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Corticosteroid responsiveness and clinical characteristics in childhood difficult asthma

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ABSTRACT: This study describes the clinical characteristics and corticosteroid responsiveness of children with difficult asthma (DA). We hypothesised that complete corticosteroid responsiveness (defined as improved symptoms, normal spirometry, normal exhaled nitric oxide fraction (F_{ENO}) and no bronchodilator responsiveness (BDR <12%)) is uncommon in paediatric DA.

We report on 102 children, mean±SD age 11.6±2.8 yrs, with DA in a cross-sectional study. 89 children underwent spirometry, BDR and F_{ENO} before and after 2 weeks of systemic corticosteroids (corticosteroid response study). Bronchoscopy was performed after the corticosteroid trial.

Of the 102 patients in the cross-sectional study, 88 (86%) were atopic, 60 (59%) were male and 52 (51%) had additional or alternative diagnoses. Out of the 81 patients in the corticosteroid response study, nine (11%) were complete responders. Of the 75 patients with symptom data available, 37 (49%) responded symptomatically, which was less likely if there were smokers in the home (OR 0.31, 95% CI 0.02–0.82). Of the 75 patients with available spirometry data, 35 (46%) had normal spirometry, with associations being BAL eosinophilia (OR 5.43, 95% CI 1.13–26.07) and high baseline forced expiratory volume in 1 s (FEV_1) (OR 1.08, 95% CI 1.02–1.12). Of these 75 patients, BDR data were available in 64, of whom 36 (56%) had <12% BDR. F_{ENO} data was available in 70 patients, of whom 53 (75%) had normal F_{ENO}. Airflow limitation data was available in 75 patients, of whom 17 (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.

KEYWORDS: Corticosteroid responsiveness, difficult asthma, eosinophil, nitric oxide, paediatric asthma

Difficult asthma (DA) in children can be challenging to treat, and leads to high rates of healthcare 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 require detailed investigation [1]. Confirmation of asthma diagnosis, identification and treatment of associated diagnoses is essential. Potential reversible factors, such as 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. As in other studies [2–4], we used a protocol involving the administration of a 2-week course of high-dose systemic corticosteroids, with investigation of noninvasive markers of inflammation before and after corticosteroids, followed by bronchoscopy at the end of the corticosteroid trial (fig. 1).

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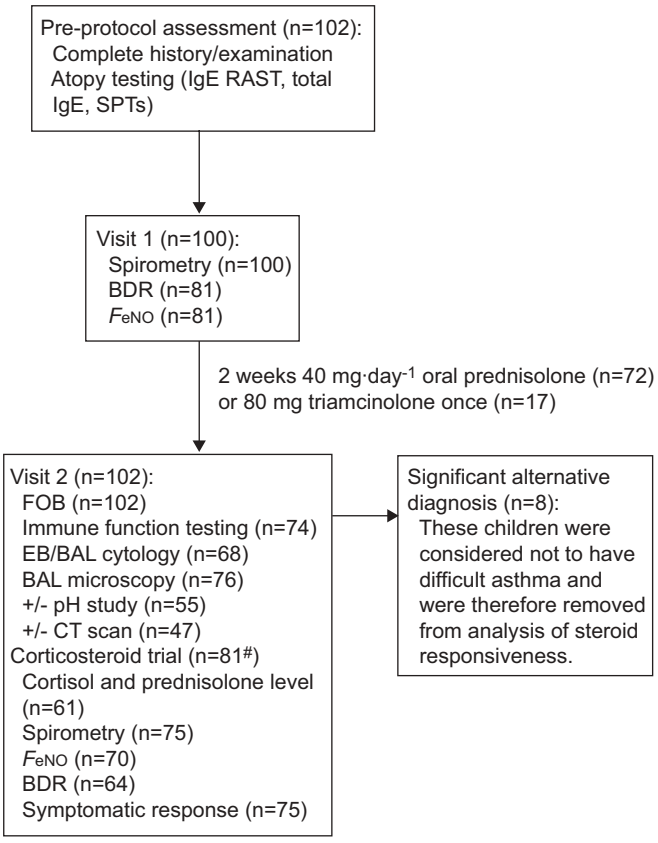

FIGURE 1. Difficult asthma investigation protocol. Ig: immunoglobulin; RAST: radioallergosorbent assay; SPT: skin prick testing; BDR: bronchodilator reversibility; *F*eNO: exhaled nitric oxide fraction; FOB: fibreoptic bronchoscopy; EB: endobronchial biopsy; BAL: bronchoalveolar lavage; CT: computed tomography. #: prednisolone n=65, triamcinolone n=16.

