

## REVIEW

# How has research in the last five years changed my clinical practice?

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*Arch Dis Child* 2005;90:832–836. doi: 10.1136/adc.2004.066241

The first instruction to examination candidates is to read and answer the question actually set. Doing so in this case leads to the following conclusions: how research has changed my clinical practice includes the act of doing research, as well as reading about the work of others. Thus, this article refers to my own clinical practice (tertiary referral paediatric respiratory medicine in a setting where we do not service an accident and emergency department), rather than that of others. This means excluding important conditions such as acute croup and uncomplicated community acquired pneumonia. I should write about what has changed my practice, not what other people think I ought to have changed. So this will be a personal view, limited to research published in a peer review format at the time of writing. I shall also assume that change is an ongoing process, so I shall include change in progress, provided it is supported by published literature.

treatment, despite the plethora of papers on airway inflammation measured using a number of non-invasive (exhaled breath and breath condensate, induced sputum) and invasive (bronchoscopy, bronchoalveolar lavage, and mucosal biopsy) techniques. This is firstly because it is much harder to do prospective, long term longitudinal studies which are relevant to clinical practice than it is to do cross-sectional or very short term studies; and secondly, the demands on a test used as a clinical tool, in terms of positive and negative predictive value, are much greater than if it is used as a pointer to basic mechanisms. Thus the compilers of the guidelines rightly rejected much of the inflammatory markers literature. However, there is now emerging evidence that monitoring inflammation may be a useful clinical tool. The majority of work in this field has come from adult studies, but the data are provocative, and paediatric work has now been published.

The practice of research is not, however, always easy. A number of well meaning individuals have tried to engulf us in an avalanche of bureaucracy regarding the process of doing research. Often such individuals have long since moved away from the cutting edge themselves. Despite their best efforts, research remains both fun, and for me, an essential spur to clinical practice. The discipline of accepting nothing uncritically in a research context, and keeping on asking “why?” like a whining toddler or an even worse adolescent, carried into the clinical arena, has undoubtedly made me a better paediatrician than I otherwise would have been. Similarly, for the clinical researcher, the stimulus of clinical practice is the major source of research questions, and keeps the questions anchored. Actually to be paid for practicing this combination is almost too good to be true.

As is well known, conventional assessment of asthma control is based mainly on history taking, occasionally with a contribution from physical signs, backed up by clinic lung function (peak flow, spirometry) and occasionally peak flow diaries, which are often unreliable.<sup>2</sup> The first paper, which suggested that something else might give added value, was from the Netherlands.<sup>3</sup> In this two year, prospective study, 75 adults with asthma were seen every three months, and underwent methacholine challenge as well as conventional assessment. Half the patients had their inhaled corticosteroid (ICS) dosage adjusted on the basis of conventional criteria, but the other half were treated on the basis of their bronchial hyper-reactivity (BHR)—that is, an asymptomatic deterioration in BHR was treated with an increase in ICS. This is not a totally logical way of measuring airway inflammation, because in many studies there is a dissociation between inflammation and BHR,<sup>4,5</sup> and measurements of BHR are extremely time consuming. At the end of two years, those patients in the BHR strategy group had used more than twice as much ICS, but had a greatly reduced rate of exacerbation. A subgroup that underwent bronchoscopy at the beginning and end of the study period showed regression of some of the changes of airway wall remodelling. What this study could not answer was whether

The rest of this article will consider, in no particular order, the papers that made me think “I wish I had thought of that”, supplemented by things that our group actually did think of, which has influenced what we now do.

