Table 1 The Glucocorticoid Toxicity Index

Composite GTI	Item weight	Specific List
BMI		
Improvement in BMI	−8	Major increase in BMI
No change in BMI	0	
Moderate increase in BMI	21	
Major increase in BMI	36	
Glucose tolerance		
Improvement in glucose tolerance	−8	Diabetic retinopathy
No change in glucose tolerance	0	Diabetic nephropathy
Worsening of glucose tolerance	32	Diabetic neuropathy
Worsening of glucose tolerance despite treatment	44	
Blood pressure		
Improvement in blood pressure	−10	Hypertensive emergency
No change in blood pressure	0	Posterior reversible encephalopathy syndrome
Worsening hypertension	19	
Worsening hypertension despite treatment	44	
Lipids		
Improvement in lipids	−9	
No change in lipids	0	
Worsening hyperlipidaemia	10	
Worsening hyperlipidaemia despite treatment	30	
Bone density		
Improvement in bone density	−1	Major decrease in bone density
No change in bone density	0	Insufficiency fracture
Decrease in bone density	29	
Steroid myopathy		
No steroid myopathy	0	Severe steroid myopathy
Mild steroid myopathy	9	
Moderate steroid myopathy or greater	63	
Skin toxicity		
No skin toxicity	0	Severe skin toxicity
Mild skin toxicity	8	
Moderate skin toxicity or greater	26	
Neuropsychiatric toxicity		
No neuropsychiatric symptoms	0	Psychosis
Mild neuropsychiatric symptoms	11	GC-induced violence
Moderate neuropsychiatric symptoms or greater	74	Other severe neuropsychiatric symptoms
Infection		
No significant infection	0	Grade IV infection
Oral/vaginal candidiasis or uncomplicated zoster	19	Grade V infection
Grade III infection or greater	93	
Endocrine		Adrenal insufficiency
Gastrointestinal		Perforation
		Peptic ulcer disease
Musculoskeletal		Avascular necrosis
		Tendon rupture
Ocular		Central serous retinopathy
		Intraocular pressure elevation
		Posterior subcapsular cataract
Total	−36 to 439	

BMI, body mass index; GC, glucocorticoid; GTI, Glucocorticoid Toxicity Index.

Appendix III - Composite Glucocorticoid Toxicity Index

1. Body Mass Index (BMI) (compared to baseline)

a. Improvement in the direction of the normal range by more than 2 BMI units [normal range = 18.5-24.9 kg/m^2]
b. No significant change (BMI remains within +/- 2 BMI units compared with baseline)
   OR BMI remains within the normal range
c. Moderate increase in BMI (increase by more than 2 but less that 5 BMI units, to above the upper limit of normal BMI [24.9 kg/m^2])
d. Major increase in BMI (increase by at least 5 but less than 8 BMI units above normal BMI [24.9 kg/m^2])

2. Glucose Tolerance (compared to baseline)

a. Improvement in glucose tolerance:
   - HbA1c declined >10% from baseline without medication increase
     OR
   - Decrease in diabetic medication without an increase in HbA1c of >10% or HbA1c < 5.7%

b. No significant change in glucose tolerance:
   - HbA1c within 10% of baseline or HbA1c < 5.7% AND no change in medication
     OR
   - HbA1c increased to > 10% of baseline with a decrease in medication
     OR
   - HbA1c decreased by > 10% of baseline with an increase in medication

c. Worsening of glucose tolerance or medication status:
   - HbA1c > 5.7% and increased to >10% of baseline without a change in medication
     OR
   - Increase in diabetic medication with < 10% increase in HbA1c

d. Worsening of glucose tolerance despite increased treatment:
   - HbA1c > 5.7% AND increased to >10% of baseline AND an increase in diabetic medication

3. Blood Pressure (BP) (compared to baseline)

a. Improvement in BP:
   - Decrease in BP of >10% of baseline without medication increase, unless baseline systolic BP ≤ 120 and diastolic BP ≤ 85
     OR
   - Decrease in medication without an increase in BP of >10%, unless baseline systolic BP ≤ 120 and diastolic BP ≤ 85

b. No significant change in BP:
   - BP within 10% of baseline or systolic BP ≤ 120 and diastolic BP ≤ 85 AND no change in medication
     OR
   - Increase in either systolic or diastolic BP >10% with a decrease in medication
     OR
     - Improvement in systolic or diastolic BP of > 10% with an increase in medication

c. Worsening of hypertension:

