PAEDIATRIC RHEUMATOLOGY **[Au: Every news and views article is assigned a subject category ‘strapline’ – Ok, understood and happy with this]**

# Paediatric glucocorticoid toxicity index: new possibilities in assessment

Charlotte King and Daniel B. Hawcutt

Standfirst

Glucocorticoids are common medications used in research trials and clinical practice. Measuring the toxicity of glucocorticoids in children is complicated by various factors such as age and growth. A standardised tool could help record these toxicities across different specialities in a systematic manner **[Au:OK? Yes]**.

*Refers to* Brogan, P. et al., The Pediatric Glucocorticoid Toxicity Index. *Seminars in Arthritis and Rheumatism.* **56**, 152068 (2022) .

Main text

Glucocorticoids remain a cornerstone of treatment for a multitude of conditions in paediatric and adult medicine. Within paediatrics these include **[Au: Can I just check you have cited the correct reference here, as this reference seems to refer to children with asthma specifically in 1990? Is there a more recent reference that might be used instead? And does this sentence refer to children in the UK specifically or worldwide?]**, respiratory conditions (e.g. asthma), gastrointestinal disorders, Rheumatologic conditions, and more (Ref the same ref as in my comment) **[Au: You could consider citing a general Review on glucocorticoids here, to support this sentence and the next (you have room for up to 10 references in this piece - done)]**. Children and young people also receive glucocorticoids in research settings, both in trials investigating glucocorticoids as the drug of interest or as a secondary medication **[Au: Edit OK? Is this what you meant? Or do you mean they either receive glucocorticoids in clinical trials investigating glucocorticoids as the drug of interest or they receive glucocorticoids as a secondary medication? – Yes this was what I meant.. I have been looking for some reference for the latest big NIHR study of JIA induction with various steroid regimens (“STAR-JIA” as evidence that the big steroid studies are still funded, but there is no official press release yet that I can find)]**. Although the benefit of glucocorticoid treatment in these conditions is often well described, accurately capturing the harms and therefore balancing the risks versus the benefits of glucocorticoids has been challenging. Brogan and colleagues have now developed a new tool for measuring glucocorticoid toxicity in children and young adults(5), but what potential does this new tool hold? **[Au: We normally like to finish the first paragraph with a mention of the new study and a question or ‘newsy’ element to help draw the readers is. Additional text OK? Feel free to make amendments – This is fine]**

Glucocorticoids can have numerous adverse effects(2), and an individual’s susceptibility to these effects can vary depending on multiple factors including the dose, route, potency of glucocorticoid used, route of administration, length of treatment and pharmacogenomics **[Au:OK? YES]** (2, 3). The introduction of glucocorticoid-sparing treatments such as biologic drugs in inflammatory and autoimmune conditions that traditionally used high doses of glucocorticoids has helped some patients avoid glucocorticoid toxicity(4). However, expensive therapies such as biologic drugs are limited to well-funded healthcare systems, and even in countries where glucocorticoid-sparing therapies are well established, the use of glucocorticoids in paediatric patients is likely to continue for the foreseeable future owing to the wide range of conditions that glucocorticoids are used for.

Therefore, the lack of a paediatric glucocorticoid toxicity index (pGTI) has been an important unmet clinical and research need. An adult glucocorticoid toxicity index tool exists that is designed to measure the change in glucocorticoid toxicity between two time points, and has been utilised in both trials and clinical practice(4). However, this tool is not suitable for paediatric use, as various paediatric-only adverse effects, such as effects on growth, are not included **[Au:OK? YES]**. Reporting of paediatric adverse drug reactions using current systems is generally poor (REF - <https://jptcp.com/index.php/jptcp/article/view/138>), and glucocorticoid toxicity in children specifically (both clinically and in research) has been considered in a piecemeal way using a variety of scores. There is therefore limited date, presented in numerous ways, all hindering meaningful interpretation of data between studies or across different centres **[Au: You could consider including a reference here (if there is an appropriate one available) to help support this statement, as you have room for up to 10 references – extra reference added ]**.

