What and when to collect from infants with cystic fibrosis

Iolo Doull

Perspective on the papers by Cipolli *et al* and Hilliard *et al* (see pages 842 and 898)

Audit used appropriately can significantly alter our practice, and two such studies appear in this month's issue of *Archives of Disease in Childhood*. The first from Italy and Australia addresses the outcome of infants detected through newborn screening (NBS) who are pancreatic sufficient at birth, and informs us that outcome is dependent on genotype.¹ The second from London assesses the value of flexible bronchoscopy to obtain a bronchoalveolar lavage (BAL) following a clinical diagnosis of cystic fibrosis (CF), and highlights the fact that the preschool CF child often has ongoing infection despite the absence of symptoms or positive upper airway culture.²

CF is caused by mutations within the gene encoding the protein cystic fibrosis transmembrane conductance regulator (CFTR), and it is now clear that there is a hierarchy of disease severity associated with different genotypes. Mutations within the gene can be divided into five broad categories (I–V) dependant on how the gene defect affects CFTR protein production,³ and by and large CFTR function at the apical membrane decreases sequentially from milder class V to severe class I mutations. So subjects with two severe mutations (classes I, II and III) have a poorer prognosis and are less likely to be pancreatic sufficient compared to subjects with one or two milder mutations (classes IV and V).⁴ Different organ systems appear to show differential sensitivity to decreased CFTR function, and disease phenotype is a reflection of CFTR function within those organs. For example, the vas deferens is very sensitive and affected even when CFTR function is relatively well preserved, and thus male infertility is a feature even in mild cases. In contrast, severe early lung disease is generally not seen until CFTR function is very low, and so is present in more severe phenotypes. The pancreas lies between these two extremes, and those with milder CFTR mutations, and so a higher level of CFTR function, are often pancreatic sufficient.

Historically, pancreatic sufficiency was associated with greater life expectancy,⁵

and the temptation has been to be relatively more positive with parents of pancreatic sufficient infants. However, there was concern that although the majority of these infants have milder genotypes (with at least one class IV or V mutation), a small proportion of pancreatic sufficient infants carried two severe genes (class I–III). The report by Cipolli *et al* is helpful as they show that during the first decade of life 20 out of 34 infants with severe genotype became pancreatic insufficient, while none of those with a milder phenotype did. These findings are in accordance with previous smaller observational studies⁶ and with the US CFF national registry where 97% of subjects with severe CFTR genotype are pancreatic insufficient compared with 51% of those with a mild CFTR genotype.⁷

However, CF care in the UK is different from that in Italy or Australia – the NBS protocol in the UK is markedly different, and currently 80% of the UK CF population carry one or more $\Delta F508$ mutation. Furthermore, Cipolli assessed pancreatic sufficiency by the classic measurement of 3-day faecal fat; this test is unpopular both with the families collecting the samples and the laboratories who have to process them, and so is rarely performed in the UK. The majority of the laboratories in the UK now measure faecal elastase which has the advantage of simplicity of collection and excellent correlation with direct and indirect measures of pancreatic function.⁸ Nevertheless, Cipolli's findings are applicable to clinical practice in the UK.

All infants with CF, irrespective of their genotype, should have exocrine pancreatic function measured at diagnosis, and those who are pancreatic insufficient should be commenced on pancreatic enzyme replacement therapy (PERT). Measurement of faecal elastase is by far the easiest option. If in doubt it is better to start PERT as treatment does not interfere with subsequent faecal elastase measurements. In those infants who are pancreatic sufficient but carry a severe CF

genotype, faecal elastase should be monitored as part of their annual assessment, or at any time if symptoms suggest maldigestion. For those subjects with milder phenotype, there seems little need to measure pancreatic function during the first decade of life. In my limited experience, teenagers with CF seem more reluctant to supply faecal samples than virtually any other bodily material. It may therefore be reasonable to propose that pancreatic sufficient children with a mild genotype should only have assessment of pancreatic function if there is onset of symptoms suggestive of maldigestion. Cipolli's findings add to the evidence that genotype is the strongest predictor of pancreatic exocrine function, irrespective of pancreatic function at birth.

The proportion of subjects with CF who are pancreatic sufficient differs depending on how the population was identified. It is likely that the relatively lower rate of approximately 15% of pancreatic sufficiency in historical studies reflects under-diagnosis. Using the older immunoreactive trypsin (IRT)/IRT based screening protocol, the Australian authors reported a 37% rate of pancreatic sufficiency, but using IRT/DNA the proportion fell to 28%. The proportion of pancreatic sufficiency in the Italian population was lower still at 23%. However, the Australian investigators tested only for $\Delta F508$, while the Italian investigators tested for 13 mutations. In contrast, the new UK NBS programme screens for either 31 or 33 mutations. It will be interesting to see if this results in a comparatively higher proportion of identified infants being pancreatic sufficient.

