



# Never mind the biologics, just take the inhalers

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Asthma is one of the commonest paediatric diseases of Western Europe affecting some 20% of children in the UK [1], 7% in Sweden [2], 13% in Germany [3] and 10% in Italy [4], and whether the trend is still rising, plateauing or slightly falling, it still affects an awful lot of children. Even more importantly it still kills far too many people: in the UK there are ~5 deaths per 1000 000 children aged 0-19 years [5], which is similar to USA [6], but only 0.19 deaths per 1000 000 in Finland equating to only four child deaths in the whole country for the 16-year period to 2015 [7]. In 2017, in London alone I was aware of eight paediatric asthma deaths. In summary, this is a children's tragedy.

The fundamental question is "Why?" It is an embarrassing stereotype of men (at least) that they all too readily embrace all things new and asthma medications are no exception. There are tertiary UK asthma clinics where about a third of paediatric patients are on omalizumab (Xolair) for their problematic asthma. As part of the largest problematic severe asthma clinic in the UK, and probably Europe, for the past 20 years, I have learnt three very salutary lessons: 1) despite 50 years of research into asthma, it is still a blue and a brown inhaler, measuring the urinary cotinine and looking menacingly at the pet cat regardless of the 207 pages of British Thoracic Society asthma guidelines [8, 9]; 2) less is more; and 3) "It is a basic truth of the human condition that everybody lies. The only variable is about what." (Hugh Laurie as Dr House).

I am the first to admit that these lessons came slowly and was in the past an enthusiastic advocate of, for example, subcutaneous terbutaline for the severest cases [10]. Of course, it wasn't the doctors that learnt the truth about paediatric asthma, it was our asthma nurses. The single paper (which I did not author) that completely changed my practice was the study by BRACKEN *et al.* [11], which identified that 56 (79%) out of 71 children with severe asthma aged 4.5-17 years had fairly easily modifiable factors: ongoing allergen exposure in 31%, passive smoking in 25%, medication issues including adherence in 48% and psychosocial factors in 59%. Of course, more than one factor could be present in each child. They correctly emphasised that a home visit to the family of a child with severe problematic asthma was almost always illuminating: 84% of those sensitised to house dust mites did not have appropriate avoidance measures in place, medications were not present or out of date in 23% of cases, and 74% of the psychology referrals were prompted by the home visit, *i.e.* the truth came out. Most gratifyingly, as a result of the findings and the interventions put in place, 39 (54%) out of the 71 children did not need treatment escalation. Nowadays in our clinic this figure is ~80% or higher.

Even in the most well regulated countries, the problems start well before that, in primary care. It was therefore a brave study from Sweden that reviewed the primary care records of 443 asthmatic children looking for documentation



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**"It is a basic truth of the human condition that everybody lies. The only variable is about what." In paediatric asthma, patients don't take their treatments and doctors rarely ask the right questions. The end result is far too many child deaths.** <http://ow.ly/OaGK30kFtsD>



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of the five quality indicators as determined by the national guidelines: smoking, spirometry, pharmacological treatment, patient education and demonstration of inhaler technique [12]. The results were embarrassing: the presence or absence of passive smoking was documented in 14%, and in one out of 443 cases was there advice to stop smoking; the presence or absence of mould/damp was documented in 5%; and keeping or not keeping furry pets was documented in 30%. In children aged >6 years only 22% had ever had spirometry, despite all the primary care centres having a spirometer. Only 14% had received patient education and 14% were recorded as having their inhaler technique checked and sadly having an asthma nurse in the centre did not appear to help. Just as worryingly, 22% (n=88) had received nebulised salbutamol in the past year, one can only assume using an air driven nebuliser. This is so wrong for two reasons: 1) comparative studies between nebulisers and spacers show spacers are equally effective [13]; and 2) an air driven salbutamol nebuliser in critical situations is associated with sudden death. In the medicolegal cases I have been asked to give an opinion on, a common final event before death was using a nebuliser at home, either their own or one they had recently borrowed. If asthma primary care is not working in Sweden, it is unlikely to be working elsewhere. Personally, in my entire career I have never received a referral from primary or secondary care with a spirometer result.

