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Corticosteroid responsiveness and clinical characteristics in childhood difficult asthma

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Abbreviations

ATS; American thoracic society

BAL; bronchoalveolar lavage

BDR; Bronchodilator reversibility

DA; Difficult asthma

EB; endobronchial

ERS; European Respiratory society

FENO; Fractional exhaled nitric oxide

FEV1; Forced expiratory volume in 1 second

FOB; Fibreoptic bronchoscopy

GER; gastroesphageal reflux

HDM; House dust mite

HRCT; High resolution computed tomography scan

ICS; inhaled corticosteroids

Ig; Immunoglobulin

IM; intramuscular

IU/ml; international units per millilitre

LABA; long acting beta agonist

OR; odds ratio

PAL; persistent airflow limitation

RAST; radioallergosorbet assay

RBM; reticular basement membrane

SD; standard deviation

SPT; skin prick test

ABSTRACT

We describe clinical characteristics and corticosteroid responsiveness of children with difficult asthma (DA). We hypothesized that complete corticosteroid responsiveness (defined as improved symptoms, normal spirometry, normal fractional exhaled nitric oxide (FeNO), and no bronchodilator responsiveness (BDR <12%)) is uncommon in paediatric DA.

We report on 102 children, mean age 11.6 (SD: 2.8) years with DA (cross-sectional study). 89 children underwent spirometry, BDR and FeNO before and after 2 weeks of systemic corticosteroids (corticosteroid response study). Bronchoscopy was performed after corticosteroid trial.

Cross-sectional study: 88/102 (86%) patients were atopic, 60/102 (59%) were male. 52/102 (51%) had additional or alternative diagnoses. Corticosteroid response study: 9/81 (11%) were complete responders. 37/75 (49%) responded symptomatically, less likely if there were smokers at home (OR 0.31; 95% CI 0.02-0.82). 35/75 (46%) had normal spirometry, associations being BAL eosinophilia (OR 5.43; 95% CI 1.13-26.07) and high baseline FEV_1 (OR 1.08; 95% CI 1.02-1.12), 36/64 (56%) had <12% BDR and 53/70 (75%) had normal FeNO. 17/75(26%) had persistent airflow limitation, which was associated with low baseline FEV_1 (OR 0.93; 95% CI 0.90-0.97).

Only 11% of DA children exhibited complete corticosteroid responsiveness. The rarity of complete corticosteroid responsiveness suggests alternative therapies are needed for children with DA.

Difficult asthma (DA) in children can be challenging to treat, and leads to high rates of health care utilisation. These patients have continued symptoms despite high dose inhaled corticosteroids(ICS) and other therapies.[1] The reasons for their asthma being difficult to treat need detailed investigation.[1] Confirmation of asthma diagnosis, identification and treatment of associated diagnoses is essential. Potential reversible factors, like poor treatment adherence and continued allergen exposure should be addressed.

Phenotyping childhood DA according to airway inflammation and corticosteroid responsiveness is challenging.[2] However, identification of corticosteroid resistance is important, allowing the clinician to deploy alternative therapies; conversely, in the corticosteroid sensitive patient, the dose of therapy should be minimised to avoid unwanted side effects.

A protocol driven approach for the investigation of childhood DA helps identify the reasons why asthma is difficult to treat and classifies the underlying inflammatory profile. We, and others[2-4] have used a protocol involving the administration of a 2 week course of high dose systemic corticosteroids, with investigation of non-invasive markers of inflammation before and after corticosteroids, and bronchoscopy at the end of the corticosteroid trial (figure 1). Patients are characterised according to their corticosteroid response and appropriate treatment alterations made.

Adult DA patients are predominantly female,[5] with increased atopy in mild rather than severe asthma,[6] and infection rather than allergy is implicated in the pathophysiology.[7] Many present in early adulthood, not childhood, which may be associated with a poor prognosis.[8] Severe adult asthmatics seem to have a different disease compared with mild asthmatics with greater airway obstruction, a lower diffusing ability and more air trapping. Sputum neutrophilia is

more common.[6] We hypothesised that characteristics of childhood DA are different to those reported in adults and that complete corticosteroid responsiveness is uncommon in paediatric DA.[5;6;9;10] We report a consecutive observational study of children, aged over 5 years, with DA, referred to the Royal Brompton Hospital (mainly tertiary and even quaternary referrals). We aimed to describe their clinical characteristics and their response to a corticosteroid trial in terms of symptoms, spirometry and inflammation, and predictors of corticosteroid response.

METHODS

Subjects

Children with DA referred between December 1997 and April 2005 were identified. All children had been under follow-up either at our centre or another secondary care facility for at least 12 months, with repeated attempts to optimise treatment. Asthma was diagnosed according to the ATS criteria.[11] Both were required for inclusion:

1. On-going symptoms necessitating short-acting β-2 agonists at least three times per week, despite the prescription of high dose ICS (>800 mcg/day of budesonide equivalent) or regular systemic corticosteroids
2. Treatment with or failed trial of LABA and leukotriene receptor antagonist

Atopy was defined as ≥1 positive specific IgE radioallergosorbent assay (RAST) (≥0.34 kU/l) or ≥1 positive skin prick test (SPT) to aeroallergens (cat, dog, house dust mite (HDM) and grasses). The performance of pH study, HRCT and immunological testing was at the discretion of the clinician in charge of the case, and was not protocol driven.

