## PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Adrenal Suppression from Glucocorticoids: Preventing an Iatrogenic Cause of Morbidity and Mortality in Children |
| **AUTHORS** | Ahmet, Alexandra; Mokashi, Arati; Goldbloom, Ellen; Huot, Celine; Jurencak, Roman; Krishnamoorthy, Preetha; Rowan-Legg, Anne; Kim, Harold; Pancer, Larry; Kovesi, Tom |

## VERSION 1 – REVIEW

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| **REVIEWER** | Reviewer name: Dan Hawcutt<br>Institution and Country: University of Liverpool<br>UK<br>Competing interests: None |
| **REVIEW RETURNED** | 20-Aug-2019 |

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| **GENERAL COMMENTS** | This is an interesting review article about adrenal suppression in children who use corticosteroids.<br><br>Major comment:<br><br>Table 2. I am concerned that the use of threshold doses for screening will result in either unecessary screeing of many (with questionable biochemical adrenal suppression), and potentially clinicians not then considering AS in children just because they fall below this arbitrary threshold.<br><br>Minor comments:<br><br>Page 5, line 3 Currently reads "Higher dose, longer duration and timing of administration of GCs (evening vs. morning) are theoretical risks". I agree that the duration, and timing of doses is theoretical, as noone has done the longitudinal studies to confirm/refute this. But the Dose response relationship was shown in reference 15 - it was the only statistically significant relationship. Would suggest this sentence amended to "Higher dose is a risk factor (15), while longer duration and timing of administration of GCs (evening vs. morning) are theoretical risks 16.<br><br>Page 6, line 45: the DMD population also take significant oral steroid doses and are at risk of adnreal suppression - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6398538/ = they should probably get a mention here<br><br>Page 9, first sentence - This section about testing for adrenal suppression is very short - there are considerable intricacies involved (e.g. https://adc.bmj.com/content/101/9/860 ). It may not be the aim of the article, but some references here would help direct those looking for help interpreting a LDSST |

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| | Page 10, line 1 - currently reads "with higher doses in the morning to more closely mimic circadian regulation.." This seems to give tacit approval to this practice - when the guidelines (and PK data) suggest it is not optimal. Please rephrase, or if this is something the authors approve of, then some explanation (and refs) about why this might be good (??improved adherence, or other) are needed.<br><br>Page 10, point 1 (in how to reduce risk) - what is a high dose? |

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| **REVIEWER** | Reviewer name: Dr Louise Fleming<br>Institution and Country: Imperial College, London, UK<br>Competing interests: None |
| **REVIEW RETURNED** | 10-Sep-2019 |

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| **GENERAL COMMENTS** | Ahmet et al have produced a well written overview of adrenal suppression in children. It is an important topic and therefore a welcome review. They have focussed largely on clinical and practical aspects of monitoring adrenal function and have included sections on steroids administered in a variety of ways. They have also highlighted the knowledge gaps and inconsistencies and given the authorship one would hope this will lead to a much needed consensus guideline.<br><br>General comments:<br>Although a good practical overview, on the whole this is a rather superficial review with little discussion about potential mechanisms (other than glucocorticoid receptor polymorphisms). Although, I don't think there needs to be too much more added there are some areas where a little more detail would be welcome.<br>1. It would be useful for the authors to provide a little more context to the review and a brief description of the hypothalamic-adrenal axis<br>2. The Canadian (Canadian Thoracic Society 2012) and US (NAEPP 2007) guidelines are references throughout. These reflect the North American authorship, however the readership of BMJ Open is much more international. Furthermore, both these guidelines are now quite old (particularly the NAEPP). It would be better to refer to more up to date guidelines such as the GINA strategy 2019 or BTS/SIGN guideline.<br>3. The authors quite rightly highlight the risks of AS with high dose ICS, particularly fluticasone. However, there is a somewhat idiosyncratic relationship: some children do not become suppressed even on very high doses whereas adrenal suppression has been described in children on much lower doses (Blair, Clinical Endocrinology (2014), 80, 376–383; Priftis, K. Eur.Respir.J. 2006: 27:316320.) This lack of consistency has led to difficulties in defining an ICS dose threshold at which testing should take place. Based on current evidence the authors are unlikely to be able to give a definitive answer but should certainly expand a little on these conundrums<br><br>Minor comments<br>1. A number of factors are listed which can increase the risk of AS with systemic glucocorticoids. Did the authors find any evidence of a beneficial effect of alternate day dosing, a practise frequently used in paediatrics, or depot triamcinolone injections?<br>2. Page 5, line 13: the text states "ICS therapy used within current guidelines is rarely associated with clinically significant AS"; however most guidelines recommend increasing doses based on control and adrenal suppression can occur at even moderate doses. Please be clearer as to what dose you are referring. |

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| | 3. Table 2: Trade names are included however these are not necessarily the same in all regions (particularly Europe)and for clarity it may be better to delete this column. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1

Comments to the Author

This is an interesting review article about adrenal suppression in children who use corticosteroids.