- Increase in BP of >10% such that the systolic BP exceeds 120 mmHg or the diastolic BP exceeds 85 mmHg without a change in medication

OR

- An increase in anti-hypertensive medication accompanied by stability or no significant change in both the systolic and diastolic BP

d. Worsening of hypertension despite treatment:

- Increase in BP of >10% such that the systolic BP exceeds 120 mmHg or the diastolic BP exceeds 85 mmHg AND an increase in medication

4. Lipid metabolism (low-density lipoprotein [LDL] compared to baseline)

a. Improvement in lipids:

- Decrease in LDL concentration >10% of baseline toward the target range without medication increase

OR

- Decrease in medication without an increase in LDL of >10% or LDL remains within target range

b. No significant change in LDL:

- LDL within 10% of baseline or within the target range for patient AND no change in medication

OR

- Increase in LDL > 10% with a decrease in medication

OR

- Improvement in LDL of > 10% with an increase in medication

c. Worsening of LDL or medication status:

- Increase in LDL of >10% to above target range without a change in medication

OR

- Increase in medication with <10% change in LDL

d. Worsening of LDL despite treatment:

- Increase in LDL of >10% AND an increase in medication

5. Bone Mineral Density (compared to baseline)

a. Improvement – increase in BMD by >3%
b. No significant change (BMD between -3% and +3%
c. Deterioration - decrease in BMD (BMD decrease by ->3%)

% refers to total BMD in gms/cm^2

6. Glucocorticoid-induced myopathy

a. No steroid myopathy
b. Mild steroid myopathy (weakness WITHOUT functional limitation)
c. Moderate steroid myopathy (weakness WITH functional limitation)

See Steroid Myopathy definitions, below

7. Skin

a. No skin toxicity
b. Mild skin toxicity
c. Moderate skin toxicity

See Skin definitions, below

8. Neuropsychiatric toxicity

a. No neuropsychiatric symptoms
b. Mild neuropsychiatric symptoms
c. Moderate neuropsychiatric symptoms

See Neuropsychiatry definitions, below

9. Infection (since last assessment)

a. No significant infection
b. Specific infections < Grade 3 (oral or vaginal candidiasis, uncomplicated zoster)
c. Grade 3 or complicated herpes zoster

See Infection definitions, below

Glucocorticoid-induced Myopathy Definitions

Glucocorticoid-induced myopathy is defined as mild symmetrical weakness of the proximal muscles and/or neck flexors associated with steroid therapy, and NOT due to any other apparent cause. Muscle enzymes are typically within normal limits.

Mild and moderate severity of myopathy are defined by a muscle strength of 4 on the standard Medical Research Council rating scale.

A 4 means weaker than normal but greater than antigravity strength against resistance.

“Mild” is mild weakness (Grade 4) that does NOT functionally limit the patient.

”Moderate” is mild weakness (Grade 4) that does impose functional limitations on the patient enough to interfere with normal daily activities.

Note that a person may have muscle weakness consistent with glucocorticoid-induced myopathy that detectable on physical examination but might not be aware of it or have any corresponding functional limitation - this would be classified as mild.

Severe glucocorticoid-induced myopathy (defined as weakness of Grade 3 or less, which means no more than antigravity strength and unable to overcome any resistance or any degree weaker) is included in the Specific List. People who are severely weak may have difficulty rising from a chair without assistance or other major functional limitations but the formal categorization for severe should be based the degree of weakness on strength testing.

Severity of Glucocorticoid Toxicity in the Skin

Manifestations to be considered:

- Acneiform rash
- Easy Bruising
- Hirsutism
- Atrophy/striae
- Erosions/tears/ulcerations

Skin 6b. Mild	Skin 6c. Moderate	Severe (Specific Domain)
Acneiform rash (Grades 1-2)	Acneiform rash (Grade 3)	Acneiform rash (Grade 4)
Easy bruising (Grade 1)	Easy bruising (Grade 2)	
Hirsutism (Grade 1)	Hirsutism (Grade 2)	
Atrophy/Striae (Grade 1)	Atrophy/Striae (Grade 2)	Atrophy/Striae (Grade 3)
Erosions/Tears/Ulcerations (Grade 1)	Erosions/Tears/Ulcerations (Grade 2)	Erosions/Tears/Ulcerations (Grade 3)

