Newborn screening for cystic fibrosis: evidence for benefit

Ian M Balfour-Lynn

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Every year our centre is referred children with cystic fibrosis (CF) whose diagnosis has been unnecessarily delayed, having been missed by a number of health professionals. Sometimes the diagnosis is fairly obvious, for example the child has a classic history of frequent chest symptoms, but the loose stools have been put down to frequent courses of antibiotics. Some of these children have irreversible changes and we have even seen bronchiectasis, finger clubbing and mucoid *Pseudomonas aeruginosa* at presentation. Almost all of these children would have benefited from newborn screening (NBS). Currently, the median age at diagnosis in the UK is 1 month for screened babies and 6 months for those clinically diagnosed (excluding meconium ileus),[1] while in the USA it is 2 weeks and 14½ months, respectively.[2]

There has been a struggle for CF NBS to gain acceptance. Most supportive evidence comes from the randomised controlled trial in the Wisconsin Cystic Fibrosis Neonatal Screening Project that produced multiple publications (and a recent 16-year update[3]). The ethics of such a trial are worth considering; since the blood spots were not examined in the control group for 4 years, the potential to know a CF diagnosis was effectively withheld.[4] The earlier smaller randomised trial from Wales and the West Midlands in the UK was also important.[5] There have been a number of observational studies, some relatively small (summarised by Castellani[6]), others larger and based on national databases.[2 7] Although this type of evidence is inevitably more open to methodological flaws, valuable data have still been produced. However, commenting on the Wisconsin trial's early results, in 1998 a *BMJ* editorial was subtitled "No evidence of any benefit",[8] and this was met by a flurry of indignant letters.[9–11] A Cochrane systematic review in 2001 (with a follow-up literature search in 2006) analysed the two randomised trials mentioned above that involved over 1 million babies, and came down in favour of screening, although not very firmly.[12]

In 2003 (but published in 2004), the USA Centers for Disease Control and Prevention (CDC) recommended screening for all, but to date only 30/52 states have implemented it (with five planning to do so).[13] In Europe, some countries do not have NBS programs (eg, Germany, Greece, Holland, Spain, Switzerland), while others do (eg, Austria, France, Italy).[14] In the UK, there have been regional differences. NBS has been in place in Northern Ireland (1989), Wales (1996), Scotland (2003) and some regions of England for many years. In 2001, a ministerial announcement restarted discussions about extending screening to the entire UK; this was agreed in 2004 and was finally in place by July 2007. So what is the evidence of benefit and does this outweigh any potential adverse effects?

POTENTIAL BENEFITS

Advantages to the patient

Mortality

Due to the increasingly good prognosis and now infrequent mortality in childhood,[15] this has been difficult to assess and prove; fortunately survival alone is now an unsatisfactory outcome for screening studies. However, a follow-up to the Welsh/West Midlands trial found there had been four (non-meconium ileus related) early deaths (<5 years old) in the 59 patients who were not screened, compared to 0/74 in the screened group.[16] However, 2/4 had been diagnosed anyway by 8 weeks of age (before the median age of diagnosis of the screened group); this led the authors to conclude that NBS had the potential to reduce mortality but only if the diagnosis was made in the first month of life. Analysis of US CF Foundation registry data from 1986–2000 found that patients diagnosed by symptoms or meconium ileus rather than by screening had a significantly greater risk of shortened survival.[17] This did not apply if the non-meconium ileus symptomatic group was diagnosed within 1 month. A recent review of registry data comparing states in the USA that screened with those that did not, found a modest absolute difference in mortality risk (of about 2%).[18] Finally, a review of a number of European non-randomised studies found NBS "probably" reduced infant mortality and prolonged long term survival.[19]

