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Severe childhood asthma: a common international approach?

Although most children with asthma are easy to treat with low doses of safe drugs, many remain symptomatic despite every effort.[1] The nomenclature for this group is confused, and studies are difficult to compare because of the proliferation of terms that describe poorly defined clinical entities. To clarify, we propose the term problematic asthma to describe children with chronic symptoms or acute severe exacerbations, or both, despite prescription of multiple drugs. Such therapies usually include high doses of inhaled or oral corticosteroids, combined with standard add-on therapy with long-acting β_2 agonists (leukotriene-receptor antagonists and theophylline).[2,3]

Children with problematic asthma have either difficult asthma or severe therapy-resistant asthma. Careful specialist assessment is needed to ascertain into which of these subcategories the child falls. In children with difficult asthma, the predominant problem will not be resolved by prescribing a more sophisticated asthma drug (eg, concordance with a prescribed drug is poor, the environment is adverse, or if there are major underlying contributory psychological features). Severe therapy-resistant asthma needs innovative therapeutic approaches, and can be subphenotyped as responders to novel therapies, such as cytokine or other immune-specific agents.

The approach to problematic asthma might vary with the age of the child but, generally, three steps need to be taken to separate difficult from severe therapy-resistant asthma. First, confirmation that the problem is due to asthma requires complete diagnostic re-evaluation. Second, the paediatrician needs to systematically exclude substantial comorbidities, such as underlying systemic diseases, gastro-oesophageal reflux, and rhinosinusitis, and a personal or family psychosocial disorder. Third, adherence to drug, inhaler technique, and the child's environment need re-evaluation. There is no uniform agreement on how best to take all the three steps.

In one protocol,[4] a nurse-led home and school visit was used. Non-adherence was addressed by: obtaining computerised prescription records to see which drug had been collected;[5] such drugs and spacers available within the home were inspected; and the child's ability to use the inhaler was tested. Pet ownership is common even if the child is sensitised to the pet. Moreover, pets can cause steroid resistance through mechanisms mediated by interleukins 2 and 4.[6,7] At least some evidence exists to show that pets can worsen asthma by non-IgE-mediated mechanisms.[8,9] Passive exposure to smoke was observed first hand, because such exposure probably contributes to steroid resistance as has been documented with active smoking.[10,11] A long-term trial of removing pets, reducing household smoking, and taking the prescribed drug is preferable to high-dose oral corticosteroid or other immune-suppressive

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therapy. The role of psychosocial issues might become clear after an assessment of the family at home. Identification of these problems is only the first step to their resolution. Obviously, prescribing an expensive cytokine-specific therapy with potential harmful side-effects[12] is not optimum for a child who is not receiving basic management.

With all the approaches, up to 50% of patients with problematic asthma will not be categorised as having severe therapy-resistant asthma. For those that do, more detailed age-related phenotyping is recommended. Phenotypes vary with age—eg, acute severe exacerbations with only occasional symptoms or no interval symptoms are common in preschool children as are more chronic, persistent, multitrigger symptoms in school-aged children. In preschool children, combining bronchoscopy, pH study, and high-resolution CT scanning led to the identification of several potentially remediable issues.[13] In school-aged children, the next step could be assessment of steroid sensitivity with invasive and non-invasive measurement of inflammatory markers before and 2–4 weeks after an injection of a depot corticosteroid such as triamcinolone. The aim is to see whether the child is truly steroid-resistant, and to identify molecular and cellular events that make the child's asthma resistant to therapy. Ultimately, the aim is to identify specific novel agents that might be beneficial.

Within the Global Allergy and Asthma European Network (GA^{2}LEN),[14] the European network of centres of excellence, several initiatives have already been taken. A pan-European cohort of young children will be recruited to identify those with problematic asthma, which might be expanded into a worldwide initiative launched through the Global Alliance against Respiratory Diseases[15] and WHO. What needs to be decided urgently is how best to standardise the phenotyping of children presenting with problematic asthma so that randomised trials can be done and treatment optimised for this challenging group.

If we are to discover mechanisms and genes responsible for severe asthma, and use new immune-specific therapies[16,17] most appropriately, we should establish what sort of asthma we are discussing. It seems unlikely that the child with three acute severe exacerbations in a year without eosinophilic inflammation has the same gene–environment interaction and requires the same treatment approaches as the child with steroid-resistant chronic symptoms and eosinophilic airway inflammation. Therefore any progress depends on a common international approach to nomenclature, classification, and investigation and treatment algorithms. This approach is urgent, because no one centre is ever likely to accumulate sufficient data on children with particular phenotypes for meaningful trials or genetic-association studies.

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The coming of age of asthma guidelines

The first international asthma guidelines meeting was held in Toronto almost 20 years ago and the consensus conclusions from this meeting were published the following year.[1] Since then, many national and international groups have developed asthma guidelines as evidence-based documents.[2,3] For what purpose and for whom are these documents intended? The intended audience and outcomes are seldom stated explicitly by the authors of guidelines, but it is widely assumed that the documents are written to inform primary-care physicians, who care for most asthma patients, and that the intended result is to improve the outcomes of asthma management. This common failure to identify the target audience and intended outcomes might explain why the guidelines so often fail to meet the hopes of their authors.

An early innovation of the Canadian Asthma Guidelines group was to introduce the concept of asthma control as a pragmatic outcome measure after office-based treatment and as a decision-making tool, which suggests a strategic approach to asthma management that has since been widely incorporated, clarified, and refined by subsequent guideline documents. Despite widespread adoption by academic specialists, translating this consensus knowledge into improved practice patterns and outcomes has been unsuccessful.[4] The latest and largest study to document our failure to improve asthma control outcomes in primary practice has been the Personal Practice Assessment Program, in more than 350 Canadian primary-care settings where physicians surveyed the asthma control status of more than 10 000 patients.[5] Of the surveyed patients, 59% were considered uncontrolled. These uncontrolled patients were six times more likely to have an unscheduled health-care visit, almost four times more likely to seek care in an emergency department, and twice as likely to be admitted to hospital for out-of-control disease, compared with their controlled counterparts.

Such suboptimum outcomes probably reflect several management recommendations that are more often neglected than implemented. Despite universal recommendations that the diagnosis of asthma requires an objective measurement of lung function to show airway variability (ie, an increased bronchodilator response to a fast-acting β agonist), spirometry is seldom used in primary practice and methacholine challenge remains almost unknown. Environmental assessment and educational interventions are commonly neglected. Treatment remains over-reliant on high doses of inhaled corticosteroids and the introduction of combination inhaler therapy (inhaled corticosteroid plus a long-acting bronchodilator in a single inhaler) is often delayed