Skin Definitions (from National Cancer Institute Common Terminology Criteria for Adverse Events):

Acneiform rash
- Grade 1 - Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness
- Grade 2 – Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; OR associated with psychosocial impact; OR limiting instrumental ADL
- Grade 3 - Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; OR limiting self care ADL; OR associated with local superinfection with oral antibiotics indicated
- Grade 4 - Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; OR life- threatening consequences

Easy bruising
- Grade 1 – Localized or in a dependent area
- Grade 2 - Generalized

Hirsutism - In women, increase in length, thickness or density of hair in a male distribution
- Grade 1 - Hirsutism that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair
- Grade 2 - Hirsutism that requires daily shaving or consistent destructive means of hair removal to camouflage; OR associated with psychosocial impact

Atrophy / Striae
- Grade 1 - Covering <10% BSA; OR associated with telangiectasias or changes in skin color
- Grade 2 – Covering 10 - 30% BSA; OR associated with striae or adnexal structure loss
- Grade 3 - Covering >30% BSA; OR associated with ulceration

Erosions / Tears / Ulcerations
- Grade 1 – Combined area of ulcers <1 cm; OR nonblanchable erythema of intact skin associated with warmth or erythema
- Grade 2 – Combined area of ulcers 1 - 2 cm; OR partial thickness skin loss involving skin or subcutaneous fat
- Grade 3 – Combined area of ulcers >2 cm; OR full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia

Severity of Neuropsychiatric Glucocorticoid Toxicity

Manifestations to be considered:

- Insomnia
- Mania
- Cognitive Impairment
- Depression

7b. Mild	7c. Moderate	Severe (Specific Domain)
Insomnia – (Grade 1)	Insomnia – (Grade 2)	
Mania (Grade 1)	Mania (Grade 2)	Mania (Grade 3)
Cognitive impairment (Grade 1)	Cognitive impairment (Grade 2)	Cognitive impairment (Grade 3)
Depression (Grade 1)	Depression (Grade 2)	Depression (Grade 3)

Definitions of severity within the Neuropsychiatric Domain

Insomnia - Dissatisfaction with sleep quality and difficulty initiating or maintaining sleep or early morning awakening

- Grade 1: not associated with functional impairment
- Grade 2: associated with functional impairment

Mania

- Grade 1: Slightly or occasionally elevated or irritable mood and 0-1 mild or occasional additional symptoms of inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions.
- Grade 2: Frequent or moderately elevated or irritable mood and 2-3 mild additional symptoms of inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions.
- Grade 3: Severe or constantly elevated or irritable mood and 4 or more additional symptoms of inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions.

Cognitive impairment

- Grade 1: Minor cognitive complaints, no objective findings on mental status examination (i.e., not apparent to the examiner) that were not present before initiating steroids
- Grade 2: New moderate cognitive deficits that were not present before initiating steroids
- Grade 3: Frank delirium

Depression

- Grade 1: Feeling slightly down or depressed and 0-2 mild or occasional addition symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite.
- Grade 2: Frequent or moderate feelings of being down or depression and/or 3-4 symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite.
- Grade 3: Severe constant feeling of being down or depression and/or 5 or more symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite and/or suicidal thoughts.

Infection Definitions

No significant infection = No specific infections or serious infections, grade 3 or greater

Specific Infections – Oral or vaginal candidiasis or zoster infections without post-herpetic neuralgia or eye involvement

Grade 3 – Intravenous antibiotic, antifungal, or antiviral intervention or hospitalization indicated OR radiologic or operative intervention indicated OR herpes zoster complicated by post-herpetic neuralgia or eye involvement

Grade 4 or 5 - Life-threatening consequences; urgent intervention indicated OR death from infection (included in the Specific List)

References

Medical Research Council of the United Kingdom. Guide to Examination of the Peripheral Nervous System: Memorandum No 45. Palo Alto, Calif: Pedragon House; 1978.

National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 NCI, NIH, DHHS. May 29, 2009 NIH publication # 09-7473.

