

Unmet needs in the treatment of asthmatic children and adolescents: 1

J. O. WARNER

School of Medicine, Allergy & Inflammation Sciences Division, Southampton General Hospital, UK

Summary

The paediatric asthma guidelines have been successful in providing a uniform approach to the management of asthma for the medical profession as a whole. Unfortunately, the guidelines were generated without input from patients themselves and consequently do not consider issues that are important to patients such as a preference for oral treatment. Asthma is a heterogeneous group of conditions and the guidelines do not sufficiently define subgroups of patients and their particular needs. As a result, there has been a tendency to assume that all wheezing in infancy is asthma and this had led to gross overtreatment in certain patients. In contrast, severe asthma often remains underdiagnosed and undertreated. The most recent revision of the guidelines has classified asthma in terms of the patterns of disease; infrequent episodic, frequent episodic and chronic persistent. The treatment required for each of these groups is clearly defined and there is no need for stepwise therapy. Other changes to the guidelines will occur and are needed. None of the treatments available can modify the natural history of asthma; they control the symptoms not the disease process. Evidence from bronchial biopsies suggests that both inflammation and remodelling occur early, even before the first symptoms appear. We need to look for the factors in early life that predict which children will go on to develop asthma and intervene at that stage. Anti-histamines and leukotriene receptor antagonists may be interesting as interventions in that respect. Two important unresolved issues are to understand what drives remodelling and inflammation, and to look at early life origins of asthma. These approaches may provide effective therapeutic targets and, ultimately, a means of prevention.

Keywords: asthma, children, guidelines, treatment, inflammation, remodelling, early life

Asthma guidelines: how successful have they been?

Initially, when the first guidelines meeting was held, experts managing children with asthma had no uniformity of approach. If they could not agree about management, then it would be impossible to get the message through to general practitioners or patients and their families. The most important achievement of the first set guidelines was to bring experts together and persuade them that it was important to agree on basic strategy. Subsequently, the guidelines have involved primary care physicians who now feel ownership of the management strategy. Therefore, for the medical profession and for other professionals, e.g. nurses, who have become involved, there is uniformity of approach.

Where the guidelines have totally failed is in delivering that message to patients and their families. This may be partly due to the fact that patients were not involved in the generation of the guidelines. Physicians suggested what they thought patients needed rather than listened to what patients wanted. We must include older children who are able to express themselves about what they feel is appropriate to do and, more importantly, what they will not do. Often, this focuses on not using an inhaler, especially at school in front of other children. There are various issues involved and we need to understand them better. This should involve qualitative research to understand what people want. I suspect that one of the first things patients would tell us is that they do not like inhalers. A simple tablet or syrup that is going to work as effectively would be preferable. Whatever we might believe about the intrinsic safety of using inhalers rather than prescribing something

Correspondence: Professor J. O. Warner, Allergy & Inflammation Services Division, School of Medicine, Southampton General Hospital, Tremona Road, Southampton SO16 6YD.

that is absorbed and systemically active, patients prefer oral therapy and recent studies have shown this quite clearly [1]. We have to accept this and work with it.

Guidelines have tended to group all conditions together as if they are one uniform disease. However, asthma is a heterogeneous group of problems and we have not been sufficiently careful at defining subgroups and their particular needs. In particular, infancy is one area where the guidelines are weak. There is a tendency to assume that all wheezing in infancy is asthma and should be treated as such. That is clearly wrong. Some 80% of infant coughers and wheezers do not go on to develop established asthma. Instead, they have a different problem that is usually related to the geometry of the airways, often associated with maternal smoking or premature delivery. These conditions have very different outcomes and should not be treated as asthma. As a consequence of adherence to guidelines, some childhood studies show infrequent episodic wheezing (often non-atopic asthma) is being grossly overtreated [2,3,4]. On the other hand, some cases of more severe asthma are still being underdiagnosed and undertreated [5].

Are the categories 'mild', 'moderate' and 'severe' most appropriate?

In the third revision of the paediatric guidelines, the terms 'mild', 'moderate' and 'severe' asthma have been discarded. Instead, the different patterns of disease are defined. This includes infrequent episodic asthma that occurs less frequently than once a month with totally normal lung function between episodes. This sort of asthma does not need prophylaxis and there are no implications in terms of long-term outcome with or without treatment. Therefore symptomatic relief treatment is all that is required. Frequent episodic asthma occurs up to once a week but still with virtually normal lung function between episodes. This can be treated with mild prophylactics, such as cromones, low-dose inhaled steroids or, perhaps in the future, leukotriene receptor antagonists. In chronic persistent asthma where lung function is abnormal between episodes, inhaled steroids are mandatory. This classification system covers about 85–90% of childhood asthma. The rest are patients with difficult asthma and includes children with chronic severe brittle asthma and those explosive infant asthmatics who have normal lung function for long periods of time and then have very severe acute attacks. None of the currently available treatments is particularly effective in the latter group of patients.