Although the CF airway appears normal at birth, there is compelling evidence that infection and an exuberant inflammatory response occur early in life. It is now over a decade since Grimwood⁹ reported that even in young infants with CF (mean age 2.6 months) detected almost entirely through NBS, a third had lower airway bacterial infection on BAL. A third of the infected infants were asymptomatic at the time of BAL, and upper airway cultures were poorly predictive of lower airway culture. This same group of children subsequently had elective BALs performed on an annual basis for their first 3 years of life. Lower airway bacterial infection was present in a quarter of BALs, and only half of these were symptomatic at the time of testing.¹⁰ In a similar study of infants with CF diagnosed clinically who had BALs performed for their first 3 years of life, a CF pathogen was isolated annually in two thirds of subjects.¹¹

Hilliard and colleagues elected to obtain a BAL sample for microscopy and

culture in all new CF patients, the vast majority of whom had been diagnosed on clinical presentation.² Nearly half of the 25 patients had a positive culture on BAL, despite the fact that 80% of the infants were on prophylactic antibiotics at the time of BAL. Furthermore, nearly half of the 18 children who were asymptomatic at the time of BAL had a positive culture. Most importantly, five of the subjects had *Pseudomonas aeruginosa* identified on BAL while upper airway cultures were negative, confirming the often poor relationship between upper airway cultures such as cough swabs and lower airway culture. The BAL resulted in a change in management in nearly half of the cases, although it is difficult to prove that this changed outcome.

Although these infants may have been asymptomatic at the time of the BAL, the majority of them would have presented with respiratory symptoms sufficient for the diagnosis of CF to be considered, and so their lungs would in no way be considered pristine. In contrast, those of us fortunate enough to care for infants who are diagnosed through NBS recognise that many of these infants are completely asymptomatic at diagnosis, and with appropriate therapy can remain relatively asymptomatic throughout infancy. We thus hope that infants identified through NBS will still have perfect lungs at diagnosis, and that early intervention will preserve their pristine nature. The reality is that we underestimate the ongoing infection and inflammation within the infant CF lung, and that sensitive measures of pulmonary

function,¹² high resolution computed tomography¹³ and BAL^{2 9-11} all demonstrate significant ongoing damage.

How should Hilliard's observations change our practice? Current practice in infants with CF is to blindly treat with oral antibiotics at the onset of lower airway symptoms, yet in Hilliard's study, in the seven symptomatic infants BAL identified three pathogenic organisms (including one *P aeruginosa*) not identified by upper airway culture. Although numbers were small, it is arguable that we should perform BAL on all symptomatic infants with CF prior to treatment. Flexible bronchoscopy is quick, safe and informative; I would disagree that bronchoscopy always requires general anaesthesia as it can be performed simply (particularly in this age group) under sedation. Whether we should routinely collect BAL from asymptomatic CF infants is unclear. There is insufficient evidence at present, and we must await the findings of ongoing prospective trials from Australasia.

The strong message from this study is that infants with CF often have ongoing lower airway infections, and that these infections frequently will not be detected without bronchoscopy. We should have a much lower indication for culture by BAL, and it should become routine CF practice. And lastly, we need prospective trials to examine whether systematic collection of BAL will alter outcomes.

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Safeguarding children is everyone's responsibility: UK government statement on the duties of doctors

Terence Stephenson

The first duty of the paediatrician is to the child or young person

Over the past few years, some paediatricians have faced legal action as a result of their involvement in child protection cases. Others have had vexatious complaints of which only a tiny minority have been upheld.^{1 2} A survey of members of the Royal College of Paediatrics and Child Health (RCPCH) found that 13.8% of over 4500 respondents had been subject to a total of 786 complaints about child protection and that the number of complaints per year had increased from less than 20 in 1995 to over 100 in 2003.³ Of those complaints resolved at trust or NHS level (including the NHS Ombudsman), less than 3% were upheld. Of 87 referrals to the UK General Medical Council (GMC), only that against Dr David Southall was upheld. The GMC extended the 2004 ban against him working on child abuse cases by a further 12 months on 23 July 2007.

As a result of these factors, many paediatricians have been deterred from giving expert evidence in suspected child abuse cases, adding further delays to a slow system⁴ and resulting in the Chief Medical Officer's consultation document *Bearing good witness*.⁵ This is against a backdrop of some health professionals describing a reluctance to report suspected child abuse,⁶ a worrying situation and potentially taking us back to the days before Henry Kempe's seminal work on non-accidental injury.⁷ A stratified random sample of 979 nurses, doctors and dentists working in primary care in Northern Ireland were sent a postal questionnaire; 419 responded, giving a 43% response rate. The data were collected in 2002–2003. In their working lives, 60% (251) said that they had seen a suspicious child physical abuse case; however, only 47% (201) had reported a suspicious case to the authorities, leaving a 13% gap in reporting.⁶

Lord Laming wrote "staff who undertake the work of protecting children and supporting families on behalf of us all deserve both our understanding and our support" and "staff doing this work

need... persistence and courage".⁸ However, neither his report nor the government subsequently addressed how paediatricians were to be supported and understood when parents, who may be implicated in child abuse, used complaints procedures and the media to attack them.

