis and tuberculosis infection in adults and children. Am Rev Respir Dis 1986 Aug; 134 (2): 355-63
117. Menzies D, Pai M, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. Ann Intern Med 2007 Mar 6; 146 (5): 340-54
118. Winston DJ, Ho WG, Schiffman G, et al. Pneumococcal vaccination of recipients of bone marrow transplants. Arch Intern Med 1983 Sep; 143 (9): 1735-7
119. Spika JS, Halsey NA, Fish AJ, et al. Serum antibody response to pneumococcal vaccine in children with nephrotic syndrome. Pediatrics 1982 Feb; 69 (2): 219-23
120. Patel H, Macarthur C, Johnson D. Recent corticosteroid use and the risk of complicated varicella in otherwise immunocompetent children. Arch Pediatr Adolesc Med 1996 Apr; 150 (4): 409-14
121. Dowell SF, Bresee JS. Severe varicella associated with steroid use. Pediatrics 1993 Aug; 92 (2): 223-8
122. Adhami N, Arabi Y, Raees A, et al. Effect of corticosteroids on adult varicella pneumonia: cohort study and literature review. Respirology 2006 Jul; 11 (4): 437-41
123. Satoh N, Abe T, Nakajima A, et al. Recurrent varicella-zoster virus retinitis in a patient treated with systemic corticosteroids: ocular immunology and inflammation. 1998 Sep; 6 (3): 185-8
124. Salisbury DM, Begg NT. Varicella: immunisation against infectious diseases. London: HMSO, 1996: 251-61
125. Feher MD, Simms JP, Lant AF. History of chicken pox and steroid cards: a new warning? BMJ 1996 Mar 2; 312 (7030): 542-3
126. Vento S, Cainelli F, Longhi MS. Reactivation of replication of hepatitis B and C viruses after immunosuppressive therapy: an unresolved issue. Lancet Oncol 2002 Jun; 3 (6): 333-40
127. Magy N, Cribier B, Schmitt C, et al. Effects of corticosteroids on HCV infection. Int J Immunopharmacol 1999 Apr; 21 (4): 253-61
128. Tur-Kaspa R, Burk RD, Shaul Y, et al. Hepatitis B virus DNA contains a glucocorticoid-responsive element. Proc Natl Acad Sci U S A 1986 Mar; 83 (6): 1627-31
129. Vassiliadis T, Garipidou V, Tziomalos K, et al. Prevention of hepatitis B reactivation with lamivudine in hepatitis B virus carriers with hematologic malignancies treated with chemotherapy: a prospective case series. Am J Hematol 2005 Nov; 80 (3): 197-203
130. Hanania NA, Sockrider M, Castro M, et al. Immune response to influenza vaccination in children and adults with asthma: effect of corticosteroid therapy. J Allergy Clin Immunol 2004 Apr; 113 (4): 717-24
131. Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. Lancet 2003 Nov 29; 362 (9398): 1828-38
132. O'Donnell MR, Schmidt GM, Tegtmeier BR, et al. Prediction of systemic fungal infection in allogeneic marrow recipients: impact of amphotericin prophylaxis in high-risk patients. J Clin Oncol 1994 Apr; 12 (4): 827-34

133. Marr KA, Carter RA, Boeckh M, et al. Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. Blood 2002 Dec 15; 100 (13): 4358-66
134. Iriya SM, Capelozzi VL, Calich I, et al. Causes of death in patients with systemic lupus erythematosus in Sao Paulo, Brazil: a study of 113 autopsies. Arch Intern Med 2001 Jun 25; 161 (12): 1557
135. Nucci M, Colombo AL. Risk factors for breakthrough candidemia. Eur J Clin Microbiol Infect Dis 2002 Mar; 21 (3): 209-11