Patients were characterised according to their corticosteroid response and appropriate treatment alterations were 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 cases present in early adulthood, not childhood, which may be associated with a poor prognosis [8]. Severe adult asthmatics appear 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 >5 yrs, with DA who were referred to the Royal Brompton Hospital, London, UK (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 (Royal Brompton Hospital) or another secondary care facility for at least 12 months, with repeated attempts to optimise treatment. Asthma was diagnosed according to the American Thoracic Society (ATS) criteria [11]. Both of the following were required for inclusion. 1) Ongoing symptoms necessitating short-acting β_2-agonists at least three times per week, despite the prescription of high-dose ICS (>800 $\mu g \cdot day^{-1}$ of budesonide equivalent) or regular systemic corticosteroids. 2) Treatment with long-acting β_2-agonists (LABA) or a failed trial of LABA and a leukotriene receptor antagonist.

Atopy was defined as at least one positive specific immunoglobulin (Ig)E radioallergosorbent assay (RAST; $\geqslant 0.34$ $kU \cdot L^{-1}$) or at least one positive skin prick test to aeroallergens (cat, dog, house dust mite and grasses). The performance of pH, high-resolution computed tomography (HRCT) and immunological testing was at the discretion of the clinician in charge of the patient, and was not protocol driven.

Spirometry and bronchodilator reversibility

Spirometry was performed using a compact Vitallograph 2120 (Vitalograph, Buckingham, UK). Normal forced expiratory volume in 1 s (FEV_1) was defined as $\geqslant$80% predicted in accordance with European Respiratory Society/ATS guidelines [12]. Spirometry was performed before and 15 min after the administration of 1 mg salbutamol *via* a large volume spacer. Bronchodilator reversibility (BDR) was defined as a change in (FEV_1 % pred/baseline FEV_1 % pred) $\times$ 100, with $\geqslant$12% being deemed a positive test. Persistent airflow limitation (PAL) was defined as post-bronchodilator, post-corticosteroid trial FEV_1 <80% pred.

Exhaled nitric oxide fraction measurement

Exhaled nitric oxide fraction (*F*eNO) was measured according to current guidelines during the study period [13]. In total, 20% of the measurements obtained early in the study were performed using a Logan analyser (LR 2000 series; Logan research, Rochester, UK) at a flow rate of 250 $mL \cdot s^{-1}$, values of <12.5 ppb were considered normal [14]. The remainder of the measurements were made using the NIOX chemiluminescence analyser, (Aerocrine, Solna, Sweden) at a flow rate of 50 $mL \cdot s^{-1}$, and compared to normal [15]. The results were converted into z scores and categorised as ''normal'' or ''abnormal''.

Immunological abnormalities

Serum 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.

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, CA, USA) [16] and reported by a consultant radiologist.

Corticosteroid trial

The corticosteroid trial consisted of either a 2 week course of oral prednisolone (40 mg daily) or a single 80 mg dose of intramuscular 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 four parameters (symptoms, FEV_1, BDR and F_{ENO}) being normal at the end of the corticosteroid trial, partial response if at least one parameter was satisfied and nonresponse if no parameters were satisfied.

Adherence assessment

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

Oesophageal pH testing

A single channel pH probe was inserted at the time of bronchoscopy. Oesophageal pH was monitored over 18–24 h using a Synectics Digitrapper Mark III (Synectics Inc., Irving TX, USA). A positive test was defined as a pH <4 for $\geqslant$4% during the study period. Severe reflux was defined as a pH of <4 for $\geqslant$15% during the study period.