For the majority of patients, it is possible to define what treatment is required and there is less need to step-down or step-up therapy other than perhaps to titrate the dose of inhaled corticosteroid in chronic persistent asthma. For the majority of patients, it is possible to predict accurately

therapeutic requirements and go directly to the appropriate prescription without going through a step-up or step-down process.

How else should we change the guidelines?

The problem is that when people have looked at the guidelines, they have interpreted every component of the guidelines as having equal weight. That is the fault of the people who wrote the guidelines. They should identify where information is reasonably well established as the result of well-controlled trials and meta-analysis, and areas where there are no data and it is merely the opinion of experts. This would avoid the problem of administrators imposing an inappropriate standard of care on clinicians due to misinterpretation of guidelines.

Have we got the best treatment strategy?

The most important point is that no treatment has been shown to modify the natural history of asthma. Treatment can improve symptoms and quality of life, but it does not change whether the patients will continue to have mild, moderate or severe disease. The degree of lung function abnormality and the degree of bronchial hyperresponsiveness at the time of first presentation are all that will predict outcome of childhood asthma through to adulthood. This suggests that the whole pathology is established very early. So, we can control the symptoms but not the disease process. A fundamental basic intervention that is going to switch off the process is the answer, but this has yet to be discovered.

Is intervention in remodelling the answer?

Remodelling, like airway inflammation and eosinophilic bronchitis are events that occur in asthma. However, there is some other fundamental process that is driving both. Inflammation does not cause remodelling or vice versa and they both occur very early in the disease process. There is evidence from bronchial biopsy studies that components of remodelling are present even before the first symptoms appear. This is because to begin to manifest airway abnormalities, there must be fairly extensive abnormalities present in the small airways. Therefore, it will have been building up for some months or years before the patients present with their first symptoms and it is too late for any intervention to have much impact. From my perspective as a paediatrician, I am looking for interventions before the first symptoms. If we can predict which children are going to develop asthma then we can treat them with something that may prevent the process producing both inflammation and remodelling.

Screening for at risk individuals?

Factors in the first year of life that predict a high probability of a child developing asthma must be examined, and then an intervention can be made at this stage. Some possible interventions already exist. Two trials of antihistamines given to babies with atopic eczema have shown a reduction in subsequent asthma [6,7]. These antihistamines have an effect on eosinophil trafficking. They are not very useful for established asthma, but they certainly seem to prevent a process building up in the first place. The leukotriene receptor antagonists are equally interesting in that respect and clearly have effects on some inflammatory processes. Therefore, as drugs are already available, the patients must be identified and the appropriate clinical trials performed.

Unresolved issues

It is important to try and understand the remodelling and inflammation process. The notion that inflammation somehow switches on the remodelling process should be avoided and we must consider instead a basic abnormality that drives both and examine this. Is it an abnormality in the epithelium or something else? This is where we need to focus and where I think the best ideas for effective therapeutic targets will emerge.

Secondly, the early life origins of asthma need to be studied. I believe that we ought to be able to identify the pre-symptomatic asthmatic and be able to 'switch things off' before they have started. This has to be the fundamental approach. Prevention is far better than attempts to treat established disease.

References

- 1 Kelloway JS, Wyatt RA, Adlis SA. Comparison of patients' compliance with prescribed oral and inhaled asthma medications. *Arch Intern Med* 1994; 154:1349–52.
- 2 Warner JO, Gotz M, Landau LI *et al.* Management of asthma: a consensus statement. *Arch Dis Child* 1989; 64:1065–1079.
- 3 International Paediatric Asthma Consensus Group. Asthma: a follow-up statement. *Arch Dis Child* 1992; 67:240–248.
- 4 Warner JO, Naspitz CK, Cropp GJA. Third International Pediatric Consensus Statement on the management of childhood asthma. *Pediatr Pulmonol* 1998; 25:1–17.
- 5 Warner JO. A review of prescribed treatment for children with asthma in 1990. *Br Med J* 1995; 311:663–666.
- 6 Iikura Y, Naspitz CK, Mikawa H *et al.* Prevention of asthma by ketotifen in infants with atopic dermatitis. *Ann Allergy* 1992; 68:233–236.
- 7 ETAC Study Group. Allergic factors associated with the development of asthma and the influence of cetirizine in a double blind randomised placebo controlled trial: first results of ETAC. *Pediatr Allergy Immunol* 1998; 9:116–124.