## ASTHMA

The BTS/SIGN asthma guidelines<sup>1</sup> represent a monumental effort to distil the accumulated evidence in the literature to allow the evidence based treatment of children with asthma. One searches in vain for references to the utility of the measurement of inflammatory markers to guide

**Abbreviations:** BHR, bronchial hyper-reactivity; CF, cystic fibrosis; CT, computed tomography; CXR, chest x ray; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; GTT, glucose tolerance test; ICS, inhaled corticosteroid; PCD, primary ciliary dyskinesia

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Accepted 26 March 2005

the benefits of the higher dose of ICS outweighed the potential side effects; and the important question of adrenal failure and hypoglycaemia<sup>6</sup> was not addressed at all. A subsequent adult study posed the separate but related question as to whether measurement of airway inflammation could predict an exacerbation of asthma.<sup>7</sup> Seventy eight adults treated with ICS had their treatment stopped abruptly. Importantly, 18 were apparently no worse for this, and this underscores the need for a constant re-evaluation of therapy to prevent the over-treatment of patients. They were followed up with serial measurements of exhaled nitric oxide (NO), sputum induction with measurement of eosinophils, and BHR to saline inhalation (sPD<sub>15</sub>). An increase in exhaled NO of 10 or 15 ppb, or a rise >60% over baseline was 80–90% predictive of loss of control (similar to sputum eosinophils and sPD<sub>15</sub> but easier to measure). In the most challenging study,<sup>8</sup> 74 adults were seen every three months and underwent conventional assessment as well as sputum induction with measurement of sputum eosinophil count. Half were managed conventionally, the other half had the ICS dose adjusted to normalise sputum eosinophil count, irrespective of symptoms; an asymptomatic person with a high sputum eosinophil count had the ICS dose increased, a symptomatic person with sputum eosinophils ≤2.5% had the ICS dose reduced. At the end of one year, the total ICS and oral steroid intake was equal in the two groups, but there was a major reduction in exacerbations in the sputum eosinophil strategy group (total 35 for the group versus 109 controls,  $p < 0.05$ ). Taken together, there is no doubt that measurements of airway inflammation can improve asthma care compared to conventional methods.

The paediatric data are more scanty. Roberts and colleagues<sup>9</sup> prospectively followed up 44 asthmatic children who were only symptomatic in the pollen season. eNO was measured before the pollen season, and every four weeks as far as was possible during the season. A post-hoc analysis of the data was undertaken to see whether a rise in eNO could predict a loss of asthma control. The median standard eNO (that is, eNO expressed as a fraction of the individual baseline when the child was well) was 1.93 (interquartile range 1.6 to 2.4) in the five day period prior to an exacerbation; beyond that time period, neither absolute nor standardised eNO was useful as a predictor. Clearly, the significance of this finding cannot be assessed until publication of the study in which this finding is evaluated prospectively. We have studied 40 asthmatic children in whom a reduction of ICS dosage was indicated on clinical grounds.<sup>10</sup> We determined sputum eosinophil count, bronchial hyper-reactivity, and eNO, and collected exhaled breath condensate to determine whether any marker could predict the likelihood of success or failure of ICS reduction. The most clinically significant finding was that absence of eosinophils from induced sputum was completely predictive of a successful step down in ICS dosage.

Overall, these studies imply to me that clinical practice must change from merely measuring lung function, and start to incorporate one or more measurements of airway inflammation. The data are incomplete, and it is unclear what is likely to be the best measurement to make, but it is no longer possible to believe that symptoms and conventional physiology are the best way of monitoring asthma in children. The challenge for researchers is to do the taxing, prospective longitudinal studies which will more precisely define the role of individual measurements, rather than the easier and quicker cross-sectional studies which may buy peace during the research assessment exercise, but do not advance the state of clinical knowledge. The current clinical bottom line for me is that I would now use exhaled NO and sputum eosinophil count as part of the information on which

to base clinical decisions were I able to get funding from the NHS for the technical staff to make the measurements. All of us should be clear that things have moved on since the guidelines,<sup>1</sup> and our standard asthma monitoring is not optimal.

There are other important areas on which I could have focused. For example, are high dose inhaled steroids useless and dangerous,<sup>6</sup> or is the real problem that *overdosage* is the important factor? Supporting the latter is a study showing that systemic absorption was much greater in normal adults than asthmatics.<sup>11</sup> The asthmatics had an appropriate dose of fluticasone, the normals by definition were over-treated. What is the role of long acting  $\beta_2$  agonists in children? More data needed. Does peak flow monitoring help asthma management? I do not know, because no one in real life does it consistently<sup>2</sup> (including myself when one of my children was treated for asthma; if you doubt me, try it sometime yourself). A recurring theme in these and other areas is that we do not have the evidence base to drive rational change.