Fibreoptic bronchoscopy, bronchoalveolar lavage and endobronchial biopsy

Fibreoptic bronchoscopy (FOB) was performed under general anaesthetic at the end of the corticosteroid trial, as previously described [18, 19]. Bronchoalveolar lavage (BAL) and endobronchial biopsy (EB) were taken and processed as previously described [19]. Eosinophilia was defined as >1.19% [20] and neutrophilia as >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 (A.G. Nicholson). Inflammation was classified as eosinophilic, neutrophilic or mixed. RBM thickness was classified by a consultant histopathologist and scored as normal (0), mild (1), moderate (2) or severe (3). RBM thickness of >1 was considered to be abnormal.

Statistical analysis

Nonparametric tests were used. Numerical data was analysed using the Mann–Whitney U-test and ordinal data was analysed 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 the predictors listed in tables 1 and 2. Analysis was

TABLE 1 Demographic and clinical baseline characteristics

	Whole group	Steroid trial group
Subjects n	102	81
Atopy#	88 (86)	74 (91)
Sex M:F n#	60:42	48:33
Age yrs#	11.58±2.8 (6–19)	11.8±2.6 (6–19)
Height percentile	50 (2–99)	50 (2–99)
Age at first symptoms yrs	1.25 (0.2–10)	1.5 (0.17–10)
History of smokers at home#	37/100 (37)	31/79 (39)
History of previous intubation for asthma#	14/101 (14)	10/81 (12)
History of rhinoconjunctivitis on treatment	32/101 (31)	27/81 (33)
Positive SPT/RAST to grasses/pollen	61/87 (70)	53/72 (74)
Positive SPT/RAST to HDM present	67/95 (70)	59/77 (77)
IgE IU·mL^{-1}#	584 (2–11355)	654 (8–11355)
Pets in household	41/102 (40)	29/81 (36)
Positive specific IgE/SPT to pet if pet present	21/34 (62)	16/24 (67)
Medication		
Inhaled corticosteroid mg·day^{-1}	2 (0.4–4)	2 (0.4–4)
LABA	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)
FEV_1 % pred#	67.1±19.2	65.4±19
FEV_1 post-bronchodilator % pred	79.4±18.3	78.5±18.6
BDR % pred	18 (0–130)	19.5 (0–130)
BDR present $\geqslant$12%#	56/81 (69)	48/68 (71)
F_{ENO} raised above normal#	35/81 (43)	32/65 (49)

Data represented as n (%), mean±SD (range), median range, N/n available (%) or mean±SD, unless otherwise stated. M: male; F: female; SPT: skin prick test; RAST: radioallergosorbent assay; HDM: house dust mite; Ig: immunoglobulin; LABA: long-acting β_2-agonist; FEV_1: forced expiratory volume in 1 s; % pred: % predicted; BDR: bronchodilator reversibility; F_{ENO}: exhaled nitric oxide fraction. #: these factors were used as predictors of steroid response in multiple logistic regression.

TABLE 2 Comparison of atopic and nonatopic subjects

	All	Atopic	Nonatopic	p-value
Subjects n	102	88	14	
FEV1 at baseline % pred[#]	67.1±19.2	66.3±18	72.2±25	NS, 0.8
BDR at baseline %[#]	18 (0–130)	22 (0–130)	3.5 (0–42.5)	0.002
Children with BDR ⩾12% at baseline[#]	56/81 (69)	53/71 (75)	3/10 (30)	0.004
Baseline *F*eNO50 ppb[¶]	21.5 (5–257)	24 (5–257)	10 (6.6–20.6)	0.026
Baseline *F*eNO250 ppb	5.65 (1.2–25.9)	7.15 (1.2–25.9)	2.9 (1.8–5.7)	0.027
Baseline *F*eNO[#,+]	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[f]	41/55 (75)	31/43 (72)	10/12 (83)	NS, 0.71
Severe GER[##]	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 (11)	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%[#]	25/68 (37)	22/59 (37)	3/9 (33)	NS, 1
BAL neutrophilia >3.5%[#]	30/68 (44)	26/59 (44)	4/9 (44)	NS, 0.7
EB eosinophilia[#]	36/68 (53)	32/58 (55)	4/10 (40)	NS, 0.5
EB neutrophilia[#]	36/68 (53)	30/58 (52)	6/10 (60)	NS, 0.7
EB reticular basement membrane thickening[#]	41/56 (73)	33/50 (66)	3/7 (42)	NS, 0.08

