

# The dark side of the moon: severe therapy-resistant asthma in children

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**ABSTRACT:** *The dark side of the moon: severe therapy-resistant asthma in children. F.M. de Benedictis, I. Carloni, A. Bush.*

Problematic severe asthma is the term used to describe children whose asthma is not responsive to standard therapy with high-dose inhaled corticosteroids and additional controllers. These children need to be assessed by a step-wise systematic protocol in order to confirm the diagnosis, evaluate co-morbidities, assess the adherence to treatment, and finally evaluate the basic management. More than half of these children have “difficult-to-treat asthma”, which improves if the basic management is correct. Children whose asthma remains uncontrolled despite resolution of any reversible factors are termed “severe therapy-resistant” asthmatics; for them, an individualised

treatment plan is developed after a detailed and invasive protocol of investigation. Therapeutic options for these patients can be divided into medications used in lower doses for children with less severe asthma, and those used in other pediatric diseases but not for asthma. Most treatments are unlicensed and there is a lack of high-quality evidence. Children with recurrent severe exacerbations, in particular in the context of good baseline asthma control, are particularly difficult to treat, and there is no evidence on which therapeutic option to recommend. International collaborations, using standard protocols of investigation, are needed to better understand mechanisms of severe therapy-resistant asthma and to deliver evidence-based treatments in the future.

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... and if the band you're in starts playing different tunes  
(PINK FLOYD)

## Introduction

“Problematic severe asthma” is an umbrella term which encompasses the description of children referred to specialist care with asthma not responding to standard therapy [1]. Although the majority of children with asthma respond well to low-dose inhaled corticosteroids (ICS) administered regularly with an age-appropriate device, a significant proportion still have problematic, severe disease that is not controlled with high-dose ICS and additional controller therapies, such as long-acting beta-agonist (LABA), leukotriene receptor antagonist (LTRA) and low-dose theophylline. The exact number of patients with problematic severe asthma is hard to determine, but it is probably less than 5% of all children with asthma. These children usually present with chronic symptoms of poor baseline control and/or acute exacerbations, despite the prescription of multiple drug therapies.

Patients with problematic severe asthma warrant age-appropriate assessment using a step-wise approach, in order to be placed in one of four categories [2]:

– “not asthma at all” (wrong diagnosis);

- “asthma plus” (presence of important co-morbidities);
- “difficult-to-treat asthma” (asthma which improves if the basic management – i.e. adherence to treatment, allergen and other adverse exposures, psychological issues – is properly modified);
- “severe therapy-resistant asthma” (asthma which remains uncontrolled even after the resolution of any reversible factor and optimization of the basic management).

The latter category of patients merits assessment with a detailed and invasive protocol of investigation in order to verify the pattern of inflammation, any degree of steroid responsiveness, the presence of persistent airflow limitation and the concordance between symptoms and airway inflammation, before an individualised treatment plan is assigned [3].

A significant unmet clinical need remains in this group of patients, specifically a requirement for therapies which reduce systemic steroid exposure [4]. Most treatments are not licensed, except for omalizumab. Treatment options to be considered for truly severe therapy-resistant asthmatic children do not stand upon high quality randomised trials, and the level of evidence is still poor. Data is mainly extrapolated from adults with severe asthma and children with mild to moderate asthma not controlled on ICS. Medications can be

divided into drugs used in lower doses for children with less severe asthma (conventional medications) and those used in other paediatric diseases but usually not in asthma (experimental therapies).

The aim of this article is to review the scientific evidence on the therapeutic options in children with severe therapy-resistant asthma with a particular focus on what is new since our previous report [5].

### Conventional asthma medications

Several therapeutic options may be considered for a child with truly severe, therapy-resistant asthma. A summary flow chart of recommendations for treatment is given in figure 1.

