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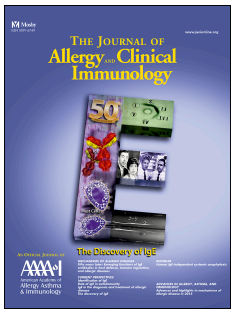

Predicting steroid responsiveness in asthmatic children: are we there yet?

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Predicting steroid responsiveness in asthmatic children: are we there yet?

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Asthma, for the vast majority of children, is more of an inconvenience than a serious condition; controlled relatively easily with low dose inhaled corticosteroids (ICS) plus or minus long acting beta-agonists or leukotriene receptor antagonists. For a small minority this is not the case and asthma is a severe disease that causes major morbidity that can include severe exacerbations requiring hospitalization, loss of lung function, social isolation and behavioural problems (1). The definition of severe asthma in children varies but generally includes persistent symptoms and/or exacerbations despite being prescribed high doses of ICS and other therapies that may include oral steroids and biologicals (2). A number of phenotypes contribute to severe asthma in children, including poor medication adherence, difficult to treat asthma and steroid resistant asthma (2,3). Various attempts have been made to distinguish between children with difficult to treat and steroid resistant asthma using measures of asthma control, pulmonary physiology and pulmonary inflammation with little consensus (2, 4-6). Major clinical advantage would come from being able predict reliably which children with severe asthma are unlikely to respond to ICS. Attempts to predict risk of steroid resistance have included risk genotypes and haplotypes (7) and assessment of cysteine oxidation impaired glucocorticoid receptor function (8). It is fair to say that, at this stage, these attempts have identified risk factors but are not sufficiently predictive to guide treatment of individual children.

In the current issue of the journal, Goleva et al. (9) report results of a study examining expression of corticosteroid regulated genes in children with asthma to predict steroid resistance. They recruited 125 children, aged 6 to17 years, with asthma participating in the Inner City Asthma Consortium's Asthma Phenotypes in the Inner City study. A more comprehensive report of clinical aspects of the study and of the study population has been published (6). The study by Govea et al. (9) needs to be read in conjunction with this previous report as their description of the patient population and flow through the study is insufficient (Figure 1). Screening included checking the physician's asthma diagnosis, children's medication usage and adherence, and asthma control. Children with less than 50% estimated medication adherence were excluded in an attempt to study true medication responses (7). A predefined, computerized algorithm guided asthma therapy at each visit based on symptoms, lung function and recent exacerbations. Six months into the study on algorithm-guided therapy children were classified as having: difficult-to-control (requiring fluticasone propionate (FP) $\geq$ 500 µg/day ± other treatment on at least 4 visits); easy-to-control (FP $\leq$100 µg/day; or indeterminate (didn't fall into the other categories). Children were not reclassified during the remaining 6 months of the study.

Goleva et al. (9) reported on 95 of these children (45 difficult-to-control, 31 easy-to-control, 19 indeterminate) who gave paired blood samples at the first and last study visits, visits 0 and 6, respectively. Peripheral blood mononuclear cells were either lysed immediately or after 3 hours culture, with or without 10^{-8}M FP. Outcome measures included: expression of mRNA encoding glucocorticoid receptor alpha (GRα) and cytochrome P450 Family 24 subfamily A Member 1 (cyp24a); FP-induced induction of corticosteroid transactivation (FK binding protein 5 [FKBP5]); and FP-induced suppression of IL-8 and TNFα. They reported, on grouped data that children with difficult-to-treat asthma had significantly lower GRα that those with easy-to-treat asthma at visit 0, but not lower than those in the indeterminate group. There was no relationship between GRα expression and level of asthma control in the difficult-to-treat group. GRα expression fell over the study period in those with easy-to-treat asthma but not in the difficult-to-treat group. Children in the easy-to-treat group showed an increase in FP suppression of IL-8 (30%, p=0.04) and TNFα (p=0.07) between V0 and V6. No changes in GRα, IL-8 and TNFα were seen in children in the other groups. An increase in FP induction of FKBP5 occurred in the difficult-to-treat group between V0 and V6. Again, there were no associations between these data and asthma control levels. The authors should be commended for showing individual data points in addition to the group means and 95% CI. Examination of these data show marked overlap in individual values for all outcome variables between groups.