Appendix IV - Specific List

	At Baseline or Before	New Since Baseline
Body Mass Index - An absolute increase in BMI of more than 8 units (and >24.9 kg/m^2)		
Blood Pressure - Hypertensive emergency (see definition, below) - PRES (Posterior reversible encephalopathy syndrome) (see definition, below)		
Endocrine - Symptomatic adrenal insufficiency		
Bone Health - Osteonecrosis of one joint - Osteonecrosis of more than one joint - Bone mineral density decrease > 6% - Insufficiency fracture - Insufficiency fracture in more than one bone		
Muscle & Tendon - Severe glucocorticoid myopathy (see definition) - Tendon rupture - More than one tendon rupture		
Eye - Central serous retinopathy - New-onset or worsened elevation of intra-ocular pressure requiring treatment or change in treatment - Posterior subcapsular cataracts (or history of same)		

Infection - Grade 4 infection (see definition, below) - Grade 5 infection (death from infection)		
Glucose Tolerance - Diabetic nephropathy - Diabetic neuropathy - Diabetic retinopathy		
Gastrointestinal Tract - Gastrointestinal perforation (occurring in the absence of regular nonsteroidal anti-inflammatory drug use) - Peptic ulcer disease confirmed by endoscopy (excluding *H. pylori*)		
Skin - Severe skin toxicity (see definition, below)		
Neuropsychiatric - Psychosis, defined as hallucinations, delusions, or disorganized thought processes (occurring in the absence of mania, delirium, or depression) - Glucocorticoid-induced violence toward self or others		
Other glucocorticoid toxicities Please specify**:** _____ _____ _____		

DEFINITIONS:

Hypertensive emergency: The blood pressure has reached levels that are damaging organs. Hypertensive emergencies generally occur at blood pressure levels exceeding 180 mmHg systolic OR 120 mmHg diastolic, but can occur at even lower levels in patients whose blood pressure have not been elevated before. Complications can include: stroke, loss of consciousness, memory loss, myocardial infarction, hypertensive retinopathy or nephropathy, aortic dissection, angina, pulmonary edema.

Posterior reversible leukoencephalopathy syndrome (PRES): A clinical radiological entity. Clinical features may include headaches, altered mental status, seizures, and visual loss, depending on the affected neuroanatomy. Characteristic Magnetic Resonance Imaging (MRI) findings include vasogenic edema involving the white matter that predominantly affects the posterior occipital and parietal lobes of the brain, although other brain regions may also be affected. Confirmation by MRI is required as is exclusion of other potential causes (including hypertensive emergency).

Severe glucocorticoid myopathy: Grade 3 or worse myopathic weakness or respiratory myopathic weakness attributable to glucocorticoid myopathy.

Central serous retinopathy: a fluid detachment of macula layers from their supporting tissue. Requires formal ophthalmology examination, typically accompanied by optical coherence tomography and/or fluorescein angiography for diagnostic confirmation.

Grade 4 infection: Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis).

Diabetic nephropathy: Macroalbuminuria; i.e., a urinary albumin excretion > 300 mg in a 24-hour collection or a urinary protein: creatinine ratio > 300mg/g.

Diabetic neuropathy: Any of four types of peripheral neuropathy occurring in the setting of diabetes mellitus, namely: 1) a distal sensory polyneuropathy; 2) autonomic neuropathy (hypoglycemia unawareness, bladder or bowel problems, erectile dysfunction, and other autonomic nervous system issues); 3) diabetic amyotrophy (muscle infarction); or 4) mononeuritis (e.g., foot drop attributed to diabetic neuropathy).

Diabetic retinopathy: Any form of retinopathy associated with diabetes mellitus, including both non-proliferative and proliferative forms of diabetic retinopathy as well as diabetic macular edema. These complications must be confirmed by an ophthalmologist.

Severe skin toxicity: Any of the three following manifestations:
Grade 4 acneiform lesions - Papules and/or pustules covering any % body suraface area (BSA), which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated or life- threatening consequences
Grade 3 striae - Covering >30% BSA or associated with ulceration
Grade 3 ulcers - Combined area of ulcers >2 cm or full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia

References

National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 NCI, NIH, DHHS. May 29, 2009 NIH publication # 09-7473.

Medical Research Council of the United Kingdom. Guide to Examination of the Peripheral Nervous System: Memorandum No 45. Palo Alto, Calif: Pedragon House; 1978.

American Heart Association. Hypertensive Crisis. Accessed http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/AboutHighBloodPressure/Hypertensive-Crisis_UCM_301782_Article.jsp#.V0NnSzv2ZaQ. 5/1/2015.