Annals of the
RHEUMATIC DISEASES
The Eular Journal

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Journal:	*Annals of the Rheumatic Diseases*
Manuscript ID	Draft
Article Type:	Concise report
Date Submitted by the Author:	n/a
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Keywords:	Corticosteroids, Outcomes research, Treatment

Development of a Glucocorticoid Toxicity Index (GTI) Using Multi-Criteria Decision Analysis

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Word count: 1,577

This study was funded by an investigator-initiated grant from Genentech.

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Abstract:

Objectives:

To develop a Glucocorticoid Toxicity Index (GTI) to assess glucocorticoid (GC)-related morbidity and the GC-sparing ability of other therapies.

Methods:

Nineteen experts on glucocorticoid use and outcome measures from 11 subspecialties participated. Ten experts were from the United States; 9 from Canada, Europe, or Australia. Group consensus methods and multi-criteria decision analysis (MCDA) were utilized.

A Composite GTI and Specific List comprise the overall GTI. The Composite GTI reflects toxicity likely to change during a clinical trial. The Composite GTI toxicities occur commonly, vary with GC exposure, and are weighted and scored. Relative weights for items in the Composite GTI were derived by group consensus and MCDA. The Specific List is designed to capture GC toxicity not included in the Composite GTI. The Composite GTI was evaluated by application to paper cases by the investigators and an external group of 17 subspecialists.

Results:

Thirty-one toxicity items were included in the Composite GTI and 23 in the Specific List. Composite GTI evaluation showed high inter-rater agreement (investigators kappa 0.88, external raters kappa 0.90). To assess the degree to which the Composite GTI corresponds to expert clinical judgment, participants ranked 15 cases by clinical judgment in order of highest to lowest GC toxicity. Expert rankings were then compared to case ranking by the Composite GTI,

yielding excellent agreement (investigators weighted kappa 0.87, external raters weighted kappa 0.77).

Conclusions:

We describe the development and initial evaluation of a comprehensive instrument for the assessment of glucocorticoid toxicity.

INTRODUCTION

Glucocorticoids (GCs) have been a cornerstone of treatment for many diseases since their introduction more than sixty-five years ago. GC use is associated with considerable treatment morbidity.[1,2] Although the use of these medications is generally reviled by patients and physicians alike, data on the true incidence of GC-associated adverse events remain scarce because until now GC toxicity has simply been a fact of life for patients with immune-mediated diseases.[3] The development of novel immunomodulatory agents offers the potential to reduce GC use and to diminish their adverse effects.[4,5] In order to assess the true benefit of new medications with regard to their steroid-sparing properties, investigators must be able to assess their ability to prevent or reverse GC-related adverse events. Unfortunately, no reliable instrument designed to measure GC-related toxicity both broadly and accurately has been developed.

Measuring GC-related toxicity poses significant challenges.[1,6] Previous studies examining GC-related toxicity have utilized different combinations of adverse events with varied event definitions.[7,8,9] We aimed to develop a GC Toxicity Index (GTI) useful across medical disciplines to assess the impact of GC-associated morbidity.

METHODS

Participants and procedures

Twenty-two experts in glucocorticoid use and outcome measures were invited and 19 agreed to serve on the Scientific Committee (SC). Experts represented multiple specialties (rheumatology [including osteoporosis], pediatric rheumatology, pulmonology, nephrology, neurology,

ophthalmology, dermatology, infectious disease, and psychiatry) and had extensive experience in the clinical use and pharmacology of GCs. Ten investigators were from the United States, nine from Canada, Europe, or Australia.

The development process, which included ten milestones **(Figure 1)**, was conducted over ten one-hour conference calls, work between the calls, and one day-long, face-to-face meeting.

Instrument characteristics and item inclusion criteria

The SC agreed that the optimal use of the GTI would be in prospective, randomized, controlled clinical trials utilizing GCs, regardless of whether GC therapy is prescribed according to protocol or investigators' best medical judgement. Randomization and blinding serve the critical purposes of controlling for the background rate of adverse events[10] and prior GC treatment, and also limit the need for attribution.

The SC determined that the GTI would have two components: the Composite GTI and a Specific List. The Composite GTI serves as the primary instrument and is intended to capture common toxicities that are sensitive to differing cumulative GC doses over the period of a typical clinical trial (6 months to 3 years). It is weighted and measures both worsening and improvement. The complementary Specific List captures important GC-related adverse events not included in the Composite GTI. The SC agreed to not weigh Specific List toxicities due to the possible skewing that rare but serious events would introduce into the weighting scheme.