Data represented as mean±SD, median (range) or N/n available (%), unless otherwise stated. FEV1: forced expiratory volume in 1 s; % pred: % predicted; BDR: bronchodilator reversibility; *F*eNOx: exhaled nitric oxide fraction at a flow rate of x mL·s^{-1}; GER: gastro-oesophageal reflux; HRCT: high-resolution computed tomography; ENT: ear, nose and throat; BAL: bronchoalveolar lavage; EB: endobronchial biopsy; NS: nonsignificant. [#]: these factors were used as predictors of steroid response in multiple logistic regression; [¶]: NIOX chemiluminescence analyser, (Aerocrine, Solna, Sweden) readings included only; [+]: includes NIOX and Logan analyser (LR 2000 series; Logan Research, Rochester, UK) readings; [§]: Defined as more than one serum immunological abnormality or low on repeated testing; [f]: pH <4 for >4% during the study period; [##]: pH <4 for >15% during the study period.

performed using the Statistical Package for Social Sciences (version 15; SPSS Inc., Chicago, IL, USA).

RESULTS

Cross-sectional study

Tables 1 and 2 summarise the baseline demographics. For patients prescribed oral corticosteroids, the median daily dose was 10 mg (5 mg on alternate days ranging to 40 mg·day^{-1}). The reasons for the variations in denominators are explained in figure 1. Of the 102 children studied, 60 (59%) were male. 88 (86%) children were atopic, of which 32 (36%) owned a pet and of these, 21 (65%) were sensitised to their pet. Of the 102 children studied, 99 had data on history of food allergies/triggers available, of which 24 (24%) had a history of food allergy or triggers to asthma. Of these 24 children, 11 had positive RAST to the food trigger. The mean±SD FEV1 was 67.1±19.2%. A positive BDR test was observed in 53 (75%) out of 71 atopic children compared to three (30%) out of 10 nonatopic children (p=0.004). *F*eNO was normal in 10 (91%) out of 11 nonatopic patients compared with 36 (51%) out of 70 atopic patients (p=0.02). The mean±SD *F*eNO z score was 1.78±2.1. The distribution of IgE levels is illustrated in figure 2. Of the 102 children studied, 74 underwent serum immune testing and immunological abnormalities were found in 10 (14%) of the patients (table a in the supplementary data). Nonatopic children were significantly more likely to have an abnormality compared to atopic children (p=0.036). 47 (46%) patients had an HRCT performed (table b in the supplementary data) and of these three (6%) had bronchiectasis. A pH study was completed in 55 (54%) out of 102 children, of which 41 (75%) were abnormal.

Bronchoscopy

FOB was performed in all subjects (table 2), of whom three had missing anatomical data. 76 (75%) out of 102 patients had BAL microscopy and cytology was performed in 68 (67%) out of 102 patients. Positive BAL cultures were seen in 19 (25%) out of 76 BAL microscopy patients. Of the 19 patients with positive BAL culture, BAL cytology was performed in 15, of which neutrophilia was present in 10 (67%) (table c in supplementary data). BAL cytology was performed in a total of 68 patients, of which BAL eosinophilia was present in 25 (37%) patients and neutrophilia in 30 (44%) patients, including 11 (16%) with mixed cellularity (table 2). EB could be analysed in 68 (67%) out of the 102 patients. Mucosal eosinophilia was present in 36 (53%) out of 68 patients and neutrophilia in 36 (53%) out of 68, of which 17 (47%) had mixed cellularity. Increased RBM thickening was present in 41 (73%) out of 56 children.