## CYSTIC FIBROSIS

Research in this area could form several articles. Cystic fibrosis (CF) has moved from being considered as a largely paediatric disease of the lungs and pancreas, to a multisystem disorder with survival often well into adult life. Issues that I could have focused on include bone disease and its prevention,<sup>12–15</sup> once daily intravenous tobramycin,<sup>16</sup> the importance or otherwise of cross infection,<sup>17–18</sup> and stress incontinence.<sup>19</sup>

### The decade of the macrolide

If NO was the molecule of the 1990s, then the macrolides are the class of the 21st century. Interest in their non-antibacterial, immunomodulatory effects first arose from the dramatic benefits seen in patients with diffuse pan-bronchiolitis. This is a disease of middle aged people in the Far East, and is characterised by many of the phenotypic features of CF.<sup>20</sup> Presentation is with cough, chronic sputum production, and breathlessness, with coarse crackles heard on auscultation. There is a mixed obstructive and restrictive pattern physiologically. High resolution CT scanning reveals bronchiectasis. Sputum cultures are positive for *Haemophilus influenzae*, *Staphylococcus aureus*, and, most strikingly, mucoid strains of *Pseudomonas aeruginosa*. As a result of chance observations, it became clear that long term, low dose erythromycin dramatically improved prognosis, changing 10 year survival from less than 20% to more than 90%.<sup>21</sup> A series of elegant studies established that diffuse panbronchiolitis is characterised by a neutrophilic bronchoalveolar lavage, and that macrolide treatment therapy reduced lavage neutrophil chemo-attractant activity and neutrophil counts.<sup>22</sup> The response did not depend on the patient being chronically infected with mucoid *Pseudomonas aeruginosa*.<sup>23–24</sup> Treatment with erythromycin or, if this fails, clarithromycin, is essentially curative of a once fatal condition. This extraordinary result led to interest in the use of macrolides in CF.

Three different double blind, randomised, placebo controlled trials have established a role for macrolides in some patients with CF, summarised in table 1.<sup>25</sup> The first was a double blind, parallel group study<sup>26</sup> in 60 adults with stable CF. In the azithromycin group, FEV<sub>1</sub> and FVC remained stable, but in the placebo group there was a deterioration of 3.62% (1.78) ( $p = 0.047$ ) and –5.73% (1.66) ( $p = 0.001$ ) respectively. This is quite a rapid deterioration, equating to around 15% (FEV<sub>1</sub>) and 22% (FVC) annual rate of decline. We performed<sup>27</sup> a crossover study in children, and showed that FEV<sub>1</sub> improved by 5.4% (95% CI 0.8–10.5%) with azithromycin compared with placebo. Half the children had

an improvement in FEV<sub>1</sub> of at least 10%. The third study<sup>28</sup> was a parallel group design, and showed a treatment benefit of 0.094 litres or 6.2% for FEV<sub>1</sub>, and 5% for FVC (all highly statistically significant). There was marked variation in individual response; around 12% increased FEV<sub>1</sub> by  $\geq$ 15% on azithromycin (none on placebo), but some actually deteriorated. Any benefit was lost within 28 days of discontinuing therapy. There was a 40% reduction in infective exacerbations defined as the use either of intravenous antibiotics or quinolones. The azithromycin group gained 700 g in weight compared with placebo.