Spirometry and bronchodilator reversibility (BDR)

Spirometry was performed using a Compact Vitallograph 2120 (Vitallograph, UK). Normal forced expiratory volume in one second (FEV_1) was defined as ≥80% predicted in accordance with ERS/ATS guidelines.[12] Spirometry was performed before and fifteen minutes after the

administration of 1mg salbutamol via a large volume spacer. BDR was defined as change in percent predicted FEV_1/baseline percent predicted FEV_1 X100, ≥ 12% being deemed a positive test. Persistent airflow limitation (PAL) was defined as post bronchodilator, post corticosteroid trial FEV_1 < 80% predicted.

Fractional exhaled nitric oxide measurement (FeNO)

FeNO was measured according to guidelines current during the study period.[13] Twenty percent of measurements, early in the study, were performed using a Logan analyser (LR 2000 series, Logan research, Rochester, UK) at flow rate 250 ml/s, values <12.5ppb were considered normal.[14] The remainder of the measurements were made using the NIOX chemiluminescence analyser, (Aerocrine, Sweden) at a flow rate of 50ml/s, and compared to normals.[15] The results were converted into z scores and categorised as 'normal' or 'abnormal'.

Immunological abnormalities

Serum immunoglobulins (Ig) including IgA, G, M and IgG subclasses and vaccine antibody responses (Haemophilus, tetanus and pneumococcus) were measured. An immunological abnormality was defined as the presence of low Ig levels with reduced vaccine antibody responses, or repeated low levels of either of these.

High-resolution CT scan (HRCT)

The need for HRCT was determined clinically, and was not a routine part of the protocol. HRCT was performed using an electron beam ultrafast scanner (Imatron Inc.: San Franciso, USA)[16] and reported by a consultant radiologist.

Corticosteroid trial

The corticosteroid trial consisted of either a 2 week course of oral prednisolone (40mg daily) or a single 80mg dose of intramuscular (IM) triamcinolone. Symptom response was determined from parental and patient reports and defined as no change, an improvement in

symptoms, or becoming symptom free. Complete corticosteroid responsiveness was defined as all 4 parameters (symptoms, FEV_1, BDR and FeNO) being normal at the end of the corticosteroid trial, partial response if ≥1, and non-response if none were satisfied.

Adherence assessment

Children who received oral corticosteroids had serum prednisolone and cortisol levels measured. Adherence was considered satisfactory if prednisolone was detectable and serum cortisol<100 nM.[17] In samples taken >24 hours after the last prednisolone dose, adherence was considered adequate if serum cortisol<100 nM. Compliance was assured in children given IM triamcinolone.

Oesophageal pH testing

A single channel pH probe was inserted at the time of bronchoscopy. Oesophageal pH was monitored over 18-24 hours using a Synectics Digitrapper Mark III, (Synectics Inc.; Irving TX, USA). A positive test was defined as pH < 4 for ≥ 4% of the time. Severe reflux was defined as pH<4 for ≥15%.

Fibreoptic bronchoscopy (FOB), bronchoalveolar lavage (BAL) and endobronchial biopsy (EB)

FOB was performed under general anaesthetic at the end of the corticosteroid trial as previously described.[18;19] BAL and EB were taken and processed as previously described.[19] Eosinophilia was defined as > 1.19%,[20] and neutrophilia >3.5% of the total cell count.[21] Submucosal inflammation and reticular basement membrane (RBM) thickness were determined using a clinical score by a histopathologist (AGN). Inflammation was classified as eosinophilic, neutrophilic or mixed. RBM thickness was classified as normal (0), mild (1), moderate (2), or severe (3), >1 was considered abnormal.

Statistical analysis

Non-parametric tests were used, numerical data was analysed using the Mann-Whitney U test and ordinal data using Fisher's exact or Chi squared tests as appropriate. Paired data was analysed using paired t tests and Wilcoxon matched paired t test. Multiple regression analysis was performed using predictors marked in tables 1&2. Analysis was performed using Statistical Package of the Social Sciences version 15.

RESULTS

Cross-sectional study

Tables 1&2 summarise the baseline demographics. For those prescribed oral corticosteroids, the median daily dose was 10 mg (5mg alternate days – 40 mg/day). The reasons for the variations in denominators are explained in figure 1. There were 60/102 boys (59%). Eighty eight (86%) children were atopic, 32/88 (36%) of atopic children owned a pet and of these, 21/32 (65%) tested were sensitised to their pet. 24/99 (24%) had a history of food allergy or triggers to asthma, of which 11 had positive RASTs to the food trigger. The mean FEV_1 was 67.1% (SD: 19.2). A positive BDR test was seen in 53/71 (75%) atopic compared to 3/10 (30%) non-atopic subjects (p=0.004). FeNO was normal in 10/11 (91%) non-atopic compared with 36/70 (51%) atopic patients (p=0.02). Mean FeNO z score was 1.78 (SD: 2.1). Distribution of IgE levels is illustrated in figure 2. Immunological abnormalities were found in 10/74 (14%) (table a, online supplement), non-atopic children being significantly more likely to have an abnormality compared to atopic children (p=0.036). Forty seven (46%) patients had an HRCT performed (table b, online supplement) and of these three (6%) had bronchiectasis. A pH study was completed in 55/102 (54%) of children, 41/55 (75%) of which were abnormal.