Lungs

Lung function is often used as predictor of mortality. Disappointingly, the Wisconsin trial found no difference in FEV_1 at 7–8 years, and no difference in quantitative chest radiography in the screened group.[20] However, there were important confounding factors, namely imbalance of genotype and pancreatic status, mild lung disease in both groups, and earlier acquisition of *P aeruginosa* in screened patients in one of the centres. These factors may well have disadvantaged those children and thus skewed the lung function results towards the non-screened group. In fact, later analysis has shown that while those in the control group (with later diagnosis) had the worst initial chest radiograph scores, over time there were no differences between the two groups, until the effects of chronic *P aeruginosa* supervened, when the scores were then worse in the screened group after 10 years due to the problem of earlier *P aeruginosa* acquisition.[3] This shows that NBS only provides the opportunity for better pulmonary outcomes, but that prevention of early *P aeruginosa* is even more important than early diagnosis.[3] A smaller Australian study has shown significantly better lung function in screened children up to 15 years of age, compared to a non-screened cohort diagnosed up to 3 years before implementation of screening (note use of historical controls).[21]

Nutrition

Improved nutrition was the initial headline news in the Wisconsin trial, with children diagnosed by screening having significantly greater height, weight and head circumference centiles at the time of diagnosis than conventionally diagnosed children.[22] Using height or weight below the 5th or 10th centile as a marker of malnutrition, the outcome was also better in the screened group.[22] The differences were particularly evident in the pancreatic insufficient and homozygous ΔF508 children. After 6 months, improvement was seen in the control patients due to good nutritional care, but they never quite reached levels of the screened children. Longer follow-up, though, has shown a persistent advantage in the screened

Correspondence to: Dr Ian M Balfour-Lynn, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK; i.balfourlynn@ic.ac.uk

group still present at 16 years. This was particularly significant since, by chance, there was a disproportionate number of pancreatic sufficient children (with their expected better nutritional status) in the non-screened group (21% vs 8%).[3] Furthermore, at diagnosis plasma α-tocopherol (vitamin E) levels were less than 300 μg/dl (which is the lower limit of normal for biological antioxidant function) in 49% of screened babies compared to 73% of the control group.[23] After diagnosis, reduced vitamin E levels in the pancreatic insufficient children lasted longer in the non-screened group (37% vs 4% at 6 months).

Brain

Most importantly, the Wisconsin study has linked early poor nutrition in the non-screened children with later cognitive differences. Testing of cognitive function was carried out at 7–16 years of age, and overall the results were in the normal range, and the same for screened and non-screened children with CF. However, control children with vitamin E deficiency at diagnosis (plasma α-tocopherol <300 μg/dl) had a significantly lower Cognitive Skills Index compared to screened children who had initial low vitamin E levels, and all the children with normal vitamin E levels.[23 24] The difference found was both statistically and clinically significant, and likely to translate into a functional difference such as lower academic achievement. These children also had the lowest head circumference z scores at diagnosis.

Other systems

There is no evidence yet that screening provides advantages in terms of other CF complications such as liver disease, CF-related diabetes, arthropathy, sinusitis, etc. Longer follow-up from the Wisconsin trial may clarify this in time, although numbers may be too small with the less common complications. It will be particularly interesting to see whether there are differences in outcomes that may relate to early nutrition, such as low bone mineral density and perhaps diabetes.

Early specialist care

Regardless of screening, advantage has been shown for children treated in CF specialist centres,[25] although this can be cancelled out if cross-infection is a problem, as was seen in the earlier *P aeruginosa* acquisition in screened children treated in one of the Wisconsin centres.[20] One reason no advantage was seen in nutrition or chest radiology in the Wales/West Midlands study may have been that once diagnosed, children were not referred to a CF centre.[5] It is likely, therefore, that NBS will result in proper CF care from the start, which will be an advantage for the children as long as referral pathways result in care in specialist centres and cross-infection is prevented.

Pre-symptomatic treatment

NBS should allow early pre-symptomatic treatment, one of the main principles behind any newborn screening program. The problem, however, is that currently the evidence is not too convincing for such treatments (eg, anti-staphylococcal prophylaxis, chest physiotherapy, anti-inflammatory therapy, etc). In time, however, this may be a critical issue, as for future therapies (including gene therapy) to make a significant impact, it is likely they will need to be given early, that is, before the lungs have become infected and damaged.

