Arguably, the most significant event in the life of a person with cystic fibrosis (CF) is the acquisition of chronic pulmonary infection with *Pseudomonas aeruginosa*. It heralds, in many cases, more hospitalisations,1 a more rapid decline in pulmonary function and a shorter life expectancy.2 *P. aeruginosa* has the ability to form biofilms which are composed of non-motile organisms embedded in an exopolysaccharide matrix and which confer resistance to antibiotics.3 In individuals with CF, biofilms have been observed in lungs examined at autopsy and explanted lungs from transplant recipients.4 The extraordinary persistence of infection with *P. aeruginosa* in the CF lung is thought to derive from biofilm formation. The mucoid phenotype of *P. aeruginosa* is a marker of biofilm formation,5 and this phenotype is in turn associated with a worse prognosis compared with non-mucoid organisms.5 However, in the initial stages of infection when the organism is mainly in planktonic form, there is an opportunity to eradicate the infection before it becomes persistent.

The first randomised controlled trial of an eradication regimen for early *P. aeruginosa* infection was reported by Valerius and Koch in 1991.6 This evaluated a 3-nosacidal regimen for early infection before it becomes persistent. The organism is mainly in planktonic form, initial stages of infection when the mucoid organisms.5 However, in the initial stages of infection when the acquisition of chronic pulmonary infection to around 11% in children with CF attending UK centres.17 A Cochrane review concluded that eradication is achieved, at least initially, but does not recommend one regimen over another.14 The ELITE study has provided the first randomised comparison of eradication regimens of different durations. Studies of eradication regimens comparing different drugs or different approaches to drug administration are badly needed. A number of important studies are ongoing or are due to report their findings in the near future.

The recently completed EPIC study has randomised over 300 children with newly acquired *Pseudomonas* infection to either culture-directed therapy or quarterly cycles of inhaled tobramycin (28 days of tobramycin followed by 56 days off treatment) for 18 months. Patients in each group were further randomised to receive 14 days of either ciprofloxacin or placebo orally—again either directed by culture or in quarterly cycles.15 The results of the trial will be published within the next year. The Australasian Cystic Fibrosis Bronchoalveolar Lavage (ACFBAL) study16 takes the concept of culture-directed therapy a stage further by randomising children to receive either a single bronchoalveolar lavage (BAL) at 5 years of age, or BAL at baseline, a further BAL specimen to confirm any upper respiratory isolates of *P. aeruginosa*, BAL with intravenous antibiotics and a final specimen at 5 years of age. In both groups a robust eradication regimen (2 weeks intravenous antibiotics, 4 weeks ciprofloxacin and 8 weeks nebulised tobramycin) is given where isolates are positive for *P. aeruginosa*. Again, the results are expected within a year. In contrast, the TORPEDO study (http://www.controlled-trials.com/ISRCTN02734162/TORPEDO-CF), which will commence shortly in the UK, will compare 2 weeks of intravenous antibiotics with 3 months of oral ciprofloxacin, both combined with 3 months of nebulised colistin.

It has been a major achievement of the last two decades of CF care to make eradication treatment for *P. aeruginosa* routine. Eradication, along with meticulous microbiological surveillance and measures to prevent cross-infection, has reduced the median prevalence of chronic *Pseudomonas* infection to around 11% in children with CF attending UK centres.17 The ELITE study is the first step in determining the optimal eradication regimen. Optimal therapy will be of the shortest duration compatible with
long-term eradication, will minimise drug side effects and antibiotic resistance, but with the least possible upset to schooling, work and family life. Getting there will require every CF centre to participate in multicentre trials and the timely application of evidence to clinical practice. Who will join the ELITE?

Competing interests ARS is Director of the Trent Local Children’s Research Network, part of the UK NIHR Medicines for Children Network.

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References

Is postmenopausal HRT a risk factor for adult-onset asthma?

A E Tattersfield

Adult onset asthma is often progressive1 and the cause of considerable morbidity. Some asthma developing de novo in adults can be attributed to environmental factors, such as occupational sensitisers. When such an association is recognised, asthma can often be prevented, so searching for aetiological factors is well worthwhile. Hormone replacement therapy (HRT) may be one such factor.

Postmenopausal HRT was used widely until recently, being seen as the way for many women not only to appear more youthful and glamorous following the menopause but also to be healthier. Various observational studies had suggested a reduced risk of diseases such as osteoporosis, heart disease and possibly dementia. However, when the results of prospective studies became available the picture was, alas, rather less positive. Not only did these studies fail to confirm many of the alleged benefits of HRT, they suggested or confirmed important adverse effects including an increased risk of breast cancer, ovarian cancer, venous thrombo-embolism, heart disease, cognitive decline and, more recently, mortality from lung cancer.2—8

Should late-onset asthma be on this list?

Cross-sectional studies have shown an association between the use of HRT and a diagnosis of asthma and asthma symptoms.9—11 The studies have varied in design and in how asthma was diagnosed, but the findings have been fairly consistent in showing a modest association between HRT use and reported asthma, with ORs ranging from 1.38 to 1.57.9,11

The associations with symptoms and asthma medication were of similar magnitude.9—11 Two studies found the strongest association in never smokers,9 11 and two showed an interaction with body mass index (BMI), in that the effects of HRT were seen largely in women with a low BMI.9 10 Having a high BMI per se was associated with asthma,9 but there was no additional effect from HRT in these more overweight women. Cross-sectional studies have limitations, and none of these studies looked at the type of HRT used, nor did they distinguish between new-onset and established asthma.

Data from the large US Nurses Health Study were published in 199512 and 2004.13 This was the first prospective study to look at the relationship of postmenopausal hormone use to the development of new cases of physician-diagnosed asthma, using biennial questionnaires to determine HRT use. The analyses covered a quarter12 and half13 a million person-years of follow-up, respectively, with some overlap for the middle period. Both analyses showed an increased risk of developing asthma in association with current use of HRT, and this was similar for oestrogen alone and oestrogen/progestin preparations. The increased risk with unopposed oestrogen showed a dose—response relationship in the first study.12 In the more recent study, by Barr et al,13 the rate ratio for newly diagnosed asthma amongst current users of oestrogen only was 2.29 (95% CI 1.59 to 3.29), and this tended to be greater in women with a low BMI. HRT was not a risk factor for developing chronic obstructive pulmonary disease.13

This issue of Thorax contains a further prospective study, from Romieu et al (see page 292), looking at the relationship of HRT use to new-onset asthma amongst postmenopausal women in the E3N study, a cohort of 98 995 French women using...
Pseudomonas eradication in cystic fibrosis: who will join the ELITE?

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