Bronchoscopy

FOB was performed in all (table 2), of whom 3 have missing anatomical data. Seventy six (75%) had BAL microscopy and 68/102 (67%) cytology performed. Positive BAL cultures were seen in 19/76 (25%), of which neutrophilia was present in 10/15 (67%) (table c, online supplement). BAL eosinophilia was present in 25/68 (37%) and neutrophilia in 30/68 (44%), including 11/68 (16%) with mixed cellularity (see table 2). EB could be analysed in 68/102 (67%) patients. Mucosal eosinophilia was present in 36/68 (53%) and neutrophilia in 36/68 (53%), including 17/36 (47%) with mixed cellularity. Increased RBM thickening was present in 41/56 (73%).

Fifty two (51%) children had an additional or alternative diagnosis. This was more common in non-atopic compared to atopic subjects (10/14 vs 42/88 respectively). Eight of these children were subsequently thought not to be suffering from DA, and their treatment was modified accordingly. They were therefore removed from analysis of corticosteroid response. These diagnoses included bronchiectasis, primary ciliary dyskinesia, Job's syndrome, vascular ring, severe sinusitis, severe gastro-oesphageal reflux, immune abnormalities and vocal cord dysfunction (tables d & e online supplement)

Table 1 Demographic and clinical baseline characteristics

	Whole group n =102 (%)	Steroid trial group N=81 (%)
Atopy[1]	88/102 (86)	74/81 (91)
Sex (M:F) [1]	60:42	48:33
Age in years[1]	11.58 (2.8)	11.8 (2.6)
(mean, standard deviation (SD), range)	(6-19)	(6-19)
Median height percentile (range)	50th (2^{nd}-99^{th})	50^{th} (2^{nd}-99^{th})
Median age (years) at first symptoms (range)	1.25 (0.2-10)	1.5 (0.17-10)
History of smokers at home[1]	37/100 (37)	31/79 (39)
History of previous intubation (for asthma)[1]	14/101 (14)	10/81 (12)
History of rhinoconjunctivitis (on treatment)	32/101 (31)	27/81 (33)
Positive SPTs/RASTs to grasses/pollen	61/87 (70)	53/72 (74)
Positive SPTs/RASTs to HDM present	67/95 (70)	59/77 (77)
Median IgE (range) IU/ml[1]	584 (2-11355)	654 (8-11355)
Pets in household	41/102 (40)	29/81 (36)
Positive specific IgE/SPTs to pet (if pet present)	21/34 (62)	16/24 (67)
Medications		
Median Inhaled Corticosteroid dose (range) mg/day	2 (0.4-4)	2 (0.4-4)
Long-acting β2 agonist	92/102 (90)	73/81 (90)
Leukotriene receptor antagonist	50/102 (49)	38/81 (47)

Maintenance oral prednisolone	36/102 (35)	29/81 (37)
Maintenance triamcinolone	1/102 (1)	1/81 (1)
Oral theophylline	14/102 (14)	12/81 (15)
Mean % predicted FEV_1 (SD)[1]	67.1 (19.2)	65.4 (19)
Mean % predicted FEV_1 post bronchodilator (SD)	79.4 (18.3)	78.5 (18.6)
BDR median, % predicted (range)	18 (0-130)	19.5 (0-130)
Number with BDR present (≥12%) [1]	56/81 (69)	48/68 (71)
Number with raised FeNO above normal[1]	35/81 (43)	32/65 (49)

Data represented as number positive/number we have information (%).[1]These factors were used as predictors of steroid response in multiple logistic regression. BDR, % bronchodilator reversibility; FeNO, fractional exhaled nitric oxide; FEV_1, Forced expiratory volume in 1 second expressed as % predicted for height; ; HDM: House dust mite IgE: Immunoglobulin E; IU/ml: international units per ml; RAST, radioallergosorbent assay; SD, standard deviation. SPT: skin prick testing