### High-dose conventional inhaled corticosteroids

There is marked variation across Europe in the definition of high-dose ICS in childhood. High-dose ICS has been arbitrarily defined as either 500 mcg/day fluticasone propionate equivalent, or 800 mcg/day beclomethasone dipropionate [5]. The level of the plateau of the dose-response curve to ICS in asthmatic children is a matter of debate [6]. Despite the fact that in many it can be as low as 200 mcg/day fluticasone [7], there is reason to believe that in some children higher than conventional doses of ICS (>800 mcg/day beclomethasone equivalent) may be beneficial and even safe. First, steroid resistance is a spectrum rather than an all-or-nothing phenomenon, and relative steroid

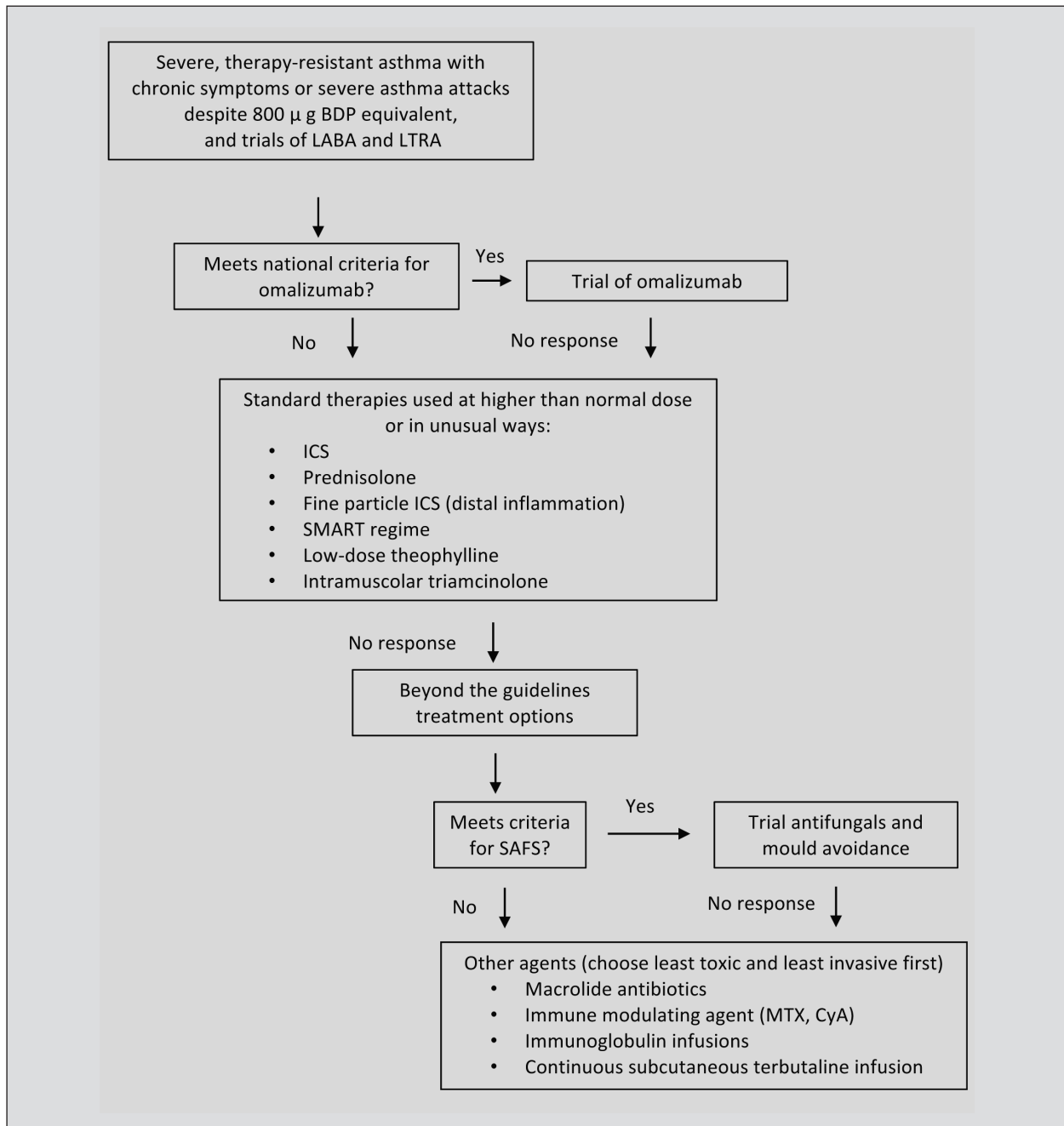


Fig. 1. - Suggested sequence for consideration of therapy for severe steroid-resistant asthma. BDP: beclomethasone dipropionate; LABA: long-acting b2-agonist; LTRA: leukotriene receptor antagonist; ICS: inhaled corticosteroids; SMART: symbicort maintenance and reliever therapy; SAFS: severe asthma with fungal sensitisation; MTX: methotrexate; CyA: cyclosporine A [Reproduction with permission from reference n. 5].

insensitivity may be overcome by higher doses [8]. Secondly, studies in adults demonstrate that high doses of ICS may be less well absorbed from the airway, thus suggesting that these doses of ICS, appropriate to degree of airway inflammation, may be safer than is thought [9].

There are few studies on high-dose ICS in severe asthma in children [10]. The evidence that higher than conventional ICS doses allows children on oral corticosteroids (OCS) to reduce the dose is anecdotal. Although firm recommendations cannot be made, in a severe asthmatic child on OCS it would nevertheless seem reasonable to try to reduce the oral intake by increasing ICS to higher than conventional doses (perhaps to as high as 2000 mcg beclomethasone equivalent per day). In case of benefit, ICS should be tapered to the lowest effective dose; in case of no response, ICS should be reduced to the daily dose prescribed prior to the increase. In any case, the use of high-dose ICS should only occur under the careful supervision of a specialist, in order to closely monitor potential side effects.