136. Kontoyiannis DP, Vaziri I, Hanna HA, et al. Risk Factors for Candida tropicalis fungemia in patients with cancer. Clin Infect Dis 2001 Nov 15; 33 (10): 1676-81
137. Gumbo T, Isada CM, Hall G, et al. Candida glabrata Fungemia: clinical features of 139 patients. Medicine 1999 Jul; 78 (4): 220-7
138. Yale SH, Limper AH. Pneumocystis carinii pneumonia in patients without acquired immunodeficiency syndrome: associated illness and prior corticosteroid therapy. Mayo Clin Proc 1996 Jan; 71 (1): 5-13
139. Gluck T, Geerdes-Fenge HF, Straub RH, et al. *Pneumocystis carinii* pneumonia as a complication of immunosuppressive therapy. Infection 2000 Jul-Aug; 28 (4): 227-30
140. Davidson RA, Fletcher RH, Chapman LE. Risk factors for strongyloidiasis: a case-control study. Arch Intern Med 1984 Feb; 144 (2): 321-4
141. Nucci M, Portugal R, Pulcheri W, et al. Strongyloidiasis in patients with hematologic malignancies. Clin Infect Dis 1995 Sep; 21 (3): 675-7
142. Fardet L, Genereau T, Poirot JL, et al. Severe strongyloidiasis in corticosteroid-treated patients: case series and literature review. J Infect 2007 Jan; 54 (1): 18-27
143. Centers for Disease Control and Prevention, Infectious Disease Society of America, Transplantation ASoBaM. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. MMWR Recomm Rep 2000; 49 (RR-10): 1-125, CE1-7
144. Carpenter Jr WT, Gruen PH. Cortisol's effects on human mental functioning. J Clin Psychopharmacol 1982 Apr; 2 (2): 91-101
145. Naber D, Sand P, Heigl B. Psychopathological and neuropsychological effects of 8-days' corticosteroid treatment: a prospective study. Psychoneuroendocrinology 1996 Jan; 21 (1): 25-31
146. Fauchais AL, Boivin V, Hachulla E, et al. Psychiatric complications of corticoid therapy in the elderly over 65 years of age treated for Horton disease [in French]. Rev Med Interne 2002 Oct; 23 (10): 828-33
147. Hall RC, Popkin MK, Stickney SK, et al. Presentation of the steroid psychoses. J Nerv Ment Dis 1979 Apr; 167 (4): 229-36
148. Brown ES, Khan DA, Nejtek VA. The psychiatric side effects of corticosteroids. Ann Allergy Asthma Immunol 1999 Dec; 83 (6 Pt 1): 495-503
149. Glaser GH. Psychotic reactions induced by corticotropin (ACTH) cortisone. Psychosom Med 1953 Jul-Aug; 15 (4): 280-91
150. Satel SL. Mental status changes in children receiving glucocorticoids: review of the literature. Clin Pediatr (Phila) 1990 Jul; 29 (7): 383-8
151. Acute adverse reactions to prednisone in relation to dosage. Clin Pharmacol Ther 1972 Sep-Oct; 13 (5): 694-8
152. Wolkowitz OM. Long-lasting behavioral changes following prednisone withdrawal. JAMA 1989 Mar 24-31; 261 (12): 1731-2
153. Venkatarangam SH, Kutcher SP, Notkin RM. Secondary mania with steroid withdrawal. Can J Psychiatry 1988 Oct; 33 (7): 631-2
154. Campbell KM, Schubert DS. Delirium after cessation of glucocorticoid therapy. Gen Hosp Psychiatry 1991 Jul; 13 (4): 270-2
155. Klein JF. Adverse psychiatric effects of systemic glucocorticoid therapy. Am Fam Physician 1992 Nov; 46 (5): 1469-74
156. Urban Jr RC, Cotlier E. Corticosteroid-induced cataracts. Surv Ophthalmol 1986 Sep-Oct; 31 (2): 102-10
157. Garbe E, LeLorier J, Boivin JF, et al. Risk of ocular hypertension or open-angle glaucoma in elderly patients on oral glucocorticoids. Lancet 1997 Oct 4; 350 (9083): 979-82