52 (51%) children had an additional or alternative diagnosis. This was more common in nonatopic compared to atopic subjects (10 out of 14 *versus* 42 out of 88, respectively). Eight of these children were subsequently thought not to be suffering

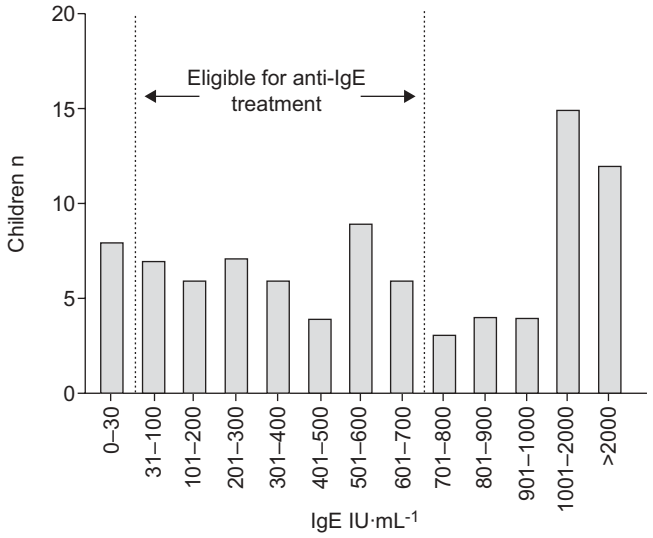

FIGURE 2. Distribution of immunoglobulin (Ig)E in children with difficult asthma and eligibility for anti-IgE therapy.

from DA, and their treatment was modified accordingly. Therefore, they were 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 and e in the supplementary data).

Corticosteroid response study

89 (87%) subjects underwent a corticosteroid trial as part of the clinical protocol. Data to assess corticosteroid response was available in 81 subjects. There was no difference between the responses of those who were and were not prescribed systemic corticosteroids (refer to supplementary data). Nine (11%) out of the 81 subjects were complete responders, 65 (80%) were partial responders and seven (9%) were nonresponders (fig. 3).

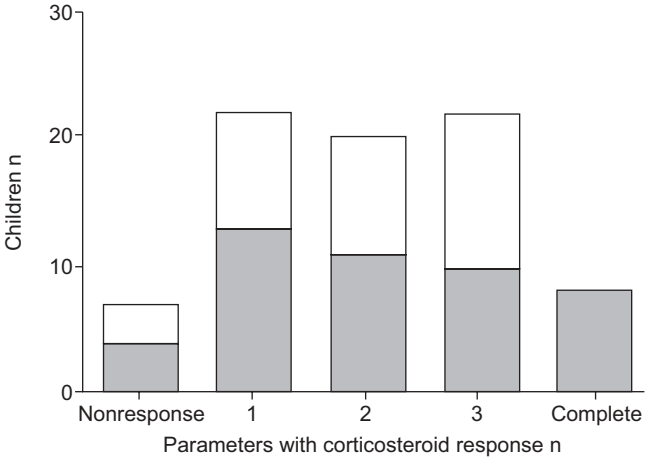

FIGURE 3. The number of parameters with corticosteroid response for each patient divided according to sex. The tested parameters included symptom improvement, absent bronchodilator reversibility, normal forced expiratory volume in 1 s and normal exhaled nitric oxide fraction at the end of corticosteroid trial. □: female; ■: male.

Of the 57 (83%) children with evidence of adequate adherence, nine (16%) were complete responders, 47 (82%) were partial responders and one (2%) was a nonresponder. All children that demonstrated complete corticosteroid response had evidence of treatment adherence compared to 48 (84%) out of 57 children who were partial or nonresponders ($p=0.14$). None of the steroid nonresponders (none out of seven) were receiving maintenance systemic steroids compared with 30 (41%) out of the 74 subjects with partial or complete responders ($p=0.03$). In a *post hoc* analysis, there was evidence that the 16 subjects given triamcinolone may have had slightly better responses compared with the 65 subjects given prednisolone (refer to supplementary data). 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 seven subjects with single and 65 subjects with multiple allergies. Although the numbers are small, children with a single allergy had a poorer BDR response after the steroid trial (refer to supplementary data). The significant predictors of response in individual parameters are shown in table 3.

Symptom response

Symptom data was available for 75 patients who underwent the corticosteroid trial, of which 37 (49%) reported an improvement in symptoms. Symptomatic response was less likely if there was a history of smokers in the home (OR 0.31, 95% CI 0.02–0.82) (table f in the supplementary data).