Avoidance of early complications

With prompt diagnosis, treatment can be initiated in time to avoid some of the early complications, such as electrolyte imbalances due to salt loss, and oedema from hypoproteinaemia due to protein energy malnutrition. These complications are much less common in properly treated screened babies, for example, 9% of babies diagnosed from clinical symptoms had electrolyte imbalance or oedema compared to 3% of screened babies.[2]

Advantages to parents and family

Quality of life

Any early advantages in quality of life resulting from NBS are going to affect the parents and family rather than the infant, as clearly these can not be measured in the very young. A small study that attempted to assess quality of life in children aged 10–15 years did not find any differences in those who had been screened, but numbers were probably too small to be able to show any differences, which were likely to be somewhat small at that stage anyway.[26] Further work from the Wisconsin group is in progress.

Greater trust in the medical profession

There is no doubt that parents whose children have been diagnosed late, have an innate mistrust of doctors and health care workers and are often angry. This is especially the case when the parents have been saying there is something wrong with their child and are treated as neurotic parents, so not surprisingly, delayed diagnosis is associated with greater parental anxiety.[27] Sometimes the child has had repeat hospital admissions and poor control of symptoms.[6] A Dutch study showed that a short pre-diagnostic period (defined as time from first parental concern over the child's health to confirmation of CF diagnosis of less than 3 months) was associated with less negative feelings in the parents, and increased confidence in the medical profession compared to those diagnosed after 3 months.[28] This can sometimes create a problem since the CF multidisciplinary team and parents need to form a close co-operative bond.

Reproductive decision-making

Early diagnosis of an affected child allows genetic counselling for the parents and provides an opportunity for them to make informed decisions about having further children. One study showed that in a third of families with a second affected child, the delayed diagnosis of the first child meant it was too late for reproductive decisions to be made.[29] In the Brittany study, a third of couples with a child diagnosed by NBS, opted for prenatal diagnosis of a subsequent pregnancy; 30% of fetuses were affected and all were terminated.[30] Ultimately this would reduce the number of children born with CF and might reduce the number of families with more than one affected child. However, not all parents opt for termination, and often the early diagnosis of an affected child has no impact on reproductive decision-making.[31] There is also the option of pre-implantation diagnosis with only unaffected embryos being implanted.[32] Finally, NBS has an impact for the extended family of a screened infant, as cascade screening can be done to enable family members of reproductive age to find out their own carrier status in good time.[33]

Advantages to society

Financial

Cost analysis favours NBS, and direct medical costs of screening compared with making the diagnosis by other methods were $8000 less per patient (based on USA costs in 2000).[12] If anything, this is an underestimate of the financial benefit, as the analysis did not include tests other than sweat testing in the clinically diagnosed group, and many would have had a series of other investigations performed. Further cost benefits of NBS result from

less time spent in hospital in those diagnosed by screening, particularly in the first year of life.[2 5 19] Most recently, a "cost of illness retrospective snapshot cohort study" compared the costs of long term therapies and intravenous antibiotics in screened versus clinically diagnosed children aged 1–9 years in the UK.[34] It was found that savings from the cost of treatment would offset a significant part of the actual costs of adding CF screening to the existing national newborn screening program.

Clinical trials

Diagnosis by NBS also presents an opportunity to enrol babies into suitable randomised controlled trials before lung disease has progressed. This benefits the CF population as a whole, although it may also benefit the patient as well, since participation in clinical studies often has subsidiary benefits.[35]

