PATRON
HRH The Princess Royal

Royal College of Paediatrics and Child Health

50 Hallam Street, London W1W 6DW

Tel: (020) 7 307 5600 Fax: (020) 7 307 5601 E-mail: enquiries@rcpch.ac.uk

Review of NICE HTA Corticosteroids for the treatment of Chronic Asthma in Children under 12 years – Assessment Report

Thank you for inviting the Royal College of Paediatrics and Child Health to comment on the Assessment Report of the above guidance. Overall the comments on the guideline were very positive and the reiewers praised NICE for this comprehensive review of the available evidence.

Inclusion of Children <5

Should the report should have an alteration to its title. At present it appears as if this report is relevant to any child under 12 years of age. I would suggest that in the absence of evidence the report should read "For children between 4 and 12 years of age". What evidence is available about the use of inhaled corticosteroids in pre-school children would suggest that its efficacy is very much less than in school age children and in many circumstances may not be justified.

This review does not sufficiently consider children 5 years and under. Neither is this age group adequately discussed in the most recent BTS/SIGN guidelines (E.g. Figure 4; page 11). To consider this age group, symptom definition is critical as the majority have intermittent symptoms solely in relation virus infections. The limited evidence available suggests that in such a situation continuous treatment with ICS is not beneficial even when the symptoms are frequent or severe. On the other hand, symptoms occurring in the absence of viral infections are very responsive even in < 5 year olds. Doctor diagnosis of asthma is inadequate as a definition, as some doctors include all bronchodilator responsive wheezing. Only studies that have used FEV_1 or PEF as measures of lung function have been included. This excludes the majority of studies in children < 6 years. It is not surprising therefore that no trials in this age group were identified (page 201)

Comment on the Evidence

Much of the research is industry-funded, and carries the inevitable bias in outcomes focus. The review demonstrates fairly clearly the relative paucity of relevant research data available in children in what is the commonest chronic disease in children.

Did the search strategy include data on commercial trial databases (e.g. http://ctr.gsk.co.uk/ welcome. asp) ?

Prevalence of Athsma

Over the last 10years the prevalence of asthma in children has fallen by about 30%. This has not been mentioned. The reasons for this should be considered. One of the reasons advanced is diagnostic transfer, suggesting that the diagnosis of asthma has not always been sound. It is quite possible that many of the trials quoted included children who did not have asthma. If this is true, then it is a limitation of the review. Whatever the reason, diagnostic transfer, and the labelling of respiratory symptoms such as persistent isolated cough as asthma need mentioning. Without up to date data the review could appear somewhat dated.

Adherence to Treatment Guidelines

There is no mention of the lack of studies which examine how well treatment guidelines are followed. In practice, it is not unusual for children with more than one or two episodes of wheeze to be moved to Step 2 without meeting the criterion for having interval symptoms. If the purpose of this document is to encourage prescribers to use the preparation which gives the best value for money then the correct use of guidelines needs to be mentioned. In the limitations section it should be acknowledged that there are no studies that examine how well guidelines are followed.

There is a perception that the cost of unnecessary prescriptions of ICS is significant. Maybe this could be mentioned in areas for research.

The problem of poor treatement adherence has been correctly emphasised. One reason for this could be that patients and their parents perceive no value because the drug is unecessary for the reasons mentioned above. Prescribers could step up treatment and therefore the cost when either the drug is not being given or the diagnosis is wrong.

Description of Phenotypes
The review attempts to describe the different phenotypes of paediatric asthma. However, phenotypes of preschool wheeze identified retrospectively in epidemiological studies, do not necessarily map onto the phenotypes that predict response to therapy (clinical phenotypes). Currently the only clinically useful phenotypic distinction for preschool children is; i) wheeze occurring only with colds (viral-wheeze – which does not respond to regular inhaled corticosteroids) and ii) other phenotypes expressing themselves as a combination of viral-triggered attacks /and/ interval symptoms (e.g. atopic asthma).

Gastrointestinal Absorption
The executive summary should highlight the differences in gastrointestinal absorption between the cheaper and more expensive corticosteroids at higher doses. This increases the weighting towards FP and Budesonide at doses over 400 micrograms BDP equivalent per day.
The executive summary should highlight that comparison of BUD/FF and FP/SAL combination can only be done for older children – i.e. FP/SAL is the only option in children who only use an MDI/spacer. Furthermore, the BUD/FF combination is the only one that offers the flexibility of parent/patient-initiated increased dosing during periods of asthma instability.

Systemic activity of Inhaled Steroids
Clearly there is a diversity of view as to the concerns about side effects of inhaled cortico-steroids. I feel that the document does not emphasise strongly enough that there is systemic activity of inhaled steroids even in the conventional dose range. The key issue is whether these are of any clinical significance. I think they underplay the study published in Arch Dis Child on adrenal crises in children receiving inhaled cortico steroid. There was an overwhelming predominance of the prescription of Fluticasone in those with adrenal crises. I believe that this should be emphasised rather more strongly particularly in the summary which is after all what the majority of clinicians will read. Few will delve into the 250 page detail. However as indicated above there is a diversity of view and I suspect that some colleagues are not as concerned about this.