158. Garbe E, Suissa S, LeLorier J. Association of inhaled corticosteroid use with cataract extraction in elderly patients. JAMA 1998 Aug 12; 280 (6): 539-43
159. Nishigori H, Hayashi R, Lee JW, et al. Preventive effect of ascorbic acid against glucocorticoid-induced cataract formation of developing chick embryos. Exp Eye Res 1985 Mar; 40 (3): 445-51
160. Nagata M, Hikida M, Mibu H, et al. Effect of ascorbic acid 2-O-alpha-glucoside on hydrocortisone-induced cataract formation in developing chick embryos: II. Influence on glutathione and lipid peroxide contents in the lens. J Ocul Pharmacol 1994 Fall; 10 (3): 537-42
161. Tripathi RC, Parapuram SK, Tripathi BJ, et al. Corticosteroids and glaucoma risk. Drugs Aging 1999 Dec; 15 (6): 439-50
162. Tripathi RC, Kipp MA, Tripathi BJ, et al. Ocular toxicity of prednisone in pediatric patients with inflammatory bowel disease. Lens Eye Toxic Res 1992; 9 (3-4): 469-82
163. Spaeth GL, Rodrigues MM, Weinreb S. Steroid-induced glaucoma: A. Persistent elevation of intraocular pressure B. Histopathological aspects. Trans Am Ophthalmol Soc 1977; 75: 353-81
164. Katz HI, Prawer SE, Mooney JJ, et al. Preatrophy: covert sign of thinned skin. J Am Acad Dermatol 1989 May; 20 (5 Pt 1): 731-5
165. Sutton RD, Benedek TG, Edwards GA. Aseptic Bone Necrosis and Corticosteroid Therapy. Arch Intern Med 1963 Oct; 112: 594-602
166. Fisher DE. The role of fat embolism in the etiology of corticosteroid-induced avascular necrosis: clinical and experimental results. Clin Orthop Relat Res 1978 Jan-Feb; 130: 68-80
167. Richards JM, Santiago SM, Klaustermeyer WB. Aseptic necrosis of the femoral head in corticosteroid-treated pulmonary disease. Arch Intern Med 1980 Nov; 140 (11): 1473-5
168. Bomelburg T, von Lengerke HJ, Ritter J. Aseptic osteonecroses in the treatment of childhood acute leukaemias. Eur J Pediatr 1989 Oct; 149 (1): 20-3
169. Weiner ES, Abeles M. Aseptic necrosis and glucocorticosteroids in systemic lupus erythematosus: a reevaluation. J Rheumatol 1989 May; 16 (5): 604-8
170. Haajanen J, Saarinen O, Laasonen L, et al. Steroid treatment and aseptic necrosis of the femoral head in renal transplant recipients. Transplant Proc 1984 Oct; 16 (5): 1316-9
171. Patton PR, Pfaff WW. Aseptic bone necrosis after renal transplantation. Surgery 1988 Jan; 103 (1): 63-8
172. Yoshizawa Y, Ogasa S, Izaki S, et al. Corticosteroid-induced pancreatitis in patients with autoimmune bullous disease: case report and prospective study. Dermatology 1999; 198 (3): 304-6
173. Keefe M, Munro F. Acute pancreatitis: a fatal complication of treatment of bullous pemphigoid with systemic corticosteroids. Dermatologica 1989; 179 (2): 73-5
174. Jain R, Ramanan SV. Iatrogenic pancreatitis: a fatal complication in the induction therapy for acute lymphocytic leukemia. Arch Intern Med 1978 Nov; 138 (11): 1726
175. Oppenheimer EH, Boitnott JK. Pancreatitis in children following adrenal cortico-steroid therapy. Bull Johns Hopkins Hosp 1960 Dec; 107: 297-306

176. Liddle GW. Effects of anti-inflammatory steroids on electrolyte metabolism. Ann N Y Acad Sci 1959 Oct 14; 82: 854-67
177. Bartter FC. The role of aldosterone in normal homeostasis and in certain disease states. Metabolism 1956 Jul; 5 (4): 369-83