THE GOVERNMENT AND THE MEDIA

The UK government has appeared reticent to openly support UK paediatricians. Behind the scenes, the RCPCH has worked hard to persuade ministers and civil servants of the need for such a signal. At 10:06 on Friday 20 July, the Children's Safeguards Policy Unit released a two line "email shot" announcing that a "Joint DCSF/DH Statement on the duties of doctors and other health professionals in investigations of child abuse" had been placed on the government departments' websites⁹ - there was no fanfare, no press launch and not even a press release. However, 23 days after Gordon Brown assumed the office of prime minister and created the new ministerial Department for Children, Schools and Families, this is a welcome if muted recognition of paediatricians' invaluable contribution. The accompanying ministerial letter stated "the government has made the problem of tackling child abuse and improving safeguards for children a top priority".

This quiet announcement contrasted with coverage relating to child protection in the UK national newspapers for the same day. *The Guardian* newspaper¹⁰ quoted two paediatricians writing in the *British Medical Journal*¹¹: "Uncertainty over what constitutes a sudden unexpected infant death means some deaths may be wrongly reported as being due to 'natural causes'". *The Times* and *The Independent* ran with the same story. *The Guardian* continued: "The debate over cot death intensified when Professor Sir Roy Meadow gave evidence at the trial of solicitor Sally Clark in 1999. She was

convicted of murdering her two sons but freed by the Court of Appeal in 2003. Prof Meadow told the jury at her trial there was a "one in 73 million" chance of two children dying from cot death in the same affluent family. Mrs Clark was found dead at her home in March, more than 18 months after Prof Meadow was found guilty of serious professional misconduct by the General Medical Council (GMC) and struck off. Both of those decisions were later overturned after an appeal at the High Court".

The following working day, *The Guardian* followed up with a piece about Dr David Southall¹²: "Why should a doctor be punished for raising concerns he believes are valid? *The entire child protection system hinges on the willingness of individuals to raise such concerns, whether proved right or wrong* [my italics]; and that willingness depends on them being free to do so without fear of losing their livelihood. For the past decade the GMC has lacked the courage to deal with vexatious complainants and, in its determination to show it doesn't favour doctors over patients, has allowed itself to be exploited by campaigners dedicated to disrupting child protection. Southall, a cot-death pioneer who has saved countless lives, has been a marked man since his research led him to the unpalatable conclusion that some mothers deliberately harm their own children". It is of note that, unlike controversial MMR research for example, Southall's research on smothering has never been disproved or withdrawn by a journal.¹³

Dr Southall faces further disciplinary proceedings following an allegation he kept more than 4000 "special cases" files on children: "He now faces a series of GMC hearings, all linked to the same group that has campaigned tirelessly against him... Accused parents have lawyers, campaigners, the media and, it seems, the GMC to speak up for them. Infants have only frontline professionals, and under the Children Act it is their responsibility to put the child's interests before any other consideration. If society continues to vilify them, the price will be paid with the suffering and death of society's weakest members".¹²

THE JOINT DEPARTMENT FOR CHILDREN, SCHOOLS AND FAMILIES/DEPARTMENT OF HEALTH STATEMENT

So what do the eight pages of 2223 carefully chosen words,⁹ all scrutinised by lawyers, say and do they provide solace for paediatricians? There are seven key messages for us all:

1. In child protection work, paediatricians' first duty is to the children

concerned, even if the consequences of acting in good faith are distressing for the parents.

2. In the case of *D vs East Berkshire*, the House of Lords stated unequivocally that "when considering whether something does not feel "quite right" a doctor must be able to act single-mindedly in the interests of the child".¹⁴
3. Paediatricians undertaking child protection are part of multi-agency teams and need to be aware of legislation and guidance relevant to child protection work, in particular, the desirability of working with parents whenever possible, the law regarding consent to treatment and examination and the concept of "Fraser competence", and the recognition that sharing appropriate information with relevant authorities is neither a breach of patient confidentiality nor of the UK Data Protection Act. The sentiments of the 1989 Children Act still inform such judgements: "the welfare of the child is paramount".
4. The European Convention of Human rights does not prevent paediatricians doing their job well. The Court of Appeal stated that the principal purpose of Article 8 ("everyone has the right to respect for his or her private and family life"), at least where there are children, must be the safety and welfare of the child.¹⁵
5. In reaching sound judgements, paediatricians should (as in all clinical work) take account of all relevant factors, keep an open mind and consider all reasonable alternatives,

consult appropriately, recognise the limits of their expertise, and acknowledge where there is lack of information. (I would add that it is also good practice to document, date and sign all clinical findings and the decision making process.)

6. If giving evidence in court, the obligation of a paediatrician as a professional witness is to be an independent advisor to assist the court, not an advocate for a particular party or theory.
7. Paediatricians would not be liable for defamation unless it could be proved that they acted maliciously.

Whilst the legal references are drawn from English case law, I believe that all paediatricians in the UK and Ireland could draw on these principles unless their jurisdiction explicitly states otherwise.

SUMMARY

Paediatricians' first duty is to the child or young person. Paediatricians should not be distracted by a parallel duty to anyone else, including parents. At last we have confirmation publicly that these are also the views of the UK government.

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