Even if all these issues are addressed and the prescriptions written we still do not know whether the prescriptions were “cashed” and even more crucially whether the medications are actually being taken. Hence the study of electronic inhaler monitoring by JOCHMANN *et al.* [14] is a big step towards the truth. 108 children from our difficult asthma clinic were prospectively recruited, 15 of whom did not complete the study, because the study inhaler was “lost” for example, which is valuable information in its own right. They were followed for a median of 92 days (range: 56–200 days) and all the children and families knew they were being monitored. The monitors note the date and time the inhaler was actuated and how many times, but not whether it was inhaled or whether the inhaler technique was adequate although it will highlight “drug dumping”. Using standard definitions, good adherence (>80% of prescribed doses taken) occurred in only 42% of children, remember these are patients attending a tertiary clinic because their asthma is so difficult to control. 27% had sub-standard adherence (60–79% of prescribed doses taken) and 31% had poor adherence (<60% of prescribed doses taken) even though they knew they were being monitored leading me to conclude that adherence was probably an overestimate compared with real life. No clinical determinant predicted the adherence rate. Families’ subjective rating of adherence was universally good and uniform across

the adherence groups, demonstrating either that “everybody lies” or that they truly believe this and therefore being deluded is one possible conclusion. The number of parents who categorically state that every inhaler dose is being taken and express incredulity when I present the monitoring data is huge. Most importantly, and insufficiently emphasised in the paper, was that when comparing prescription uptake to electronically monitored adherence, while the correlation was just significant (*i.e.* more prescription uptake led to more electronic adherence) the relationship was very weak with only 8% of the variance explained by the relationship. Of the 12 families with 100% prescription uptake the actual adherence rated varied between 27% and 99% with half (six out of 12) having sub-standard or poor adherence.

The conclusion from all of the above is that doctors in particular have no idea what is actually going on in an individual family. A home visit will shed a lot more light, but nothing apart from electronic monitoring will give any true objective indication of adherence in difficult asthma situations. What the study did highlight was that there are several relevant subgroups and it did identify the very small and diminishing group, 17 (18%) out of 93 children in an already highly selected group, whose adherence was good but still had significant symptoms and could therefore be categorised as truly severe therapy-resistant asthma. It also highlighted a larger (26%) over-treated group, *i.e.* those with good asthma control despite adherence <80%. Taking this further still, in 239 adults with severe asthma, a microphone was attached to the electronic monitor and showed that actual adherence was 22% less than judged by the electronic monitor alone, which is a very sobering thought [15].

It is all very well knowing that overall adherence, even in this highly selected problem severe asthma group, is very disappointing, and I would speculate it will be even worse in primary and secondary care settings, the next question is why does this happen and what can be done to improve it. From my own experience, I find it quite incredible that families who have had their children have asthma admissions to intensive care in the past routinely still have poor adherence with simple inhalers. Is this wilful child endangerment? Occasionally, yes. Is it a chaotic lifestyle? More commonly, yes. Is it that the parents/carers genuinely believe they are carrying out what is required and simply don't realise or delude themselves? Yes, to an extent. Clearly healthcare is missing an awful lot in trying to understand a family's particular situation. Poor adherence is not a problem peculiar to paediatric asthma, it is routine in any chronic condition such as cystic fibrosis [16], diabetes [17] and even maintenance treatment for leukaemia [18]! These are not new problems and there are whole books on the subject from 30 years ago which list the ≥200 factors that may be present in any family

situation [19]. Therefore, the need for a paediatric clinical psychologist as part of a difficult asthma multidisciplinary team cannot be overemphasised.