The pGTI developed by Brogan et al.(5) represents a notable step forward, and has the potential to improve the quality of data collected and standardise the type of data recorded **[Au:OK? YES]**. The researchers use an example of a clinical trial participant when discussing this new tool **[Au:OK? YES]**, but the pGTI might also have clinical applications as well as research applications(5). The pGTI comprises a set of ten different domains with a weighted scoring system amongst the sub-domains **[Au: Is it worth expanding on what these ten different domains and/or what the sub-domains were (or would that be unnecessary detail)? You could also consider having a display item (such as a box or figure) that summarizing the pGTI (see note at the end relating to the display item) – A table showing the key domains would be good – but I was keen to avoid too much granular detail in the text (or it is just a reprint of the original article)]**. A key aspect of this tool **[Au:OK?YEs]** is the appreciation that normal physiological parameters in children (such as the range of normal blood pressures in health, and the normal range for individual blood tests, as well **[Au: What do you mean by “blood result ranges” here? Is it possible to be more specific? ADDED] as** BMI) change with age(4) **[Au: Can I just check whether you meant to cite reference 5 (Brogen et al.) here?]**. The researchers incorporated these dynamic changes **[Au:”This” requires a noun. Addition of “dynamic” OK? Added “changes”]** into the pGTI by considering age, growth and effect of other medications on glucocorticoid toxicity. The pGTI demonstrated good reliability and validity when measured against reported cases of toxicity **[Au:OK? YEs]**. The digital platform also provides various beneficial features, including help with data input, calculations that consider age and developmental changes (such as blood pressure) and automation of data capture **[Au: Edits OK? YES]** .

The development of any tool such as the pGTI requires a considerable effort to obtain appropriate representation. This project has drawn in a considerable range of glucocorticoid uses **[Au: Are you referring to the range of types of glucocorticoids, range of glucocorticoid toxicities or range of indications that use glucocorticoids here? Amended for clarity]** using paediatric sub-specialities from international centres of expertise, ranging from nephrology, rheumatology, oncology, endocrinology, genetics, psychiatry to maternal-fetal medicine. In an ideal world, the development of this tool would also have included other specialities that commonly use glucocorticoids, such as respiratory medicine or dermatology **[Au:OK? Yes]**. Nevertheless, the desire for a perfect tool should not prevent the appreciation of what is a notable advance in the field, especially given the lack of any current pGTI or equivalent **[Au: Edit OK? Is this what you meant? Yes - absolutely]**. It will be interesting to see whether the tool can used in glucocorticoid toxicity studies in these other specialities, and whether additionally minor tweaks might become necessary. Certainly, within the field of respiratory medicine, patients with asthma seem to struggle with both the local adverse effects **[Au:OK? yes]** (such as hoarse voice and oral candidiasis) and systemic adverse effects (such as adrenal suppression and growth velocity) of glucocorticoids **[Au: Could you please reference this statement.]** . Although growth is well covered by the pGTI, and oral candidiasis is specifically captured in the infection domain, neither symptomatic adrenal suppression nor hoarse voice are included in the weighting information provided (although symptomatic adrenal suppression is captured in the damage checklist).

A potentially important omission in the development of the pGTI is the voice of the parents, as well as the voice of the children and young people being treated **[Au:OK? YES]**. The weighting given to each symptom seems to have been assigned purely from a medical perspective and will therefore not capture the relative importance of the toxicities to the children and young people affected. Acne or hirsutism, for example, can have a much greater effect on the quality of life and mental health of teenagers compared with older adults. It would be interesting to know whether children and young people agreed with the relative weightings created by the adult researchers, and whether the relative weightings change with age for certain domains (for example, whether acne is weighted higher in teenagers compared with toddlers) **[Au:OK? Yes]**. The supplementary data section includes a very helpful video showing a person completing the score and the images and text provided to ensure standardisation. The case study used is of an African American Teenager, but the images presented involve lighter skinned individuals that might not help accurately score dermatological outcomes in patients who are not white.

However, despite these minor and addressable points, overall, the pGTI provides a well-constructed system for the systematic recording, and scoring, of glucocorticoid toxicity. We are genuinely keen to use this tool both for data capture in research studies and in clinical practice.

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## Competing interests

The authors have no conflicts of interest relevant to this article to disclose.

 **[Au: You have the option of including one display item (such as a box, figure or table) to accompany this piece. Did you have a display item in mind? For example, you could have a figure or box that summarizes the new tool. Do note that, ideally, the display item shouldn’t be based on a display item in the published article, as that might require permissions to adapt or reproduce. Alternatively, we can source a general stock image to accompany this piece.] The table with the domains of the pGTI would be my preference – but otherwise a generic picture is fine…**