These trials have confirmed that for many, but not all, individuals with CF, azithromycin therapy improves pulmonary function. No one can predict which patients will benefit from treatment, nor is the mechanism of action known. Unlike in diffuse panbronchiolitis, there does not seem to be an effect on airway neutrophilia, but as with diffuse panbronchiolitis, chronic *Pseudomonas aeruginosa* infection is not a prerequisite for benefit. The optimal dose and dosing frequency is not known. There are worldwide differences in how macrolides are used in CF. The Danish clinic<sup>29</sup> use it as part of their routine treatment of chronic infection with *Pseudomonas aeruginosa*. We are more cautious, having account of the lack of knowledge of possible long term side effects in children; we carry out a four to six month therapeutic trial of daily azithromycin in children who are not doing well on conventional therapy, irrespective of their sputum bacteriology, and discontinue the medication if there is no benefit. This is clearly an area where more work is needed, but also an area in which clear-cut benefit for patients has been established.

### Insulin deficiency: a growing problem

The importance of insulin as an anabolic, not merely hypoglycaemic hormone is being increasingly appreciated.<sup>30</sup> The main mechanism appears to be reduced insulin production, rather than insulin resistance.<sup>31</sup> Who should get a glucose tolerance test (GTT) is still unclear; the more that are done, the more abnormal tests will be found. The differentiation of clinically important from clinically trivial findings remains unclear. For example, in a large series of CF children who had annual GTTs, many had an abnormal test, which normalised on no treatment the following year.<sup>32</sup> Despite this, the authors advocated a policy of annual GTT in CF. A case series from The Royal Devon and Exeter<sup>33</sup> reveals that the "gold standard" GTT is no such thing. Four CF patients aged between 15 and 23 years were deteriorating on conventional therapy. All had normal GTT and glycosylated haemoglobin levels. However, home glucose monitoring revealed in all four cases evidence of transient "asymptomatic" hyperglycaemia. So what? (the most important question in research). So these patients were commenced on low dose insulin (6–12 units daily) as the only intervention, with improvement in nutrition and lung function over the ensuing months.

This case study clearly indicates the need to aggressively chase insulin deficiency in the CF patient who is not doing well, even when apparently there is no significant hyperglycaemia, and with a normal GTT; and that the deleterious effects of insulin deficiency in CF are apparent and correctable long before anything like a diabetic state is reached. It also underscores that the GTT is not a great test in the context of early CF insulin deficiency. I have become less trusting in the GTT as the gold standard in this context as a result of this paper. My take on this study is that if clinical suspicion of CF related diabetes is high, then a normal GTT should be followed by a period of intensive home glucose monitoring. Low dose insulin is an important addition to our therapeutic armamentarium; and as a final thought, if in the future it can be given by the inhaled route,<sup>34</sup> this would be a major boon for the children.

**Table 1** Summary of published clinical trials of azithromycin (modified from Hilliard and Balfour-Lynn<sup>25</sup> with permission from the authors)

Centre (reference)	Trial design	Azithromycin dose	n	Length of treatment period (mth)	FEV <sub>1</sub> (drug v placebo)	Other clinical outcomes	Inflammatory markers	Adverse effects
Australia Two centres <sup>16</sup>	Parallel	250 mg daily	60 adults	3	Mean relative difference +3.6%	↓ intravenous antibiotics ↓ quality of life	↓ CRP	Nil
UK Single centre <sup>17</sup>	Crossover	250 or 500 mg daily	41 children >8 y	6	Median relative difference +5.4%	↓ oral antibiotics	No difference sputum IL-8, neutrophil elastase	Nil
USA Multicentre <sup>19</sup>	Parallel	250 or 500 mg 3/week	185 children >6 y and adults	6	Mean relative difference +6.2%	↓ nonquinolone antibiotics ↓ exacerbation ↓ weight	Modest ↓ sputum elastase, no difference IL-8	Nausea, diarrhoea, wheezing