Goleva et al. (9) suggest that their PBMC analyses could form the basis for future tests to determine which children are likely to be steroid resistant. However, their study has several limitations which need to be addressed in followup studies before proceeding further. Firstly they focussed on expression of only a small proportion of the genes known to be steroid responsive in PBMC, and consequently their findings may represent the tip of a much more interesting and informative iceberg. The technology exists to cast the net far wider, and in an unbiased way, employing genome wide expression profiling, including utilization of system level approaches that could assess steroid effects at the level of gene networks (10) But before this is contemplated, there are a series of more fundamental clinical issues that need to be considered. As outlined above, severe asthma, referred to in this study as difficult-to-treat asthma, contains several phenotypes. Children's asthma can be difficult to treat for various reasons, including lack of adherence, poor inhaler technique, failure to use a spacer adequately, continued exposure to a poor environment containing inflammatory triggers, and steroid resistance (1, 2). The marked variability in the individual responses to FP suggest that some children in the difficult-to-treat group did respond well to ICS while others were resistant. The lack of any association between the steroid regulated genes and asthma control is also a concern. Analysis of the outcome variables was undertaken separately. A combined analysis may have been informative and may have identified individual children who truly steroid resistant.

So where does that leave the assessment of steroid resistance in children with severe asthma? Any test of steroid resistance would need to be useful for individual children and not simply show group differences. The data presented by Goleva et al (9), together with earlier studies (7,8) do suggest that studies of the mechanism(s) underlying steroid resistance will be informative, but we clearly have a long way to go before a "clinic-ready" test will be available. In the meantime, we must rely on clinical first principles. As the vast majority of children with asthma will be controlled by low dose ICS, this is the place to start. For children who do not come under control within a short period, say one month, further assessment is warranted. This should include: re-visiting the diagnosis – does the child have asthma?; examining inhaler/spacer technique; addressing medication adherence; and if control is poor, additional therapy. Some children will continue to receive high dose steroids, with the associated adverse effects when they are not able to respond. At this time, there is no easy way to tell who these children are.

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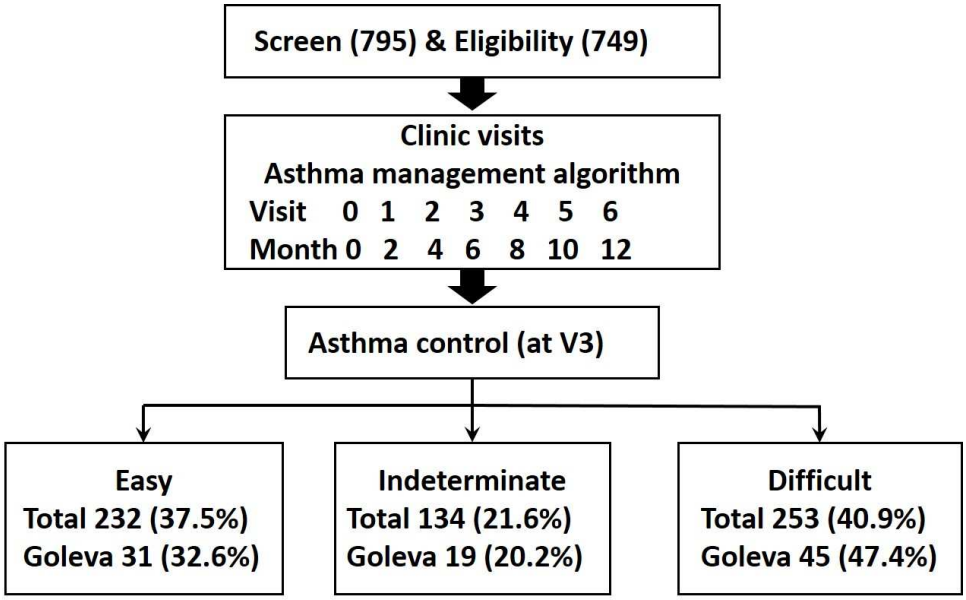
Figure Legend

Figure 1: Schematic representation of the total study population (Pongracic et al (6), the sub-population reported by Goleva et al. (9) and the study outcomes. FP = fluticasone propionate.



Biomarker change with FP V0-V6			
TNFα suppression	Marginal increase	No change	No change
IL-8 suppression	Increased	No change	No change
FKBP5 induction	Increased	No change	No change