Table 2 Comparison of atopic and non-atopic subjects

	All n=102	Atopic n=88	Non atopic N=14	p value
Mean % predicted FEV_1 at baseline (SD)[1]	67.1 (19.2)	66.3 (18)	72.2 (25)	NS (0.8)
Median (range) % BDR at baseline[1]	18 (0-130)	22 (0-130)	3.5 (0-42.5)	0.002
Children with BDR (≥12%) at baseline[1]	56/81 (69)	53/71 (75)	3/10 (30)	0.004
Baseline median $FeNO_{50}$ (ppb) (range)†	21.5 (5-257)	24 (5-257)	10 (6.6-20.6)	0.026
Baseline median $FeNO_{250}$ (ppb) (range)	5.65 (1.2-25.9)	7.15 (1.2-25.9)	2.9 (1.8-5.7)	0.027
Baseline FeNO normal‡[1]	46/81 (57)	36/70 (51)	10/11(91)	0.02
Immunological abnormality*	10/74 (14)	5/62 (8)	5/12 (42)	0.036
Positive pH study (pH <4 for >4% of time)	41/55 (75)	31/43 (72)	10/12 (83)	NS (0.71)
Severe GER (pH<4 for >15% of time)	7/55 (13%)	6/88 (13)	1/14 (7)	NS
Bronchiectasis on HRCT	3/47 (6)	1/39 (3)	2/8 (25)	NS(0.07)
Anatomical abnormality on bronchoscopy	11/99 (11)	10/85 (12)	1/14 (7)	NS (0.53)
ENT abnormality	11/99	8/85 (9)	3/14 (21)	NS
Bronchoscopic macroscopic inflammation or excess mucus	42/99 (42)	36/85 (42)	6/14 (43)	NS (0.48)
Bacterial growth from BAL	19/76 (25)	15/62 (24)	4/13 (31)	NS (0.83)
BAL eosinophilia (>1.19%)[1]	25/68 (37)	22/59 (37)	3/9 (33)	NS (1)
BAL neutrophilia (>3.5%)[1]	30/68 (44)	26/59 (44)	4/9 (44))	NS (0.7)
EB eosinophilia[1]	36/68 (53)	32/58 (55)	4/10 (40)	NS (0.5)
EB neutrophilia[1]	36/68 (53)	30/58 (52)	6/10 (60)	NS (0.7)
EB reticular basement membrane thickening[1]	41/56 (73)	33/50 (66)	3/7 (42)	NS(0.08)_

Data represented as number positive/number who had test (%). *Defined as >1 serum immunological abnormality or low on repeated testing.† NIOX readings included only. ‡Includes NIOX and Logan readings. ¥note only 24 patients tested. [1] These factors were used as predictors of steroid response in multiple logistic regression. BAL, bronchoalveolar lavage.; BDR, % bronchodilator reversibility; EB, endobronchial biopsy; FeNO, fractional exhaled nitric oxide; FEV_1, Forced expiratory volume in 1 second expressed as % predicted for height; HRCT, high resolution computed tomography scan; SD, standard deviation.

Corticosteroid response study

Eighty nine (87%) subjects underwent a corticosteroid trial as part of the clinical protocol. Data to assess corticosteroid response was available in 81. There was no difference between the responses of those who were and were not prescribed systemic corticosteroids (data in

online supplement). 9/81 (11%) were complete, 65/81 (80%) partial and 7/81 (9%) non-responders (Figure 3). Of 57/69 (83%) children with evidence of adequate adherence, 9/57 (16%) were complete, 47/57 (82%) partial and 1/57 (2%) were non-responders. All children that demonstrated complete corticosteroid response had evidence of treatment adherence compared to 48/57 (84%) who were partial or non-responders (p=0.14). None of the steroid non-responders (0/7) were on maintenance systemic steroids compared with 30/74 (41%) of those with partial or complete responders (p=0.03). In a post-hoc analysis, there was evidence that those given triamcinolone (n=16) may have had slightly better responses compared with those given prednisolone (n=65) (see online supplement). Whether this reflected sub-optimal compliance with prednisolone, a dose effect, or intrinsically better anti-inflammatory properties of triamcinolone cannot be determined. In a further post-hoc analysis, we compared steroid responsiveness in those with single (n=7) and multiple (n=67) allergies. Although the numbers are small, children with a single allergy had a less good BDR response after the steroid trial (see online supplement).

Symptom Response (table f, online supplement)

An improvement in symptoms was reported in 37/75 (49%); symptomatic response was less likely if there was a history of smokers at home (OR: 0.31; 95% CI 0.02-0.82).

FEV_1 response (figure 4, table g, online supplement)

Baseline mean FEV_1 was 66.3% (SD: 19.1), increasing to 77.5% (SD: 18) post corticosteroid trial ($p<0.001$). Pre-bronchodilator FEV_1 was normal in 35/75 (47%) of children after the corticosteroid trial. Higher baseline FEV_1 (OR 1.08; 95% CI 1.02-1.12) and BAL eosinophilia (OR 5.43; 95% CI 1.13-26.07) were associated with FEV_1 response. Change in FEV_1 was associated with baseline low BDR (OR: 0.42; 95% CI 0.05-0.80). PAL was present in 17/75 (23%) of patients, and associated with a low FEV_1 pre-corticosteroid trial (OR 0.93; 95% CI 0.90-0.97).

BDR response (table h, online supplement)

Baseline BDR was 18 (0-130)% compared to 10 (0-82)% post trial (p=0.001), with no predictors of BDR <12% post trial.