Major comment:

Table 2. I am concerned that the use of threshold doses for screening will result in either unecessary screeing of many (with questionable biochemical adrenal suppression), and potentially clinicians not then considering AS in children just because they fall below this arbitrary threshold.

Response: Thank you for this important comment. We believe that it is important for clinicians to be aware of ICS doses that increase AS risk both to help support consideration of appropriate dosing and to ensure a heightened awareness in those at increased risk but agree that these doses should not be the only determining factor in consideration of evaluation for AS. We have addressed this concern by:

1) Adding the following sentence to the text: " Clinicians must also be aware that while the majority of cases of symptomatic AS have been reported in children exposed to high dose ICS, there are rare reported cases of those receiving low to moderate dosing{Kapadia, 2016 #3118}, highlighting the importance of consideration of AS in children presenting with possible signs or symptoms of AS regardless of ICS dose. "

2) Changing the title and content of the table to reflect the fact that the doses outlined are not "threshold doses" for screening but are rather doses that are associated with increased risk of AS. A table foot note has also been added to emphasize this point.

Minor comments:

Page 5, line 3 Currently reads "Higher dose, longer duration and timing of administration of GCs (evening vs. morning) are theoretical risks". I agree that the duration, and timing of doses is theoretical, as noone has done the longitudinal studies to confirm/refute this. But the Dose response relationship was shown in reference 15 - it was the only statistically significant relationship. Would suggest this sentence amended to "Higher dose is a risk factor (15), while longer duration and timing of administration of GCs (evening vs. morning) are theoretical risks 16.

Response: This change has been made

Page 6, line 45: the DMD population also take significant oral steroid doses and are at risk of adnreal suppression - https://hes32-ctp.trendmicro.com:443/wis/clicktime/v1/query?url=https%3a%2f%2fwww.ncbi.nlm.nih.gov%2fpmc%2farticles%2fPMC6398538%2f&umid=5aa3745f-06db-4915-bc59-3df8f7230ccc&auth=264e636f8a7899a1bca3b66cba6e4e44ed141273-83d49fc0f68f02f73c97f239deb14a2a59a1627f = they should probably get a mention here

Response: We agree that the DMD population is at high risk of adrenal suppression though we did not list specific conditions associated with systemic glucocorticoid exposure. We have added a relevant reference (Bowden, DMD Clinical Practice Recommendations) to the section about adrenal suppression in children treated with systemic glucocorticoids.

Page 9, first sentence - This section about testing for adrenal suppression is very short - there are considerable intricacies involved (e.g. https://hes32-ctp.trendmicro.com:443/wis/clicktime/v1/query?url=https%3a%2f%2fadc.bmj.com%2fcontent%2f101%2f9%2f860&umid=5aa3745f-06db-4915-bc59-3df8f7230ccc&auth=264e636f8a7899a1bca3b66cba6e4e44ed141273-a3e18fbe42355370e87c1c4b0be13063b0356470 ). It may not be the aim of the article, but some references here would help direct those looking for help interpreting a LDSST

Response: The sentence was modified to add associated references and a little more detail as follows "Peak cortisol thresholds of 440-600 nmol/L (16-22ug/dL) are commonly used to rule out AI but vary between studies and institutions with many factors needing to be considered when interpreting results (e.g., cortisol assay, timing of cortisol draw relative to corticotropin administration, medications affecting cortisol binding, time of day). (Gill, 2019; Park, 2016; Kazlauskaite, 2010) clinicians must therefore refer to their local protocols for guidance."

Page 10, line 1 - currently reads "with higher doses in the morning to more closely mimic circadian regulation.." This seems to give tacit approval to this practice - when the guidelines (and PK data) suggest it is not optimal. Please rephrase, or if this is something the authors approve of, then some explanation (and refs) about why this might be good (??improved adherence, or other) are needed.

Response: We have rephrased this section to highlight the reason for using the once or twice daily hydrocortisone dosing and to emphasize that it is not supported by literature. The revised section reads "While three times daily (TID) hydrocortisone dosing is standard of care in primary AI, many endocrinologists provide once or twice daily dosing in AS, with higher doses in the morning to reduce the ongoing suppression of endogenous morning cortisol production in asymptomatic patients. There is no evidence to support this approach but in practice, it is used by several members of our working group with the assumption that the AI in cases of asymptomatic AS is partial and that this approach will help to reduce the risk of prolonging suppression. Clinicians must be aware of the short half-life of hydrocortisone and provide BID or TID dosing if a child is symptomatic and during times of stress."

