

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

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Background/Purpose: Glucocorticoids (GC) are associated with substantial treatment morbidity. New immunomodulatory agents offer the possibility of limiting GC exposure. To assess the comparative benefits of such agents, investigators must accurately measure their ability to prevent or reverse GC-related toxicity. No comprehensive instrument for measuring GC toxicity has previously been developed. We aimed to develop a GC Toxicity Index (GTI) to assess GC-related morbidity and GC-sparing ability of new agents.

Methods: Nineteen experts 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 were utilized. The development process included ten 1-hour conference calls, group work between calls and a 12-hour face-to-face meeting. *GTI components* The GTI is composed of the Composite GTI (CGTI) and the Specific List. The CGTI reflects GC toxicity that is likely to change over

the course of a clinical trial. The toxicities included in the CGTI occur commonly, vary with GC exposure, and are weighted and scored. The Specific List is designed to capture GC toxicity not included in the CGTI. The CGTI was evaluated by application to paper cases by the investigators and an external group of 17 subspecialists.

Results: *Item inclusion and definitions* Thirty-one toxicity items derived from the literature were included in the CGTI, and 23 were included in the Specific List (Table). Definitions were developed by experts using group consensus methods. The CGTI items reflect both improvement and worsening of GC toxicity and account for medication effects (e.g., anti-hypertensives) in scoring. The 31 mutually-exclusive CGTI items are organized in order of severity within nine domains. Only one item in each domain can be scored. *Weighting and evaluation of the CGTI* Relative weights for each item in the CGTI were derived at a face-to-face meeting utilizing multi-criteria decision analysis. CGTI evaluation showed high inter-rater agreement (investigators kappa 0.88, external raters kappa 0.90). To assess the degree to which the CGTI 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 CGTI, yielding excellent agreement (investigators weighted kappa 0.87, external raters weighted kappa 0.77).

Conclusion: We describe the development and initial evaluation of the GTI – a comprehensive instrument intended primarily for use in prospective, randomized clinical trials for the assessment of GC toxicity. The GTI can be used across clinical disciplines in trials that employ GCs to assess the comparative value of GC-sparing therapies, and to measure the impact of GC toxicity. **Table – Composite GTI and Specific List**

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

	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 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	74	Other severe

	greater		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	

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