FeNO Response (figure 5, table I, online supplement)

The mean z scores for FeNO pre and post steroid trial were 1.78 (SD: 2.07) and 0.40 (SD: 1.98) respectively (p<0.01); low baseline FeNO (OR 0.36; 95% CI 0.18-0.72) was a predictor of FeNO response.

Table 3 Significant predictors of corticosteroid responsiveness from multivariate logistic regression

Predictor	OR	95% CI	p
Symptomatic response			
Smokers at home	0.31	0.02 - 0.82	0.03
FEV_1 response			
Baseline FEV_1	1.08	1.02 - 1.12	0.003
BAL eosinophilia	5.43	1.13 - 26.07	0.03
Percentage change in FEV_1			
Baseline BDR	0.42	0.05 - 0.80	0.03
FeNO response			
Baseline FeNO	0.36	0.18 - 0.72	0.003
Persistant airflow limitation			
Baseline FEV_1	0.93	0.90 - 0.97	<0.001

BDR, bronchodilator reversibility; FEV_1, forced expiratory volume in 1 second; FeNO, fractional exhaled nitric oxide. All those predictors shown in table 1 were tested and those which were non significant are not included in this table

DISCUSSION

In this large observational case series, which is the most detailed characterisation of DA in children in the literature, including analyses of clinical corticosteroid responsiveness, we have shown that (a) in contrast to patient series of adult DA, in which women predominate and atopy is less prominent in severe asthma compared to mild to moderate asthma,[6] in children with DA, boys predominate and atopy is very common; (b) many children are exposed to environmental influences (cigarette smoke) known to cause corticosteroid resistance; (c) associated diagnoses are common especially in non-atopic subjects; (d) response to a corticosteroid trial is difficult to predict, with the majority of subjects exhibiting only a partial

response and (e) BDR is common even after a corticosteroid trial even though most subjects were taking LABAs. The latter may reflect of non-compliance, tachyphylaxis or a genuine bronchodilator-resistant state.

The study does have a number of limitations. As this is a large observational case series, some data is missing, and not all patients underwent the corticosteroid trial, because in some cases this was not thought clinically appropriate. The data is based on a highly selected case series and may not be generalisable to all populations. As with many studies, assessment of adherence to the corticosteroid trial was suboptimal and the invasive assessments of inflammation were performed after the corticosteroid trial. This was done to optimise the safety of the procedure. Later on in the trial, when its safety was established, IM triamcinolone was introduced ensuring adherence to therapy. Due to the severity of asthma in the children evaluated, over a third of children were on maintenance systemic steroids at baseline, this may have influenced results, and we found significantly more children who exhibited a partial or complete response were on maintenance steroids compared with non-responders. This is an unavoidable disadvantage of an observational clinical study. Finally, a home visit was not performed during the study period, and may have been beneficial to explore the role of psychosocial issues, allergen exposure and compliance in symptom control.[4] We now use an adapted version of the protocol which addresses these issues and includes a home visit before we proceed to the steroid trial.

We have shown that atopic patients are more likely to exhibit bronchodilator reversibility and have higher FeNO levels than non-atopic patients, although the numbers of the latter were small. Atopy itself causes an elevation in FeNO.[22] Non-atopic patients were also more likely to have immune abnormalities. In keeping with a recent study[23], there was little difference in BAL and EB inflammation in atopic compared with non-atopic children. A large proportion of all patients (atopic and non-atopic) had gastro-oesophageal reflux. We were unable formally to assess the contribution of reflux to the severity of asthma, but in three patients

treatment for severe gastro-oesophageal reflux was associated with a significant reduction in inhaled steroid dose with improvement in their symptoms. Importantly, there was a high incidence of alternative or additional diagnoses in the whole cohort (51%), and this was more common in the non-atopic children. A study of adult DA patients found an incidence of alternative or additional diagnoses of 32%.[24] One lesson of our study is that at least potential co-morbidities are common and ideally should be sought before evaluating steroid sensitivity; our current practice has been modified in light of this.

A complete response to the corticosteroid trial was rare in our study. Our criteria for complete corticosteroid responsiveness were stringent, requiring four measurements to normalise. In other studies, steroid sensitivity was defined by > 15% improvement in pre-bronchodilator FEV_1, after a short course of oral corticosteroids.[4;25] The definition of corticosteroid responsiveness has been debated, and it may be that our definition is too rigorous. Although symptoms may be of most importance to patients, symptom perception is often poor in asthmatic children,[26] making this less than ideal as a measure of response. Spirometry is often normal in children even with quite severe asthma, and has been criticised as an end-point.[27] Conversely, inflammation may predict future outcome, thus FeNO or sputum eosinophils may be more objective measures of steroid response.[28] We opted for a spectrum of endpoints, acknowledging that this is to some extent arbitrary, and that a true definition of corticosteroid responsiveness in children not yet been achieved. As this study was based on our clinical protocol and clinicians are more likely to use a combination of endpoints, this determined our choice. Furthermore, corticosteroid responsiveness is likely to be a spectrum, rather than an all or none phenomenon, and it may be that the use of a higher dose or increased duration of prednisolone therapy might have increased the number of responders. Indeed, we have shown that spirometry may increase still further in the year after a corticosteroid trial.[2] However, prolonged high dose therapy is likely to cause side effects, so we have kept to traditional doses in order to assess steroid responsiveness. We found heterogeneity in response in symptoms and inflammation in this study. We found few robust determinants of

corticosteroid response and due to regression about the mean, baseline investigations as prediction of outcome measures should be interpreted cautiously.