178. Nabarro JD, Stewart JS, Walker G. Clinical and metabolic effects of prednisone. Lancet 1955 Nov 12; 269 (6898): 993-8
179. Bunim JJ, Pechet MM, Bollet AJ. Studies on metacortandralone and metacortandracin in rheumatoid arthritis; antirheumatic potency, metabolic effects, and hormonal properties. JAMA 1955 Jan 22; 157 (4): 311-8
180. Pechet MM BF. Studies with a new series of steroids metacordracin and metacortandralone [letter]. J Clin Endocrinol Metab 1955; 15: 851
181. Thorn GW, Renold AE, Morse WI, et al. Highly potent adrenal cortical steroids: structure and biologic activity. Ann Intern Med 1955 Nov; 43 (5): 979-1000
182. Morris GC, Egan JG, Keston Jones M. Hypokalaemic paralysis induced by bolus prednisolone in Graves' disease. Aust N Z J Med 1992 Jun; 22 (3): 312
183. Ramsahoye BH, Davies SV, el-Gaylani N, et al. The mineralocorticoid effects of high dose hydrocortisone. BMJ 1995 Mar 11; 310 (6980): 656-7
184. Yu EC, Wong SN, Yeung CY. Encephalopathy associated with steroid treated nephrotic syndrome. Int J Pediatr Nephrol 1987 Jul-Sep; 8 (3): 135-46
185. Rosenbach Y, Zahavi I, Rachmal A, et al. Severe hypokalemia after budesonide treatment for Crohn's disease. J Pediatr Gastroenterol Nutr 1997 Mar; 24 (3): 352-5
186. Lieber IH, Stoneburner SD, Floyd M, et al. Potassium-wasting nephropathy secondary to chemotherapy simulating Bartter's syndrome. Cancer 1984 Sep 1; 54 (5): 808-10
187. Gennari FJ. Hypokalemia. N Engl J Med 1998 Aug 13; 339 (7): 451-8
188. Gurwitz JH, Bohn RL, Glynn RJ, et al. Glucocorticoids and the risk for initiation of hypoglycemic therapy. Arch Intern Med 1994 Jan 10; 154 (1): 97-101
189. Fisher JE, Smith RS, Lagrandeur R, et al. Gestational diabetes mellitus in women receiving beta-adrenergics and corticosteroids for threatened preterm delivery. Obstet Gynecol 1997 Dec; 90 (6): 880-3
190. Feldman-Billard S, Lissak B, Kassaei R, et al. Short-term tolerance of pulse methylprednisolone therapy in patients with diabetes mellitus. Ophthalmology 2005 Mar; 112 (3): 511-5
191. Raul Ariza-Andraca C, Barile-Fabris LA, Frati-Munari AC, et al. Risk factors for steroid diabetes in rheumatic patients. Arch Med Res 1998 Autumn; 29 (3): 259-62
192. Almon RR, Dubois DC, Jin JY, et al. Temporal profiling of the transcriptional basis for the development of corticosteroid-induced insulin resistance in rat muscle. J Endocrinol 2005 Jan; 184 (1): 219-32
193. Andrews RC, Walker BR. Glucocorticoids and insulin resistance: old hormones, new targets. Clin Sci (Lond) 1999 May; 96 (5): 513-23
194. Fernandez-Miranda C, de la Calle A, Morales JM, et al. Lipoprotein abnormalities in long-term stable liver and renal transplanted patients: a comparative study. Clin Transplant 1998 Apr; 12 (2): 136-41
195. Becker DM, Chamberlain B, Swank R, et al. Relationship between corticosteroid exposure and plasma lipid levels in heart transplant recipients. Am J Med 1988 Nov; 85 (5): 632-8
196. Andrews WS, Shimaoka S, Sommerauer J, et al. Steroid withdrawal after pediatric liver transplantation. Transplant Proc 1994 Feb; 26 (1): 159-60
197. McDiarmid SV, Farmer DA, Goldstein LI, et al. A randomized prospective trial of steroid withdrawal after liver transplantation. Transplantation 1995 Dec 27; 60 (12): 1443-50