FEV_1 response

The FEV_1 response of the subjects before and after the 2 week corticosteroid trial is shown in figure 4 (table g in the supplementary data).

Baseline mean FEV_1 was $66.3 \pm 19.1\%$, increasing to $77.5 \pm 18\%$ after the corticosteroid trial ($p<0.001$). Spirometry data was

TABLE 3 Significant predictors of corticosteroid responsiveness from multivariate logistic regression

Predictor	OR (95% CI)	p-value
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
FEV_1 % change		
Baseline BDR	0.42 (0.05–0.80)	0.03
F_{ENO} response		
Baseline F_{ENO}	0.36 (0.18–0.72)	0.003
Persistent airflow limitation		
Baseline FEV_1	0.93 (0.90–0.97)	<0.001

All the predictors shown in table 1 were tested and those which were nonsignificant are not included in this table. FEV_1: forced expiratory volume in 1 s; BAL: bronchoalveolar lavage; BDR: bronchodilator reversibility; F_{ENO}: exhaled nitric oxide fraction.

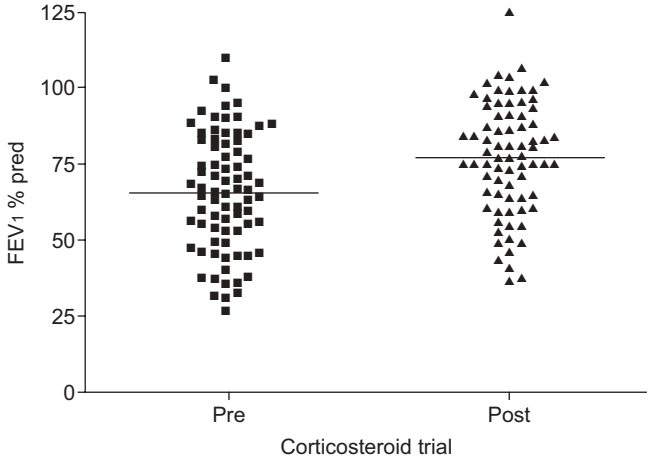

FIGURE 4. Forced expiratory volume in 1 s (FEV_1) pre and post a 2-week trial of systemic corticosteroids. % pred: % predicted. $p<0.001$.

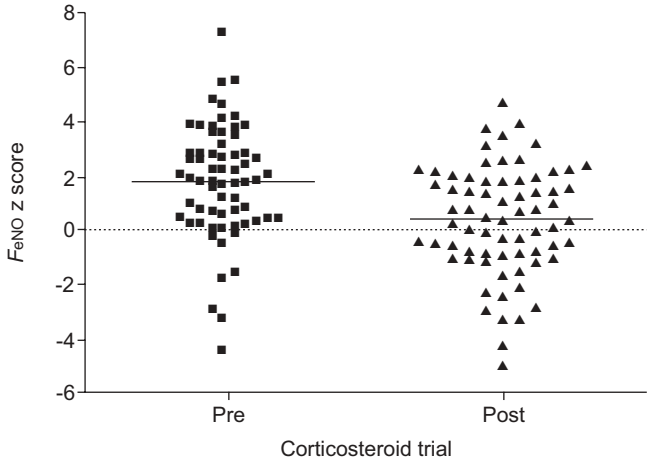

FIGURE 5. Exhaled nitric oxide fraction (F_{ENO}) pre and post a 2-week systemic cortiosteroid trial. $p<0.01$.

available for 75 patients who underwent the trial, of which 35 (47%) reported normal pre-bronchodilator FEV_1 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 (23%) out of the 75 children who underwent the trial and who had spirometry data available. PAL was associated with a low FEV_1 before the corticosteroid trial (OR 0.93, 95% CI 0.90–0.97).

BDR response

Baseline BDR was 18 (0–130) % compared with 10 (0–82) % after the trial ($p=0.001$), with no predictors of BDR of <12% following the trial (table h in the supplementary data).

F_{ENO} response

The F_{ENO} response of the subjects before and after the 2 week corticosteroid trial is shown in figure 5 (table i in the supplementary data).