Partial corticosteroid response was common, and the incomplete response may be due to ongoing exposure to environmental triggers. In keeping with previous studies,[4] we have demonstrated that environmental factors are likely to play an important role in DA. We have shown that 65% of atopic children who had pets were allergic to them, and other studies have shown that persistent allergen exposure in those sensitised can lead to an IL-2 and IL-4 mediated corticosteroid resistance.[29] Thus, it is likely that the ongoing allergen exposure contributed to their poor symptom control, despite high dose treatment. We have also shown that those exposed to tobacco smoke at home were less likely to have a symptom response after a corticosteroid trial. In adult DA, it has been shown that active smoking can have detrimental effects on symptoms, and corticosteroid responsiveness[30] and our study suggests the same may be true with passive smoke exposure. Oxidative stress caused by smoke exposure has been shown to alter histone deacetylase activity which has detrimental effects on steroid response.[31] The incomplete responsiveness to LABA and systemic corticosteroids suggest the need for other therapies in paediatric DA. It is noteworthy that only 40/90 (44%) would have been eligible for anti-IgE therapy under the current license (figure 2).[32] This leaves a large number of children with partially steroid insensitive DA with few if any evidence based options for add on therapy. New medications for this group are urgently needed.

A cross sectional study[9] of 125 children, and 150 adults with DA , in keeping with our findings, showed that children with DA had a high prevalence of atopy and a male preponderance compared with adults. Corticosteroid response was only determined *in vitro*, by contrast with our report. They found that children displayed greater *in vitro* responsiveness to glucocorticoids than adults. Ranganathan et al[4] studied a smaller cohort of children with DA and showed 60% were corticosteroid resistant although their criteria for

response was defined by>15% increase in FEV_1, thus less stringent than ours. By contrast, in a larger cohort of adolescents with DA,[25] the same spirometric criteria was used for response, but found only 25% of subjects to be steroid insensitive. Steroid insensitivity was also shown to be associated with the need for oral corticosteroids at a younger age and African American ethnicity. We had insufficient numbers of non-white children in our cohort to determine any effect of ethnicity. However, lung function did not predict lack of response to corticosteroids. A small paediatric study of difficult asthma has shown that a single dose of IM triamcinolone reduced exacerbations and reduced FeNO,[33;34] in keeping with our findings.

In conclusion, in this large observational case series, children with DA differed from reports in adults with respect to their atopic status and gender distribution. Very few children with DA were complete corticosteroid responders, and partial response was more common. There were no predictors of non, partial or complete response to corticosteroids although the statistical power was limited due to the low numbers in the complete and non responders groups. The only predictors of response in individual parameters that could be found was that of symptomatic response being less likely if there was a history of smoke exposure in the home, BAL eosinophilia and high FEV_1 pre steroids predicting lung function response. The reasons for the rarity of complete response are unknown, but it may partly be explained by continued adverse environmental exposures, including smoke, pets, and HDM in the environment. There are very few and generally weak predictors of corticosteroid response. However, the criteria for steroid response that we used are perhaps too stringent. Certainly, criteria need to be agreed in order to catergorise and target therapy in this refractory group of children. As a result of this study, we recommend a more detailed assessment of children with difficult asthma in terms of adherence, environment and psychosocial issues prior to the performance of more invasive investigations such as bronchoscopy,

and that the steroid trial should be with triamcinolone, not prednisolone to obviate the issues of adherence. Thorough investigation of children with DA is important to allow exclusion of other diagnoses and co-morbidities which when treated may obviate the need to escalate doses of corticosteroids. Confirmation of the diagnosis of asthma is especially important in non-atopic children. Prospective trials are required in carefully phenotyped children to develop an evidence base for DA treatment.

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Legends for figures

Figure 1 Difficult Asthma Investigation Protocol. BAL, broncho-alveolar lavage; BDR, bronchodilator reversibility; EB, endobronchial biopsy; FeNO, fractional exhaled nitric oxide; FOB, fibreoptic bronchoscopy; Ig, Immunoglobulin; RAST, radioallergosorbent assay; SPT, skin prick testing.

Figure 2 Distribution of Immunoglobulin E (IgE) in children with difficult asthma and eligibility for anti-IgE therapy

Figure 3 Number of parameters with corticosteroid response for each patient, divided according to gender. Tested parameters included symptom improvement, absent bronchodilator reversibility, normal forced expiratory volume in 1 second and normal fractional exhaled nitric oxide at the end of corticosteroid trial.