Item selection for the Composite GTI was based on the following principles: 1) likelihood of occurrence >5% in patients exposed to GCs; 2) item independence; 3) item equivalence (several GC toxicities could be included within a single item, provided they were within the same clinical domain and were equivalent in their degree of toxicity); 4) toxicity is more likely to be due to the effect of GC therapy than the disease itself; 5) toxicity is unlikely to be the result of GC therapy prior to trial entry (e.g., osteoporotic fracture); 6) measurement does not typically require invasive procedures or imaging.

Toxicities that did not meet these criteria but were deemed important and were not confounded by underlying disease or co-morbidities were included in the Specific List. Candidate toxicities were generated based on literature review (**Appendix I**) and selected for inclusion by nominal group technique. Definitions for each item, developed by experts from the relevant clinical area, were revised by consensus. Items were grouped by clinical domains in order of increasing toxicity such that only one item within each domain could be assigned to a given patient. The draft GTI was reviewed by the SC for clarity, format, visual design, organization, and navigability. Relative weights were then derived at the face-to-face meeting using multi-criteria decision analysis (MCDA) via the 1000Minds software platform (Dunedin, New Zealand) **(Appendix II)**.[11,12]

Instrument scoring

The SC agreed that the Composite GTI should measure change in GC toxicity rather than absolute GC toxicity in order to account for the effects of prior GC therapy and background rate of adverse events. Therefore, evaluation at two time points is required for scoring. All domains

have the potential for improvement (e.g., myopathy can improve from "mild" to "none", even though a specific improvement item is not included in the Composite GTI). When a Specific List item occurs (e.g., death from infection), the most severe corresponding item in the Composite GTI (i.e., Grade 3 infection) is also scored. The Composite GTI should be scored at 3-month intervals throughout the study, using entry assessment as the baseline. Because the bone domain should generally not be scored more often than every 12 months, it should be excluded for trials shorter than 1 year in duration. The score should be reported as both a total score and domain-specific scores, to account for scenarios when improvements in certain domains compensate for worsening in others.

Evaluation process

The performance of the Composite GTI was evaluated by both participating experts and an external, multi-specialty group of 17 testers (**Supplementary Table 1**) using paper cases. Each expert submitted four patient cases describing GC toxicity. Fifteen cases were chosen to represent the full range of GC toxicity. Both the experts and external testers then completed an on-line exercise composed of two tasks: 1) rank cases in order of greatest to least GC-toxicity (experts' rankings were then compared to the ranking assigned by the weighted Composite GTI); and, 2) assign Composite GTI items to each case.

Statistical Analysis

Interrater reliability among raters and agreement between the experts' and external testers' rankings and those of the Composite GTI were assessed using the Kappa statistic. The overall interrater reliability of the ranking agreements was then calculated by averaging pairwise Kappa

values. All statistical analyses were performed on SAS Version 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

Nine domains and 31 items were included in the Composite GTI (**Table 1**). Eleven domains and 23 items were included in the Specific List (**Table 1)(See definitions, Appendices III and IV)**. Items reflect severity and account for impact of medications (e.g., blood pressure can be stable due to an increase in anti-hypertensive regimen). Toxicities such as atherosclerosis, myocardial infarction, and stroke were not included in the GTI because the SC agreed that all are confounded by co-morbid conditions (e.g., smoking) or disease effects (e.g., systemic lupus erythematosus).[13] Except for bone mineral density, included because of its importance in GC-related toxicity,[14] items requiring imaging were excluded from the Composite GTI.

Fifteen experts participated in the weighting exercise at the face-to-face meeting. Seventeen of 19 experts and 17 independent raters completed this evaluation phase. The interrater reliability exercise revealed a high degree of agreement, with a kappa of 0.88 ($P<0.01$) for participating experts and kappa of 0.90 ($P<0.01$) for independent raters. The initial validity exercise revealed that both expert and independent rater case rankings had excellent agreement with rankings by the Composite GTI with a weighted kappa of 0.87 ($P<0.01$) and 0.77 ($P<0.01$), respectively.

DISCUSSION

A useful measurement of the steroid-sparing ability of new treatment agents requires a reliable outcomes-based instrument of GC-related toxicity.[15,16] We describe a multi-specialty effort to

develop the GTI, a comprehensive measure of change in GC-toxicity over time. The initial evaluation of the Composite GTI by participating experts and a multi-specialty group of external testers demonstrated excellent reliability and validity.

The development of two complementary assessment instruments within the GTI – the Composite GTI and the Specific List – was crucial in addressing several challenges in measuring GC toxicity. The creation of the Specific List permits documentation of certain important and often severe toxicities, leaving the Composite GTI as a relatively concise and easy to administer tool intended to detect differences between patients receiving divergent GC amounts. The inclusion of rare toxicities and those that may reflect prior GC use in the Specific List allowed us to simplify the usability, limit weight skewing, and minimize the effect of pre-trial GC therapy on the Composite GTI.