Long Acting Beta Agonists
The other issue that is perhaps not highlighted sufficiently is the potential for the long acting beta agonists to be associated with a higher risk of death or near death episode. In the detailed text, there are comments about this in relation to the so called SMART study. Furthermore they do mention the fact that Salmeterol has a black box warning on all American package inserts because of concerns about this. However, again I feel that it should be stated in the summary as well.

The cost analysis
The possibility of poor inhaler technique is alluded to with a passing mention to the possibility of the use of a spacer is made **(8.3,** p 197) but this is not included in the cost analysis. A spacer should be used in all children under 8 years with an MDI and in any child with an MDI and high-dose ICS (> 600mcg/day BUD equivalence).

The BTS guideline emphasizes the need to step-down or step-up ICS as appropriate. This point is not discussed in the context of the cost of combined ICS/LABA. As it is not necessarily

appropriate to merely double the dose (because of excess LABA) it could necessitate the use of several preparations.

When assessing the cost effectiveness of LABAs, the consequent reduction in SABA is not included.

Specific Comments

Page xiv - "No trials were identified that assessed the effects in children of the addition of a LABA to ICS versus a higher dose of ICS alone."

The following study does not appear to have been considered: Verberne A, Frost C, Duiverman EJ, Grol MH, Kerrebijn KF, Raaymakers JAM, Pocock SJ, Bogaard JM, vanNierop JC, Nagelkerke AF, Thio B, Schouten TJ, van Essen Zandvliet EEM, Denteneer A, Gerritsen J, Grol MJ, Roorda RJ, Hendriks JJE, Duiverman EJ, Kouwenberg JM, van der Laag J, Brackel HJL. Addition of salmeterol versus doubling the dose of beclomethasone in children with asthma. American Journal of Respiratory and Critical Care Medicine 1998;**158**:213-219.

Page *xviii - "There is very limited evidence available for the efficacy and safety of ICS and LABAs in children".*

Do NICE mean the <u>comparative</u> efficacy and safety? There are a number of placebo controlled RCTs showing safety and efficacy. This is an important clarification as it may be interpreted as indicating that we are treating childhood asthma without any justification of efficacy!

Page xviii and xix - There are contradictory statements about the relative cost of Bud:FF and FP:Sal combination inhalers- in fact the text is clear that the latter is cheaper at present (as stated on p xviii) but the conclusion on p xix is the other way round.

Page xviii - The statement " BDP CFC-propelled products are often currently the cheapest ICS available at both low and high dose, and may remain so even when CFC-propelled products are excluded" (2.6 conclusion) is ambiguous (i.e. removing CFC-propelled products will, by definition, remove all BDP CFC-propelled products)

Page 21

(i) What is the evidence that 1,500 mcg in adults is equivalent to 400mcg in children?

(ii) The references (last para ; 93,94) on adrenal suppression are old and probably out of date

(iii) There is a typographical error. Of those reported with adrenal crises 30/33 **(91%)** not 1% were on FP.

Page 191 – Review question 2

No difference in efficacy between preparations is assumed as this was the conclusion from the studies. However, the increase in adrenal suppression was noted with BDP was greater than BUD (page 58 – 5.2.2.1.3). Some studies show that is greater in FP but in these relatively higher doses have been used i.e. 1:1 ratio with BUD). Therefore this should be taken into account at high ICS doses, when BDP is not recommended.

Page 195 - Review question 5

Formoterol (FF) and Salmeterol (SAL) are discussed as if their onset of action and dose-response characteristics were similar. FF has a much quicker onset (Pohunek P et al Ped Allergy Immunology 2004;15:32-9). Also increasing the dose increases the response for FF, whereas SAL has a flat dose response to increasing dose (Palmqvist M et al AJRCCM 1999;48:547-53). It is stated that FF is more lipophilic than SAL but the implications are not explained. The difference between the two preparations should be noted as it could be appropriate to double the combination BUD/FF but not FP/SAL (see above).

Research Priorities
The lack of appropriate trials in children< 12 years is acknowledged. What is needed is a comparison of side effect/benefit ratios in studies powered to show differences in adrenal suppression and growth. These latter may be idiosyncratic responses so large numbers would be needed.

I think from the College's perspective, one of the most important outputs from this report is that they were unable to find any studies relevant to the use of inhaled cortico steroids and/or long acting beta agonists in children under 4 years of age. Furthermore the report highlights the relative paucity of any studies in children

The conclusion on the lack of high quality RCTs of corticosteroid therapy and long-acting beta 2 agonists is known within the paediatric research community. A study which would allow “head to head” or "non-inferiority" comparison – without the need to estimate exact “equivalence” of steroid dose – is a pragmatic RCT design where inhaled steroid is used in a step-up/step-down protocol –i.e. mirroring the BTS guideline.

With thanks to:

Professor. Jonathan Grigg,
Dr. Sheila McKenzie, on behalf of the College Respiratory Advisory Committee
Dr. Rob Primhak, on behalf of the British Paediatric Respiratory Society
Professor John Warner
Dr. Nicola Wilson