#### **Oral corticosteroids**

This therapy is usually considered the next step for treatment of children whose asthma has not been controlled by a combination of ICS, LABA and LTRA. There is insufficient evidence in the literature to recommend the starting dose, the frequency of administration (daily or alternate day), the trial duration, and how quickly to taper OCS once control has been achieved. A reasonable starting dose might be 0,5 mg/Kg daily of prednisolone administered for 2 weeks. If there is no significant benefit, medication should be stopped quickly; if there is a response, the dose should be slowly tapered to the lowest dose able to control symptoms. In this context, alternate day treatment should be initiated as soon as possible. OCS treatment, irrespective of continuous or intermittent administration, is associated with an increased risk of adrenal insufficiency, growth retardation, cataract and bone fractures [11, 12]. On this background, it is mandatory that children on regular OCS therapy are strictly monitored by specialists for potentially severe side effects [13].

#### **Anti-immunoglobulin E antibody**

Omalizumab (Xolair®; Genentech, San Francisco, CA, USA), a humanized monoclonal antibody against immunoglobulin (Ig)-E, has been successfully administered as an add-on therapy in children with severe therapy-resistant asthma who meet the following criteria: *i*) ongoing chronic symptoms or severe exacerbations despite high-dose medication, or adequate control of asthma only at the cost unacceptable side-effects; *ii*) known IgE-mediated sensitisation to one or more aero-allergens; and *iii*) every reasonable effort has been made to reduce the environmental allergen burden. The upper limit of total serum IgE recommended for therapy in children has just been raised to 1,500 I.U. Despite this, substantial numbers of children will have higher levels, and whether they will benefit from therapy is still unknown.