We also replaced the references to "daily" GC replacement with "physiological GC replacement" within our recommendations section.

Page 10, point 1 (in how to reduce risk) - what is a high dose?

Response: The recommendation has been revised as follows "1. Clinician education and awareness about the risk of AS including an understanding of the relatively high frequency of AS in patients being treated with ≥ 500µg daily of Fluticasone or high dose ICS therapy as defined by national or international asthma guideline. s"

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Comments to the Author

Ahmet et al have produced a well written overview of adrenal suppression in children. It is an important topic and therefore a welcome review.

They have focussed largely on clinical and practical aspects of monitoring adrenal function and have included sections on steroids administered in a variety of ways. They have also highlighted the knowledge gaps and inconsistencies and given the authorship one would hope this will lead to a much needed consensus guideline.

General comments:

Although a good practical overview, on the whole this is a rather superficial review with little discussion about potential mechanisms (other than glucocorticoid receptor polymorphisms). Although, I don't think there needs to be too much more added there are some areas where a little more detail would be welcome.

1. It would be useful for the authors to provide a little more context to the review and a brief description of the hypothalamic-adrenal axis

Response: Thank you for this comment. This was added to the introduction, along with a description of the basic pathophysiology of HPA axis suppression as suggested in the general comment above about potential mechanisms.

2. The Canadian (Canadian Thoracic Society 2012) and US (NAEPP 2007) guidelines are references throughout. These reflect the North American authorship, however the readership of BMJ Open is much more international. Furthermore, both these guidelines are now quite old (particularly the NAEPP). It would be better to refer to more up to date guidelines such as the GINA strategy 2019 or BTS/SIGN guideline.

Response: We have modified and now refer throughout to the GINA strategy in addition to the American and Canadian asthma guidelines.

3. The authors quite rightly highlight the risks of AS with high dose ICS, particularly fluticasone. However, there is a somewhat idiosyncratic relationship: some children do not become suppressed even on very high doses whereas adrenal suppression has been described in children on much lower doses (Blair, Clinical Endocrinology (2014), 80, 376–383; Priftis, K. Eur.Respir.J. 2006: 27:316320.) This lack of consistency has led to difficulties in defining an ICS dose threshold at which testing should take place. Based on current evidence the authors are unlikely to be able to give a definitive answer but should certainly expand a little on these conundrums

Response: We have added a paragraph within the ICS section along with associated references to address this recommendation. The revised paragraph reads as follows "While the majority of cases of symptomatic AS have been reported in children exposed to high dose ICS, there are rare reported cases of those receiving low to moderate dosing 2,33; highlighting the importance of consideration of AS in children presenting with possible signs or symptoms of AS regardless of ICS dose. Conversely, while high dose ICS therapy increases the risk of AS, many children receiving high dose therapy are not suppressed 11. A recent genome-wide association study suggests that a common genetic variant might lead to susceptibility to AS in patients exposed to ICS but further study is needed to support this finding.34 There are also many genetic variants of the GC receptor gene which are thought to explain the wide inter-individual variation in GC sensitivity5 and several single nucleotide polymorphisms that have been associated with HPA axis reactivity3, both of which likely in part explain the variability in AS susceptibility. Other possible factors contributing to inter-patient variability in the development of AS include inhaler technique, age and asthma severity which might impact both ICS deposition in the lungs and the amount of ICS absorbed into the systemic circulation."

Minor comments

1. A number of factors are listed which can increase the risk of AS with systemic glucocorticoids. Did the authors find any evidence of a beneficial effect of alternate day dosing, a practise frequently used in paediatrics, or depot triamcinolone injections?

Response: Although every other day glucocorticoid therapy should theoretically reduce the risk of AS and is noted to be an option in book chapters and some review papers, we have been unable to find any clear evidence to support this. We have therefore added it in our list of theoretical contributing factors on page 5. There are reported cases of AS after receiving depot triamcinolone injections suggesting that it's use would not reduce the risk of AS compared to other systemic GCs.

2. Page 5, line 13: the text states "ICS therapy used within current guidelines is rarely associated with clinically significant AS"; however most guidelines recommend increasing doses based on control and adrenal suppression can occur at even moderate doses. Please be clearer as to what dose you are referring.

Response: We have changed the wording of this sentence to clarify our messaging. The revised sentence reads "Symptomatic AS associated with ICS use is rare but important and can be reduced by using the lowest dose of ICS sufficient to maintain acceptable asthma control, as outlined in current asthma guidelines"

3. Table 2: Trade names are included however these are not necessarily the same in all regions (particularly Europe)and for clarity it may be better to delete this column.

Response: The column with trade names has been removed.