Figure 4 Forced expiratory volume in 1 second (FEV_1) before and after a 2 week trial of systemic corticosteroids

Figure 5 Fractional exhaled nitric oxide (FeNO) before and after a 2 week systemic cortiosteroid trial

Figure 1

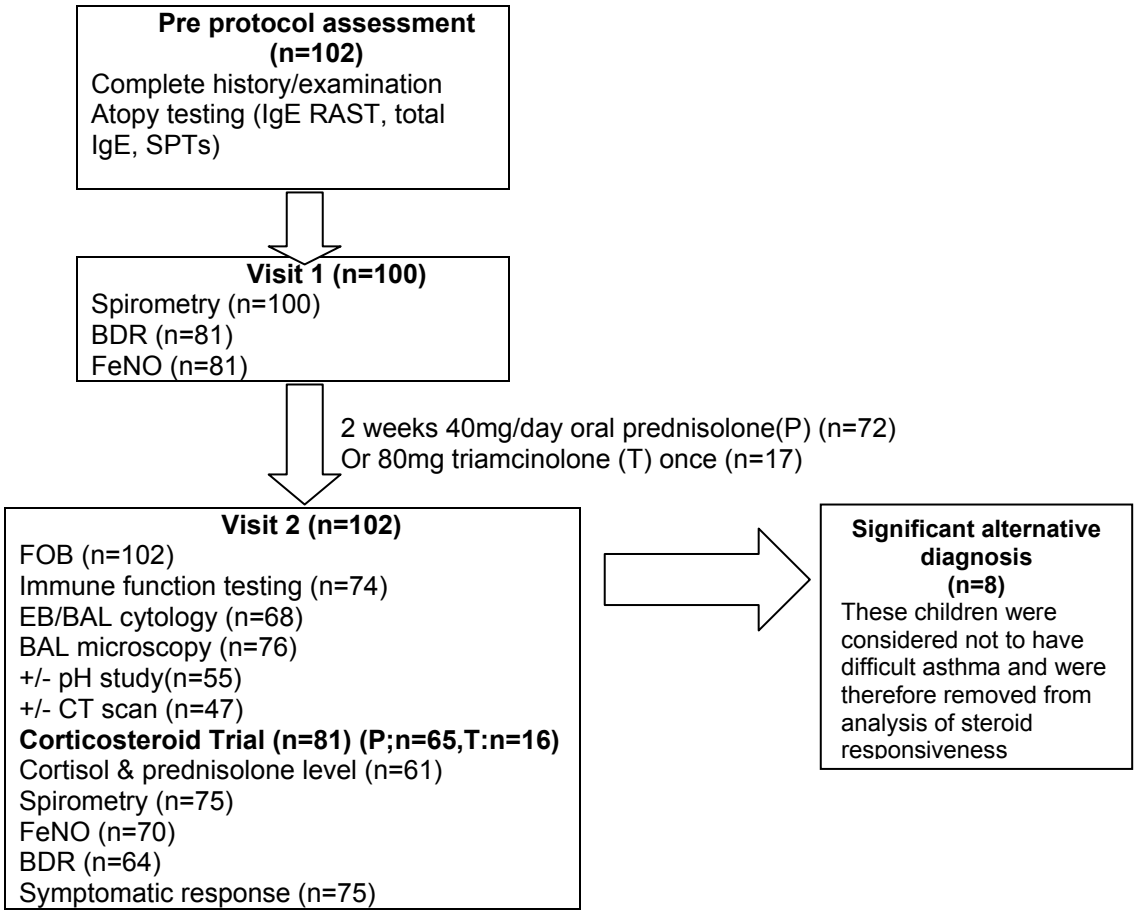
Pre protocol assessment
(n=102)
Complete history/examination
Atopy testing (IgE RAST, total IgE, SPTs)
Visit 1 (n=100)
Spirometry (n=100)
BDR (n=81)
FeNO (n=81)
2 weeks 40mg/day oral prednisolone(P) (n=72)
Or 80mg triamcinolone (T) once (n=17)
Visit 2 (n=102)
FOB (n=102)
Immune function testing (n=74)
EB/BAL cytology (n=68)
BAL microscopy (n=76)
+/- pH study(n=55)
+/- CT scan (n=47)
Corticosteroid Trial (n=81) (P;n=65,T:n=16)
Cortisol & prednisolone level (n=61)
Spirometry (n=75)
FeNO (n=70)
BDR (n=64)
Symptomatic response (n=75)
Significant alternative diagnosis
(n=8)
These children were considered not to have difficult asthma and were therefore removed from analysis of steroid responsiveness