In long-term trials in school-age children and adolescents with moderate-to-severe asthma, omalizumab administered subcutaneously was effective in significantly reducing the ICS dose and the number of exacerbations, and improving asthma symptoms and the quality of life [14-18]. Omalizumab was safe and well tolerated [16-18], but the long-term safety and efficacy of the drug has yet to be determined [19]. A recent 6-year pragmatic review showed that asthma control improved with omalizumab over time [20], thus supporting the usefulness of adding omalizumab to long-term management of patients with severe therapy-resistant asthma [21, 22]. In keeping with the known effect on airway eosinophilia in adults [23], a fall in exhaled nitric oxide fraction (FENO) was observed in a paediatric study [24]. In a post hoc analysis of patients who had an increased blood eosinophil count (>2%) and an increased level of exhaled nitric oxide (>20 ppb), those receiving omalizumab had rates of reduction in exacerbations that were significantly greater than those in patients who were treated according to standard guidelines [25]. Additional research is needed to determine whether such markers constitute a true response phenotype for omalizumab therapy [26].

Omalizumab should be tried in children who have poor asthma control and/or exacerbations in spite of daily or alternate day OCS treatment or therapy with high-dose ICS or with ICS plus LABA and/or LTRA. Currently, there are no tests which can currently be recommended in order to predict who will respond to omalizumab. Omalizumab has the inconvenience of subcutaneous administration, the need for observation of the patient after each injection for risk of anaphylaxis (0,1%), and elevated costs. Cost-benefit analysis suggests a fiscal saving if omalizumab is given to children with five or more admissions, cumulatively 20 days or more in hospital per year [27]. In children fulfilling the criteria, omalizumab should always precede trials with other steroid sparing agents.

#### **Treatment of distal airway inflammation**

Early studies with transbronchial biopsy found that distal airway inflammation was a distinctive feature of some adult asthmatics, especially those with nocturnal asthma [28-30]. Due to the risk of transbronchial biopsy in children it cannot be performed in this context, but distal airway inflammation may be investigated by partitioning FENO into proximal ( $J_{NO}$ ) and distal ( $C_{ALV}$ ) fractions by measuring FENO production at multiple flow rates [31, 32].

The relationship between FENO and eosinophilic inflammation is particularly loose in children with severe therapy-resistant asthma on high-dose ICS or OCS [33-35]. It is not clear whether distal inflammation is an intrinsic part of severe therapy-resistant asthma or reflects poor distal airway deposition of conventional ICS. There are two possible approaches to targeting the distal airways, either using OCS and relying on airway perfusion, or using small particle ICS such as  $Q_{VAR}^{TM}$  or ciclesonide [36, 37] to

ameliorate distal airway deposition. Even though the role of distal airway inflammation is still contentious, in a child with severe therapy-resistant asthma, who has evidence of distal airway disease (elevated  $C_{ALV}$ , air trapping on a high resolution CT scan or abnormal lung clearance index), a trial of at least three months of fine particle ICS or oral prednisolone should be considered.

### ***The Symbicort Maintenance and Reliever Therapy regime***

This therapy regimen relies on the use of a single inhaler for budesonide and formoterol as regular therapy and for exacerbations (Symbicort Maintenance and Reliever Therapy, SMART regime). It has mainly been studied in adults with severe uncontrolled asthma and exacerbations in spite of regular ICS or ICS/LABA combination treatment [38]. In school-age children with asthma uncontrolled on ICS, use of budesonide/formoterol 80/4.5 mcg combination once daily for maintenance plus additional inhalations of the same combination for symptom relief substantially reduced the frequency of asthma exacerbations, but had no significant effects on hospitalizations, asthma control days, need for rescue treatment and symptom free-days, when compared to identical dose of budesonide/formoterol for maintenance plus terbutaline for rescue, or fourfold-higher maintenance dose of budesonide (320 mcg once daily) plus terbutaline for rescue [39]. As far as safety is concerned, the optimal SMART daily dose for children with severe asthma has not been studied.

SMART approach is a promising strategy for paediatric asthma management, but needs to be confirmed in future studies [40]. It is worth considering especially in children with severe, therapy-resistant asthma with severe exacerbations as a major concern. A very simple regime such as SMART may be useful in poorly adherent asthmatics, but again further trials are needed to confirm this.