The first thing is to recognise the lack of adherence and try to discover the reasons behind it in a particular family and the second thing is to try to improve it. A New Zealand study randomly assigned 220 children with asthma who had visited the emergency department and were on regular inhaled steroids to receive twice daily audio-visual reminders or not, and followed them for 6 months [20]. Adherence was 84% in the reminder group and 30% in the control group, and lung attacks were considerably fewer (7% versus 24%) in the first 2 months of the study but not thereafter. Asthma control and forced expiratory volume in 1 s (FEV<sub>1</sub>) improved in both groups but more in the reminder group. So, this is a good start if it can be maintained. However, another albeit smaller study in a high-risk low socioeconomic group did not show any benefit [21]. The Cochrane review was dubious about the studies overall due to considerable risks of bias, although the study from New Zealand was much the best [22]. This is not a surprise as if there are  $\geq 200$  possible factors there will never be a single solution. Reminders may work for some with a chaotic lifestyle, but will be useless if families are convinced the inhalers have serious side-effects or don't work.

So what, dear reader, do I suggest you do when faced with any asthma patient whose symptoms persist?

- 1) Do they have asthma? As evidenced by one or more of: documented bronchodilator reversibility ( $\geq 12\%$ ); recorded evidence of spontaneous variation in FEV<sub>1</sub> ( $\geq 12\%$ ) in the past year; and airway hyperresponsiveness confirmed by direct or indirect challenge tests, *e.g.* exercise. Exhaled nitric oxide can be a help, but of course is very expensive to perform.
- 2) If they have asthma, ask about pets, the indoor environment, family history and smoking. Don't always believe the answers, measure the urinary cotinine and atopic status.
- 3) Check their inhaler technique; you will be amazed [23].
- 4) Always carry out spirometry in children aged 6 years and over.
- 5) If patients complain of exercise symptoms one can either arrange a formal exercise test or I just ran them up (and then walked them down, health and safety!) the stairs to the clinic 5–20 times until they were tired/reasonably breathless, waited 7 min and then repeated the spirometry. In the past 8 years, I have only had one child manifest exercise-induced

bronchoconstriction ( $>10\%$  drop in FEV<sub>1</sub>). The ability of families, patients and indeed healthcare professionals to distinguish breathlessness from difficulty breathing is really quite poor.

- 6) Obtain a prescription uptake report from the primary care system. This is cheap and certainly better than nothing, although it will still be misleading in a considerable proportion of patients. If available, and certainly worth the EUR 100–150, assess with an electronic inhaler monitor (*e.g.* SmartInhaler; Adherium, Auckland, New Zealand) for at least a month.
- 7) An asthma nurse home visit is often very revealing.
- 8) Ultimately if, after trying all of the above, things are still perplexing, I cannot recommend too highly a 2-week, in-patient hospital stay as it is almost invariably very revealing despite being intensive, expensive and time-consuming, but in the long run it will be worth it. This has been occurring for at least 20 years in our institution and a more detailed focussed assessment of it has been published [24]. Personally, almost every child with asthma I ever admitted immediately became symptom free, with their FEV<sub>1</sub> up and their exhaled nitric oxide down, and children who were reported to have taken salbutamol for the previous 10 years on a daily basis had no need for it at all during their 14-day stay. There will be several reasons for the improvement, *e.g.* directly observed therapy and absence from the home environment (smoke, atopy, psychology). In many cases daily oral steroids could be greatly weaned or stopped, inhaled steroid dosages reduced and prior suspicions of fabricated illness or neglect could be nailed down. In addition, there was the occasional patient who despite all this still had definite symptoms and thus could be correctly categorised as truly having severe therapy-resistant asthma. The moral question of what to do about difficult asthma patients who despite everything won't take their treatment even with directly observed therapy remains: should there be a legal remedy or should they be eligible for omalizumab?

What is the end result? In our difficult asthma clinic only eight out of 140 children need omalizumab compared with 30–40% in other clinics, and no one is now taking methotrexate, cyclosporine, *s.c.* terbutaline, *etc.* We are ever more adept at discovering the real issues in a particular child with asthma and their families. Ultimately, we really do keep it simple... and so should you!

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#### Conflict of interest

None declared.

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