Potential downsides

Acquisition of *Pseudomonas aeruginosa*

In the days before the enforcement of segregation, evidence showed that children who had been cared for in a specialist centre acquired *P aeruginosa* at an earlier age (although possibly it was simply detected earlier due to better microbiological surveillance).[25] In the Wisconsin study, a disproportionate number of screened children in one of the centres acquired *P aeruginosa* early and this adversely affected their lungs, so that no pulmonary benefit was detected in the screened population.[20] With appropriate segregation, however, it is hoped that this will no longer be the case, although evidence is not yet available. Conversely, the study based on the US database did not find earlier or more prevalent *P aeruginosa* in screened children but in fact found more mucoid *P aeruginosa* in the group presenting with symptoms,[2] and the work from the UK database also found that up to 6 years of age, there was less chronic infection with *P aeruginosa* in the screened children.[1]

The effect on parental bonding of early bad news

Learning your child has a life-limiting condition is appalling for every parent. There is recent evidence that suggests that parents may be more vulnerable to depression when their child is diagnosed during the first few months of life,[36] and it is established that maternal depression may adversely affect parental bonding. However, a review of several studies concluded that the inevitable shock and anxiety is no greater for parents of screened cases than those clinically diagnosed, nor is the mother–baby relationship more negatively affected.[31] It is hoped that parents gain some consolation from the knowledge that the condition has been detected before it has caused significant lung disease or poor nutrition. There are some data suggesting that NBS has the potential for reducing the long term adverse psychosocial consequences of a delayed diagnosis.[37]

Earlier diagnosis of mild or atypical cases

NBS will bring to light a number of mild or atypical cases at an age at which they may never have been clinically diagnosed.[12] There are also some children with two CFTR mutations who have a normal sweat test, and their diagnostic classification is still controversial.[38] Without a "curative" treatment this may well disadvantage children with mild or atypical disease, as they are likely to be exposed to treatments and interventions that may not be necessary at that stage in their disease. They also risk microbiological exposure, although segregation may reduce this risk. Finally, the family will potentially have an extra decade or so of anxiety and concern over their child's health.

False negative cases assumed not to have CF

With any complex screening regimen, some cases will not be detected, either due to errors or genuine biological variance; in three screening programs in the USA, the rate of known missed cases was 2–4%.[39] This is a concern, as some doctors may believe erroneously that a child can not have CF if they are born after screening was in place throughout the UK, and this will lead to delays in diagnosis. Vigilance must also be maintained for those who are born outside the UK in non-screening countries.

Carrier detection

A significant number (but not all) of CF carriers will be detected by the NBS program, which has been designed to identify as few carriers as possible. These children are the "false positives" of the regimen, the screen-positive babies who do not have CF. This has been shown to lead to misunderstandings and results in negative emotional responses from parents.[12] Studies have shown that even 1 year later, some parents believed their child had CF or might still develop it.[31] Some parents also believe their child is "not normal" and might become ill as a result of being a carrier. This is a tricky issue, as although CF carriers tend to be perfectly healthy, group data show an excess of CF carriers amongst adults with idiopathic bronchiectasis, pulmonary non-tuberculous mycobacterial infection, chronic rhinosinusitis and idiopathic chronic pancreatitis.[40–42] There are no studies on the long term implications for carriers identified by NBS, and little evidence they feel stigmatised (including by health insurance agencies).[31] The key is sympathetically delivered comprehensive genetic counselling for parents of carriers.[43] Further issues are that the child will need to learn of their own carrier status at an appropriate age, which is normally felt to be in the mid teens; it is also important that the parents remember to tell their child. There are also implications for the extended family as there is then an increased chance they are also carriers.

CONCLUSIONS

Largely thanks to the Wisconsin screening project, the evidence in favour of CF NBS is now convincing. On balance, there is enough evidence to support its universal introduction, particularly since the potential for causing harm is small and certainly outweighed by its potential for providing benefit. Although currently this evidence is strongest for nutritional and cognitive effects, it is likely that future respiratory therapies will lead to significant advantages for lung health as well, although attention to *P aeruginosa* must remain paramount. In time, we will hopefully see that starting appropriate treatment before chronic lung infection and damage are established should lead to a further increase in life expectancy for people with CF. Screening has become universal in the UK – the task now is to ensure it is carried out smoothly and effectively, with clear referral pathways in place. It is also vital that everything is done to minimise distress for the families.

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