198. Punch JD, Shieck VL, Campbell DA, et al. Corticosteroid withdrawal after liver transplantation. Surgery 1995 Oct; 118 (4): 783-6; discussion 6-8
199. Jefferys DB, Lessof MH, Mattock MB. Corticosteroid treatment, serum lipids and coronary artery disease. Postgrad Med J 1980 Jul; 56 (657): 491-3
200. el-Shaboury AH, Hayes TM. Hyperlipidaemia in asthmatic patients receiving long-term steroid therapy. BMJ 1973 Apr 14; 2 (5858): 85-6
201. Picado C, Deulofeu R, Lleonart R, et al. Lipid and protein metabolism in asthma: effects of diet and corticosteroid therapy. Allergy 1999 Jun; 54 (6): 569-75
202. Boers M, Nurmohamed MT, Doelman CJ, et al. Influence of glucocorticoids and disease activity on total and high density lipoprotein cholesterol in patients with rheumatoid arthritis. Ann Rheum Dis 2003 Sep; 62 (9): 842-5
203. Seipelt IM, Crawford SE, Rodgers S, et al. Hypercholesterolemia is common after pediatric heart transplantation: initial experience with pravastatin. J Heart Lung Transplant 2004 Mar; 23 (3): 317-22
204. Czeizel AE, Rockenbauer M. Population-based case-control study of teratogenic potential of corticosteroids. Teratology 1997 Nov; 56 (5): 335-40
205. Rodriguez-Pinilla E, Martinez-Frias ML. Corticosteroids during pregnancy and oral clefts: a case-control study. Teratology 1998 Jul; 58 (1): 2-5
206. Carmichael SL, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. Am J Med Genet 1999 Sep 17; 86 (3): 242-4
207. Fraser FC, Sajoo A. Teratogenic potential of corticosteroids in humans. Teratology 1995 Jan; 51 (1): 45-6
208. Levy R, Matitiau A, Ben Arie A, et al. Indomethacin and corticosteroids: an additive constrictive effect on the fetal ductus arteriosus. Am J Perinatol 1999; 16 (8): 379-83
209. Schatz M, Patterson R, Zeitz S, et al. Corticosteroid therapy for the pregnant asthmatic patient. JAMA 1975 Aug 18; 233 (7): 804-7
210. Aghajafari F, Murphy K, Willan A, et al. Multiple courses of antenatal corticosteroids: a systematic review and meta-analysis. Am J Obstet Gynecol 2001 Nov; 185 (5): 1073-80
211. Yildirim Y, Tinar S, Oner RS, et al. Gestational diabetes mellitus in patients receiving long-term corticosteroid therapy during pregnancy. J Perinat Med 2006; 34 (4): 280-4
212. Abbasi S, Hirsch D, Davis J, et al. Effect of single versus multiple courses of antenatal corticosteroids on maternal and neonatal outcome. Am J Obstet Gynecol 2000 May; 182 (5): 1243-9
213. Population reference bureau [online]. Available from URL: http://www.prb.org [Accessed 2007 Jul 25]
214. Morrison E, Crosbie D, Capell HA. Attitude of rheumatoid arthritis patients to treatment with oral corticosteroids. Rheumatology (Oxford) 2003 Oct; 42 (10): 1247-50
215. Bae SC, Corzillius M, Kuntz KM, et al. Cost-effectiveness of low dose corticosteroids versus non-steroidal anti-inflammatory drugs and COX-2 specific inhibitors in the long-term treatment of rheumatoid arthritis. Rheumatology (Oxford) 2003 Jan; 42 (1): 46-53
216. Pisu M, James N, Sampsel S, et al. The cost of glucocorticoid-associated adverse events in rheumatoid arthritis. Rheumatology (Oxford) 2005 Jun; 44 (6): 781-8

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