### ***Low-dose theophylline***

Theophylline has been rediscovered as a potentially beneficial agent in asthma [41]. Low-dose theophylline, aiming at blood levels below the conventional therapeutic range (5-10 instead of 10-20 mol/L) has a number of immunomodulatory properties. Theophylline has been proved to inhibit the late phase response to aeroallergen challenge [42], accelerate neutrophil apoptosis [43], prevent down-regulation of the  $\beta$ -receptor by  $\beta$ -2 agonists [44], and down-regulate inflammatory gene expression *via* effects on histone acetylases (HATs) and histone deacetylases (HDACs) [45]. Both these proteins are abnormal in asthma, and this is reversed by glucocorticoids as well as theophylline, leading to a reduction in many inflammatory proteins. Clinical effects of adding theophylline to ICS have been generally small, both in adults [46] and in children [47].

Since asthmatic children may react differently from adults, a therapeutic attempt with low-dose

theophylline for some months should be tried in individual children with severe therapy-resistant asthma, especially in those with predominant neutrophilic airway inflammation. However, these are very rare.

### ***Intramuscular triamcinolone***

Depot triamcinolone has the same class effects as prednisolone, with the additional risk of subcutaneous atrophy at the injection site, but may be better in the control of asthma because adherence to treatment ceases to be an issue if the injections are given [48]. A single dose of triamcinolone has been suggested to be used as a therapeutic trial of steroid resistance [3]. Since acquired steroid resistance is a spectrum, it could be argued that multiple injections of triamcinolone may be more appropriate than a single dose. Two small paediatric studies suggest that triamcinolone may improve symptoms and reduce airway inflammation in children with severe asthma [49, 50].

The exact place of depot triamcinolone as a treatment for severe therapy-resistant paediatric asthma is not clear. It would seem reasonable to offer a trial for a finite period to those children in whom poor adherence to OCS is suspected.

## **Experimental therapies**

Due to the severe side-effects of OCS when administered over long periods at high doses, many drugs have been assessed in the search for a possible corticosteroid-sparing agent [51]. At present, there are no agreed guidelines on the selection of suitable patients and on the order in which these therapies should be tried. However, it would seem irrational to give more and more powerful anti-inflammatory medications to symptomatic children in whom no evidence of inflammation can be detected (discordant phenotype). Irrespective of the therapy chosen, the use of any of the following drugs should be preceded by open discussion with the child and family to achieve awareness of safety aspects and monitoring. The characteristics of the studies with experimental drugs used in adults and children with severe asthma are shown in table 1.

### ***Macrolide antibiotics***

Macrolides have proven immunomodulatory activities in addition to their antibacterial effects [52, 53]. In adults, macrolides have been shown to reduce neutrophilic inflammation [54], bronchial responsiveness [55] and airway oedema [56], and to increase the steroid responsiveness of peripheral blood lymphocytes [57]. Some of these anti-inflammatory effects have been demonstrated also in children [58-60]. Macrolides have been formerly used with variable results in diseases where neutrophilic inflammation is predominant, such as diffuse panbronchiolitis [61, 62], cystic fibrosis [63-65] and non-cystic fibrosis bronchiectasis [66, 67]. Macrolides have the advantage of probably being the safest 'add-on' therapy.

Troleandomycin was initially proposed as a steroid-sparing agent in adults [68-70] and chil-



Table 1. - Characteristics of the studies conducted with experimental drugs in asthma