Figure 2

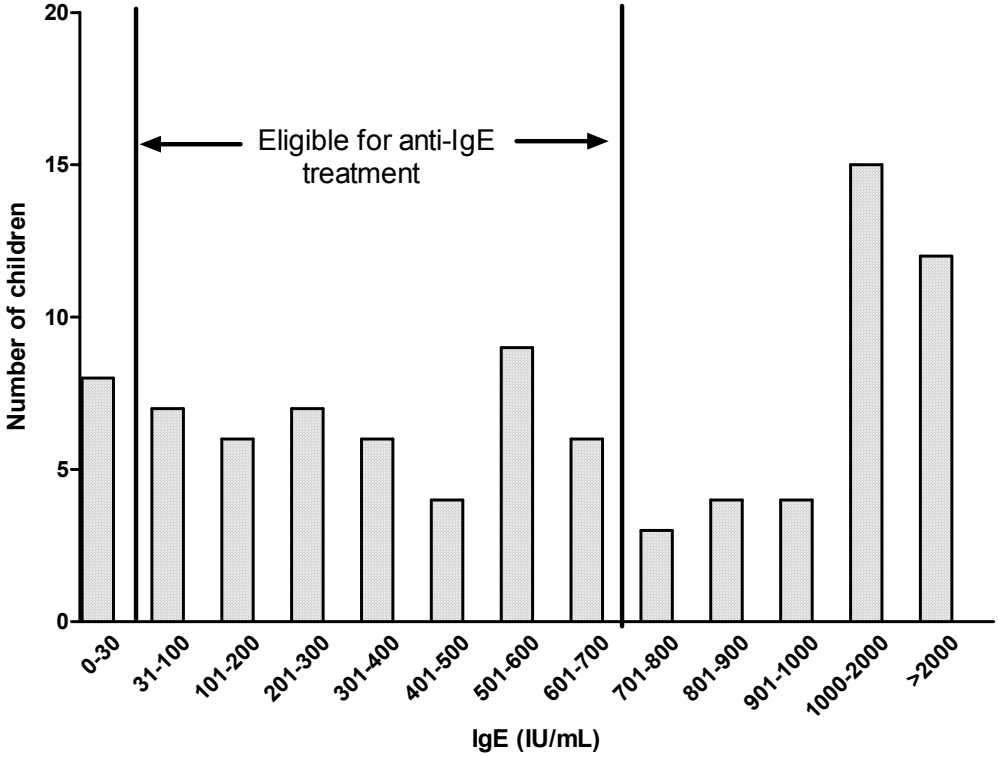
Eligible for anti-IgE treatment
Number of children
20
15
10
5
0
0-30
31-100
101-200
201-300
301-400
401-500
501-600
601-700
701-800
801-900
901-1000
1000-2000
>2000
IgE (IU/mL)

Figure 3

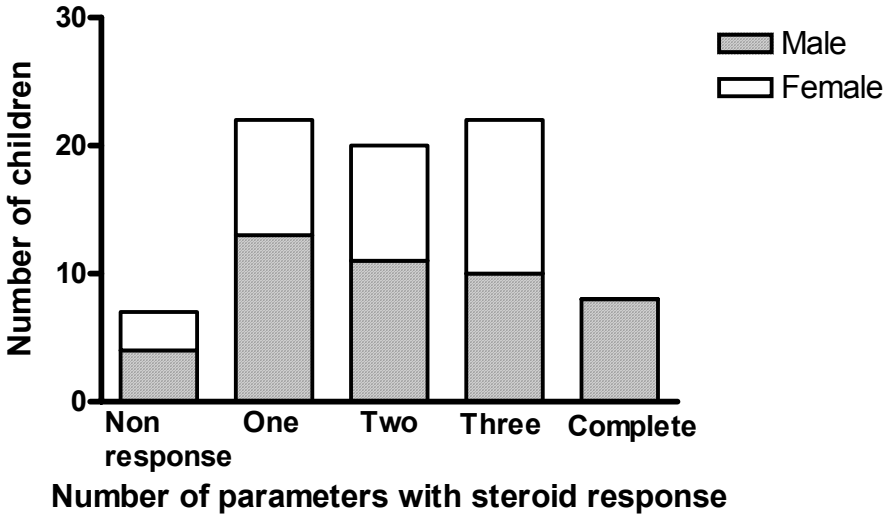
30
20
10
0
Number of children
Male
Female
Non response
One
Two
Three
Complete
Number of parameters with steroid response

Figure 4

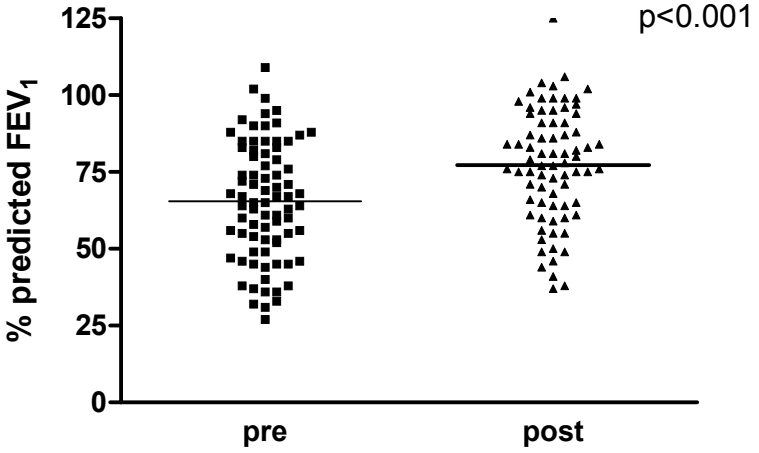

Figure 5