The mean z scores for F_{ENO} before and after the corticosteroid trial were 1.78 ± 2.07 and 0.40 ± 1.98, respectively ($p<0.01$); low baseline F_{ENO} (OR 0.36, 95% CI 0.18–0.72) was a predictor of F_{ENO} response.

DISCUSSION

In this large observational study, which is the most detailed characterisation of DA in children in the literature to date, and which includes analyses of clinical corticosteroid responsiveness, we have shown that: 1) in contrast to a study of adults with DA, in which females predominate and atopy is less prominent in severe asthma compared to mild-to-moderate asthma [6], in children with DA, males predominate and atopy is very common; 2) many children are exposed to environmental influences (cigarette smoke) known to cause corticosteroid resistance; 3) associated diagnoses are common especially in nonatopic subjects; 4) response to a corticosteroid trial is difficult to predict, with the majority of subjects exhibiting only a partial response; and 5) BDR is common even after a corticosteroid trial even though most subjects were taking LABA. The latter may reflect noncompliance, tachyphylaxis or a genuine bronchodilator-resistant state.

The study does have a number of limitations. As this was a large observational study, some data is missing, and not all patients underwent the corticosteroid trial because, in some cases, this was not thought to be clinically appropriate. The data is based on a highly selected cohort and may not be applicable 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, intramuscular triamcinolone was introduced ensuring adherence to therapy. Due to the severity of asthma in the children evaluated, over a third of the 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 nonresponders. 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]. An adapted version of the protocol is now used which addresses these issues and includes a home visit before proceeding to the steroid trial.

We have shown that atopic patients are more likely to exhibit BDR and have higher F_{ENO} levels than nonatopic patients, although the number of nonatopic patients was small. Atopy itself causes an elevation in F_{ENO} [22]. Nonatopic 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 nonatopic children. A large proportion of all patients (atopic and nonatopic) had gastro-oesophageal reflux. We were unable to formally 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 nonatopic children. A study of adult DA patients found an incidence of alternative or additional diagnoses of 32% [24]. One lesson from our study is that at least potential comorbidities 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, and required the four measurements (symptoms, FEV_1, BDR and F_{eNO}) to become normal. 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 F_{eNO} or sputum eosinophils may be a more objective measure of steroid response [28]. We opted for a spectrum of end-points, acknowledging that this is, to some extent arbitrary, and that a true definition of corticosteroid responsiveness in children has not yet been achieved. As this study was based on our clinical protocol and clinicians are more likely to use a combination of end-points, this determined our choice. Furthermore, corticosteroid responsiveness is likely to be a spectrum, rather than an all or nothing 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. In this study, we found heterogeneity in response in symptoms and inflammation. 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 interleukin (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 following 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 suggests the need for other therapies in paediatric DA. It is noteworthy that of the 90 children in whom IgE testing was performed, only 40 (44%) would have been eligible for anti-IgE therapy under the current license (fig. 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 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 [9]. Corticosteroid response was only determined *in vitro*, in 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 a >15% increase in FEV_1, thus less stringent than ours. In 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 intramuscular triamcinolone reduced exacerbations and reduced F_{eNO} [33, 34], which is in keeping with our findings.

In conclusion, in this large observational study, children with DA differed from reports in adults with respect to their atopic status and sex distribution. Very few children with DA were complete corticosteroid responders, and partial response was more common. There were no predictors of nonresponse, partial response or complete response to corticosteroids, although the statistical power was limited due to the low numbers in the complete and nonresponders 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 prior to 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 house dust mite in the environment. There are very few and generally weak predictors of corticosteroid response. However, the criteria for steroid response that we used were perhaps too stringent. Certainly, criteria need to be agreed in order to categorise 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 comorbidities which when treated may obviate the need to escalate doses of corticosteroids. Confirmation of the diagnosis of asthma is especially important in nonatopic children. Prospective trials are required in carefully phenotyped children to develop an evidence base for DA treatment.

STATEMENT OF INTEREST

A statement of interest for D.N.R. Payne can be found at www.erj.ersjournals.com/misc/statements.dtl

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