Medication	Population	Study	N° patients	Effect
Macrolides	adults	DB RPC	n=657	lung function improvement, <sup>78,79</sup> clinical improvement, <sup>79,80</sup> no efficacy <sup>81</sup>
	children	DB RPC	n=55	no efficacy <sup>82</sup>
Cyclosporin	adults	RPC	n=106	steroid sparing <sup>89</sup>
	children	CR	n=5	steroid sparing <sup>90</sup>
Methotrexate	adults	RPC	n=185	steroid sparing, no lung function improvement <sup>92</sup>
	children	CR	n=20	steroid sparing; <sup>93,94,95</sup> clinical improvement; <sup>93</sup> pulmonary function improvement <sup>94</sup>
Azathioprine	adults	RPC	n=23	no efficacy <sup>96</sup>
	children	/	/	/
Gold salts	adults	DB RPC	n=376	steroid sparing (small effect) <sup>97</sup>
	children	/	/	/
Immunoglobulins	adults	/	/	/
	mixed	DB RPC	n=78	steroid sparing, <sup>98</sup> no efficacy, <sup>99</sup> severe side effects <sup>99</sup>
	children	OL; DB RPC	n=30; n=31	steroid sparing, <sup>100,101,102</sup> pulmonary function improvement; <sup>100</sup> no efficacy <sup>103</sup>
Antifungal agents	adults	DB RPC	n=58	quality of life improvement <sup>110</sup>
	children	CR	n=1	clinical improvement <sup>111</sup>
Subcutaneous terbutaline	adults	CR	n=31	steroid sparing, reduced hospital admission, pulmonary function improvement <sup>113,114</sup>
	children	CR	n=19	steroid sparing, clinical improvement <sup>115,116</sup>

DB: double blind; RPC: randomised placebo controlled; OL: open label; CR: case report.

dren [71] with severe asthma, but it is no longer recommended for asthma treatment [72]. Indeed, a randomised controlled trial showed that benefits on asthma control were related to the reduction of steroid catabolism [73], mainly methyl prednisolone, with an increase in side-effects in face of an apparently reassuring dose reduction [74-76]. It is likely that any macrolides may increase the half-life of corticosteroids [77].

The possible role of atypical respiratory infections in asthma was another factor which led to explorations of the potential effects of macrolides in asthmatics. Clarithromycin [78], roxithromycin [79] and telithromycin [80] have been studied with promising results in asthmatic adults with respiratory infection due to *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*. A recent trial in adults with asthma suboptimally controlled by low-dose inhaled corticosteroids showed that adding clarithromycin to fluticasone did not further improve asthma control, although there was an improvement in airway hyperresponsiveness [81]. Azithromycin and montelukast were also compared as add-on therapies for children symptomatic despite ICS and LABA, but only a minority of referred children could be randomised, because most of the rest either did not have asthma at all, or were not taking their treatment [82]. Despite intrinsic limitations of this study, the authors consid-

ered that even if the recruitment target had been met, a benefit would have been unlikely. The difficulty in recruitment underscores the fact that many so-called severe asthmatics merely need to get the basics right. A recent open-label study in asthmatic children presenting with an acute exacerbation showed that a 3-week course of clarithromycin in addition to regular treatment was associated with an increase in the number of symptom-free days, reduction in the number of days with loss of control, and decrease in the duration of the initial asthma exacerbation [83]. The results of previous studies with macrolides in asthma are encouraging, but prospective controlled trials in patients with severe asthma are needed to confirm initial observations of efficacy [84].

The recent finding of a rich bacterial flora in the lower airways [85] and the association of airway microbiota with the degree of airway hyperresponsiveness among patients with suboptimally controlled asthma [86] suggest that the antibacterial role of macrolides could overweight the immunological effects, or at least should be used cautiously. This also supports the need for further studies to examine the potential contribution of airway microbiota in asthma pathogenesis.

As macrolides are safer than cytotoxic agents, it seems reasonable to propose using a therapeutic trial of macrolide antibiotics particularly in chil-

dren with severe therapy-resistant asthma who have predominantly neutrophilic airway inflammation. Possible side effects of macrolide treatment should be taken into account, the most important of these being gastrointestinal upset. Development of macrolide resistance among respiratory pathogens is very common during long-term macrolide treatment [87], and we caution about inducing macrolide resistance with this approach [88].

### **Cyclosporin**

There are three trials of cyclosporin in adults with steroid-dependent asthma [89] and the results are questionable. Paediatric data is anecdotal [90]. A trial of cyclosporine could be considered in children with persistent eosinophilic airway inflammation despite OCS therapy or requirement of unacceptable high levels of OCS to control asthma. Whether in the future nebulized cyclosporine may be beneficial with fewer side-effects is an important unanswered question [91].