## PRIMARY CILIARY DYSKINESIA

This uncommon autosomal recessive condition is often diagnosed late<sup>35</sup> or not at all.<sup>36</sup> The two probable factors<sup>37</sup> are that it may be mild, or mimic common childhood problems (glue ear, rhinitis); and that diagnostic testing requires very sophisticated and expensive apparatus. Even when the patient is referred for a nasal brush biopsy, persistent infection and inflammation, even despite topical treatment, may make harvesting healthy cilia very difficult. Viral colds are frequent in childhood, and may have prolonged effects on ciliary function and morphology.<sup>38</sup> For as yet inexplicable reasons, nasal NO is very low in primary ciliary dyskinesia (PCD).<sup>39–41</sup> In our hands, a cut off of 250 ppb nasal NO is 95% specific for the exclusion of the diagnosis.<sup>41</sup> Low nasal NO is also a feature of CF, so it is not specific for PCD, but we find the measurement useful in two diagnostic conundrums. The first is selecting patients for brush biopsy: if there is a low risk history, and a normal nasal NO, we would not usually pursue investigations further; and secondly, if repeated brushing fails to yield an answer, nasal NO may be a very helpful diagnostic pointer. The reason for highlighting this technique here is that many institutions have purchased NO analysers, which are in any case becoming much cheaper. It should be relatively easy in most parts of the country to get access to a machine, and measure nasal NO, and hopefully perhaps bring down the age at diagnosis because it becomes easier to define a high risk group to be referred for formal confirmation of the diagnosis.

## EMPHYEMA: THE USE OF UROKINASE

For reasons that are unclear, the prevalence of empyema is rising dramatically.<sup>42</sup> One could speculate that a spin-off of the ending of the “antibiotics for everything” culture has meant that some children who do have bacterial pneumonia do not start antibiotics until later in the illness; against this hypothesis, we have all seen children with pneumonia who progressed to empyema despite early and appropriate therapy. For whatever reason, the number of referrals with empyema has risen. We and others had previously advocated early surgical drainage of the pleural space in these children, rather than waiting through many days of a high swinging temperature.<sup>43</sup> Delay potentially leaves the surgeon with a difficult operation to clear extensive fibrinopurulent exudates from the pleural space. We have changed our practice as a result of a multicentre, randomised, double blind, placebo controlled trial<sup>44</sup> of intrapleural urokinase. Sixty patients were randomised to receive either 40 000 units urokinase (10 000 for those under 1 year of age) or placebo, to a total of six doses. The end point was time to discharge from hospital, which was significantly lower in the urokinase group (7.4 v 9.5 days,  $p = 0.027$ ). A post-hoc analysis suggested that the use of small pigtail drains was also associated with a shorter hospital stay, and the best results of all were obtained in children given urokinase through a pigtail drain. It may be that there was a confounding centre effect, given that most of the pigtail drains were used in Oxford, where there was clearly the widest experience with the technique at that stage. Nonetheless, it is difficult from the data to argue that the pigtail drains were inferior, and they are certainly far more comfortable for the children. Having gone over to this protocol, surgical referrals have virtually but not completely disappeared from our institution.

The lessons for paediatricians from this trial are: firstly, that almost irrespective of the appearance of the chest x ray (CXR), if the temperature settles and the inflammatory markers come down, then the child will make a complete recovery, and will have an essentially completely normal CXR within weeks. Secondly, that virtually all empyemas will respond to intravenous antibiotics and intrapleural

urokinase. Finally, big is not beautiful, and percutaneous placement of small pigtail drains is at least as effective as large chest drains. The means of securing analgesia when placing the drain will vary with the experience of the operator and the facilities available in the institution. As always, there are questions to be sorted out. Some would advocate video assisted thoracoscopy (VATS) as primary treatment, and support their claim with impressive data.<sup>45</sup> I am not aware of any true comparison between VATS and intrapleural urokinase, and in any event, for the foreseeable future, VATS is unlikely to be available freely and without delay in many parts of the country. The urokinase trial has established the evidence for a change in practice, the value of which has been borne out repeatedly by observation of results in centres which have implemented it. National empyema guidelines have just been published.<sup>46</sup>

## CONCLUSIONS

It should be obvious that a prerequisite for evidence based practice is evidence. The big challenges for the next five years are: to get evidence to inform our practice; to harness the advances in basic science to the treatment of patients; and to get that evidence in children, and not rely on adult studies.

Competing interests: none declared

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