An important strength of the Composite GTI is the assignment of relative weights to each toxicity item in a systematic manner using MCDA.[11] The MCDA approach greatly enhances the feasibility of this complex task in a way that group consensus methods struggle to approach. Further, the MCDA approach allows us to perform modifications of the Composite GTI as new data become available, including the addition and weighting of new items, without disrupting the validity of the method.

The next phase in GTI development includes the development of a web-based interface, prospective use in clinical trials, and input from patient support groups. Our initial evaluation exercise of the Composite GTI, including testing by an external group of glucocorticoid experts,

implies excellent performance characteristics. The development of a web-based interface should further increase the instrument's reliability. For the GTI to be truly valid, it must be assessed in clinical trials and compared to doses of GCs administered, quality-of-life measures, and damage indices that include GC toxicity.[17,18]

In conclusion, we describe the development and initial evaluation of the GTI, a comprehensive GC toxicity assessment instrument. The GTI can be used across disciplines to assess the clinical value of steroid-sparing therapies, as well as to measure the impact of GC toxicity. Given the widespread use of GCs and the accelerating pace of immunological drug discovery, this instrument represents a considerable advance in our ability to assess the utility of new pharmacologic agents.

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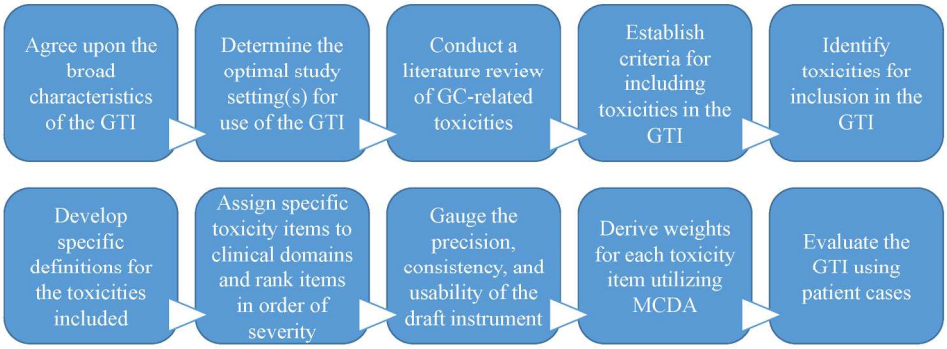
Figure Titles

Figure 1 – GTI development milestones

Composite GTI	Item Weight	Specific List
Body mass index		
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 Posterior reversible encephalopathy syndrome
No change in blood pressure	0	
Worsening hypertension	19	
Worsening hypertension despite treatment	44	
Lipids		
Improvement in lipids	-9	
No change in lipids	0	
Worsening hyperlipidemia	10	
Worsening hyperlipidemia 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	GG-induced violence
Moderate neuropsychiatric symptoms or greater	74	Other severe neuropsychiatric symptoms
Infection		
No significant infection	0	Grade 4 infection
Oral/vaginal candidiasis or uncomplicated zoster	19	Grade 5 infection
Grade 3 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	



Process steps in the development of the Glucocorticoid Toxicity Index
327x129mm (300 x 300 DPI)

APPENDIX – Glucocorticoid toxicity references

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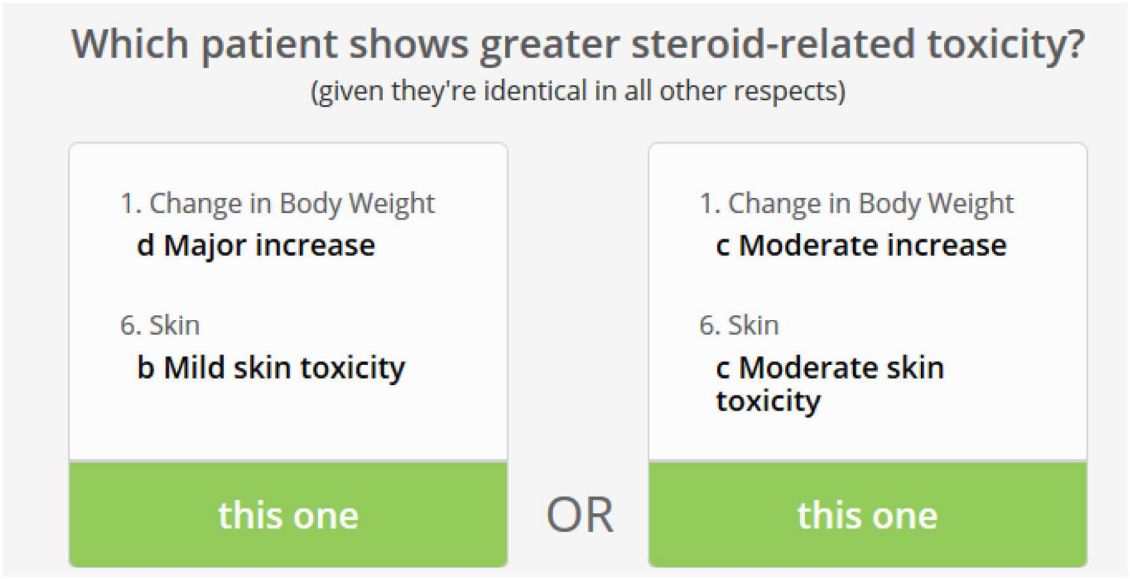
Appendix II – Multi-Criteria Decision Analysis Methods