### **Cytotoxics**

Methotrexate and azathioprine have been used in severe corticosteroid-dependent asthma.

#### *Methotrexate*

Studies in asthmatic adults showed a small benefit in reducing the OCS dose, but the appearance of significant side-effects [92]. Side-effects were uncommon in three pilot trials performed in children with steroid-dependent asthma [93-95], thus suggesting a trial of methotrexate should be considered in children with steroid-resistant airway inflammation and in those requiring high-dose OCS to maintain control of asthma.

#### *Azathioprine*

Data on azathioprine in asthma is extremely poor and limited to adults [96]. There is therefore no evidence for recommending such treatment in children with asthma.

### **Gold salts**

Studies in asthmatic adults are limited and the results of limited clinical significance [97]. Given the lack of published paediatric data and the risk of serious adverse events, this therapy cannot be recommended in children with severe therapy-resistant asthma.

### **Immunoglobulins**

Both observational and randomized trials have been conducted with intravenous immunoglobulins in adults [98, 99] and children [100-103] with severe asthma with conflicting results. Doses and frequency of administration of immunoglobulins have been variable. Given the lack of adequately powered paediatric studies and standardised treatment, a trial with intravenous immunoglobulins should probably be confined to asthmatic children who are OCS dependent. The safety profile is better than with methotrexate, although the fiscal cost, and inconvenience to the patients, is not small.

### **Anti-fungal therapy**

The concept of severe asthma with fungal sensitisation (SAFS) is becoming established [104]. There is considerable evidence that fungal sensitisation and exposure are associated with increased morbidity and severity of asthma [105-107]. If a diagnosis of SAFS is suspected, sensitisation should be tested both with skin prick tests (SPT) and specific Radioallergen Absorbent Tests (RAST), since concordance between the two tests is highly variable [108, 109]. SAFS is diagnosed in a patient of any age with evidence of sensitisation on either SPT or RAST to at least one fungus (table 2). The scientific evidence is limited to a double-blind, placebo-controlled clinical trial in adults [110] and a single case report in children [111].

Children with possible SAFS, who are not controlled after eliminating as far as possible any moulds in the environment, may be candidates for a trial of oral itraconazole or even voriconazole if symptoms persist. The interaction between ICS and itraconazole leading to Cushing's syndrome should be kept in mind [112].

### **Subcutaneous terbutaline infusion**

Continuous subcutaneous terbutaline infusion (CSTI) is hypothesised to stimulate a discrete set of  $\beta$ -receptors not accessible by the inhaled route. There is limited literature in adults [113, 114] and children [115, 116]. No randomized controlled trials exist for the use of CSTI, which therefore remains off-license for the treatment of asthma. A recent review found that CSTI led to improved outcomes in approximately 75% of patients, which included rises in lowest daily peak expiratory flow rate, diminution in diurnal variation, reduction in other medication requirements, and subjective opinion of symptoms [117].

It may be reasonable to trial this regimen in selected children in whom airway inflammation has been clearly demonstrated and in whom there is a marked peak flow variability despite high-dose ICS and concomitant therapy with additional drugs. Treatment should be commenced under close supervision, using a double-blind protocol. Placebo effect is high and the benefits of a favourable hospital environment cannot be excluded, so we are now using an out-patient protocol with eight clinic visits over a four week period. Additional problems may be due to local reactions [118], risk of hypokalaemia [119] and

Table 2. - Fungi implicated in SAFS

<i>Aspergillus fumigatus</i>
<i>Alternaria alternate</i>
<i>Cladosporium herbarum</i>
<i>Penicillium chrysogenum</i>
<i>Candida albicans</i>
<i>Trichophyton mentagrophytes</i>
<i>Botrytis cinerea</i>

skeletal myositis with elevation of creatine kinase [120].