Multi-criteria decision analysis can be utilized to assign weights to items by ranking all possible combinations in order of severity of toxicity. 1000Minds software facilitates the process by determining the point values of multi-attribute value models and has been used in studies in healthcare, corporate management, agriculture, and environmental management.[1] 1000Minds employs the "Potentially All Pairwise Rankings of all possible Alternatives" (PAPRIKA) method.[2] PAPRIKA is based on the principle that an overall ranking of items in a model can be achieved if all possible pairwise combinations of the included items can be ranked. Ranking in a pairwise manner carries less cognitive burden then ranking multiple criteria simultaneously. Because the total number of pairwise rankings can number in the thousands, 1000Minds limits the number of pairwise rankings using the property of transitivity (if A > B and B > C, then A > C). Any pairwise decision in which one option clearly has a higher weight (in this case, greater toxicity) based upon the outcomes of previous comparisons is not presented for consideration, thereby creating an efficiency of comparisons and permitting hundreds of comparisons within a few hours.

Participants were asked to assess the relative weight (toxicity) of items by selecting the higher toxicity from a paired patient scenario differing in two toxicity items. Figure 1 shows examples of the types of comparisons the Scientific Committee was made asked to make in deciding which combinations of clinical GC complications of GC use constituted the higher degree ofgreater GC toxicity. Using Turning Point voting technology (Youngstown, Ohio), experts anonymously chose the scenario with higher GC toxicity. The results of each vote were immediately presented to the full Scientific Committee and reasons for disagreement, if present, were discussed. If there was significant disagreement, the group re-voted after discussion of disagreements. This step was repeated if necessary. Consensus was achieved when all participants reached agreement or could accept the majority decision.

Based on the number of domains and toxicity items, there were 62,208 possible paired patient scenarios differing in two toxicity items. The participants completed 103 scenarios, reaching agreement on all combinations. The remaining 62,105 scenarios were then implicitly resolved using the transitivity principle within the 1000Minds software. Through iterative discrete pairwise choices, 1000Minds assigned relative weights to the items.

Figure 1



Screenshot from the exercise using 1000Minds

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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.

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

Supplementary Table 1. List of External Testers

Tester	Specialty	Institution
Dr. George Stojan	Rheumatology	Beth Israel Deaconess Medical Center
Dr. Kostantinos Tselios	Rheumatology	University of Toronto
Dr. Charis Papadopoulou	Pediatric Rheum	Great Ormond Street Hospital
Dr. Despina Eleftheriou	Pediatric Rheum	Great Ormond Street Hospital
Dr. Lorcan McGarvey	Pulmonology	Queen's University, Belfast
Dr. Julianna Desmarais	Rheumatology	Oregon Health Sciences University
Dr. Sheenal Patel	Allergy/Immunology	University of Texas-Southwestern
Dr. Zachary Wallace	Rheumatology	Massachusetts General Hospital
Dr. Marlies van der Goes	Rheumatology	University of Utrecht
Dr. Matthew Cascino	Rheumatology	University of California-San Francisco
Dr. Stephen McAdoo	Nephrology	Hammersmith Hospital
Dr. Sandra Hermann	Rheumatology	Charite Hospital
Dr. Alexa Shipman	Dermatology	West Midlands Deanery, Birmingham, UK
Dr. Cory Perugino	Rheumatology	Massachusetts General Hospital
Dr. Matthew Tremblay	Neurology	University of California-San Fran
Dr. Erin Wilfong	Rheumatology	University of California-San Francisco
Dr. Mark Matsos	Rheumatology	McMaster University, Canada