### Treatment of the exacerbating phenotype

There is evidence that poor baseline control and exacerbations may overlap, but are not the same [121]. The first is characterised by chronic symptoms of airway obstruction and marked diurnal variability of the peak flow despite high-dose ICS and other controllers; the latter are usually virally mediated and are characterized by a steep decline in peak flow without increased diurnal variability. Persistently poor baseline control and previous severe exacerbations are both predictive of future acute exacerbations [122-125]. However, good baseline control does not prevent the child having exacerbations, and no study has succeeded in completely abolishing exacerbations by any strategy [126].

There is a clear interaction between viral respiratory infections and allergens in asthma. One study showed that the combination of viral upper respiratory tract infection, allergen sensitisation, and high level of allergen exposure in the child's home was strongly predictive of an exacerbation severe enough to merit admission to hospital [127]. Although no study has convincingly shown that reducing allergen burden reduces exacerbations in children with severe, therapy-resistant asthma, such an approach, described in more detail elsewhere [128], would seem reasonable.

Management should include every effort to identify allergic triggers and minimise allergen exposure, and to optimise asthma control and lung function with lowest possible dose of ICS, in order to reduce airway inflammation in between exacerbations. Low-dose ICS are able to reduce the risk of exacerbations in children with mild-to-moderate asthma [124, 125]. There is some evidence that the use of oral LTRA [129], or very high dose ICS [130, 131], at the time of exacerbation, may reduce the need for OCS in exacerbations. There is no study exploring the effects of high-dose ICS and LTRA together, but this combination could be considered, if appropriate. There is no evidence that the use of ever-increasing doses of ICS between exacerbations in children with good baseline control is effective. There is also no evidence suggesting that, in the child with repeated exacerbations mandating oral prednisolone bursts, the prescription of daily or alternate low-dose OCS will prevent these exacerbations. These strategies are therefore not recommended.

Finally, the rare child who has catastrophic drops in lung function over a few minutes on the background of apparent excellent control (Type 2 brittle asthma) may on an anecdotal basis benefit from being given injectable adrenaline (for example, Epipen™) for emergency treatment of these deteriorations, enabling very rapid administration of a sympathomimetic ( $\alpha$  and  $\beta$ ) intramuscularly, while more selective inhaled treatment is being prepared. Food allergy is common in this group

and should be actively sought as part of the treatment programme [132, 133].

### Monitoring therapy

In the context of adult and less severe paediatric asthma, the use of FENO has not been shown to improve daily asthma control or reduce the daily dose of ICS [134]. However, some trials using tools such as induced sputum or bronchial responsiveness to monitor asthma suggested that using inflammometry may lead to better control without the need for bigger ICS doses [135, 136]. From adult data, it would appear that the greatest benefit of inflammometry is in those with more severe disease [137]. In children, FENO has been used to predict successful reduction in ICS dose [138] and relapse after stopping ICS altogether [139]. The only study which has tested this in children with severe, therapy-resistant asthma showed only trends in benefit for inflammometry [140]. One problem may be that sputum phenotypes in children may be less stable than in adults [141]. A recent study in school age children with asthma showed that both exhaled breath condensate IL-5 level and asthma control score were significant predictors of asthma exacerbation, thus opening up the possibility of assessing the potential of such parameters to titrate asthma treatment in future studies [142]. More work is needed to determine how best to monitor treatment to minimise side-effects and maximise benefits in this challenging group of patients.

### Conclusions and future directions

There is a limited evidence for the various treatment options for children with severe, therapy resistant asthma. Therefore, before employing any of them, every effort must be made to confirm the diagnosis, and to ensure that the basic management is right. Several subtypes of severe asthma are now recognized [143,144], and in the future it will be necessary to find biomarkers that may predict responses to specific, individualised therapies [145]. It will be also important to ensure that children are part of clinical trials in severe, therapy-resistant asthma, allowing new promising therapies, such as new anti-cholinergic agents [146], anti-IL5 [147, 148], anti-IL13 [149], and even bronchial thermoplasty [150, 151] to be trialled in suitable children. In this context, the need for international collaboration with standard assessments of the children across Europe, is strongly warranted [152, 153].

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