Dear All

We have got a little behind this year with our newsletter so are taking the opportunity to update you promptly on the June European CF Conference that took place in Dublin, where it rained and blew a gale throughout! As always we hope that you find this interesting and please feed back to us to let us know how it might be improved next time. Scientists and clinicians continue to make progress in CF care so we have much to tell you.

First a couple of issues affecting the Adult Unit -

Sadly a small number of patients are using social network sites to abuse the unit and to make personal attacks on members of staff. This is not unique to the Leeds Unit and is clearly behaviour that should not be tolerated by any of us. There are defined channels for complaints to be made in a proper fashion if you are unhappy with any aspect of care and you should use these if you have a grievance. You will be heard by an independent person. We hope that those of you who have used network sites to abuse the Unit will consider your actions and realise that they are not acceptable.

Secondly we are going to try to get a greater number of sputum as opposed to cough swab samples by encouraging you to collect a sputum sample at home shortly before your clinic visit. Daniel has written about this below.

So, again we hope you enjoy this newsletter and that at some point before Autumn we see some English sun!

Steven Conway

Firstly, I would like to wish you all a very HAPPY SUMMER and hope that the sun soon comes out!

I am really writing to ask for some help from you as for some years we have had real problems obtaining sputum samples from some individuals in clinic. What is very noticeable is that a lot of people are able to cough before clinic but then for some reason they cannot provide a sample. As you know, a lot of the segregation as well as treatments are all based on identifying pathogens early and I think it is really important we try and reduce the number of cough swabs, which has increased recently, and get good quality sputum specimens instead. I should be very grateful when you attend clinic if you could ask for a sterile sputum pot and then on the day or the evening before you next attend clinic/ward try and produce a sample, which you can then give to the physiotherapists at the clinic visit. The information provided from good quality samples will be key to improving management and ensuring that everybody has the best possible treatment.

Should you have any anxieties or wish to pass on some good ideas with reference to treatment then please mention this when you next see us in clinic.

Daniel Peckham

Long Term Consequences of Care

This session concentrated on three areas - metabolic complications, renal problems, and drug-induced complications. The main message is that complications that we all felt were not high priority in care because of the reduced life expectancy in the past have now become important because people with CF are living well into adult life. Today’s children with CF should live longer than their parents. All adult units have patients in their 40’s and 50’s. So we need to take account of the following - and to treat them optimally:

Diabetes - most adults with CF will develop diabetes at some point. Although there are
discussions about the best screening test it is accepted that annual screening tests are essential so that treatment can begin early and complications minimised. Diabetes in CF is going to cause the same complications as it does in those without CF. Good blood sugar control is needed. Expert diabetic care overseen by a specialist is needed.

**Bone complications** - CF predisposes to early osteoporosis (thin bones). Many factors contribute to low bone strength. Annual blood tests can screen for vitamin D and calcium levels etc and abnormalities can be corrected to prevent bone loss. Thin bones need to be picked up early by a special scan, the DXA scan, so that treatment can be started before there are bone fractures. In a presentation by Dr Etherington from our adult unit it was highlighted how the number of patients with bone problems has decreased markedly over the last 10 years because we have worked hard with you to maximise nutrition and to correct any predisposing factors.

**Kidney problems** - Good renal function may be compromised by aminoglycoside antibiotics (tobramycin) and colomycin. Whenever we use these drugs we need to monitor renal function with regular blood tests and only to use them when they are the best attack on respiratory infection. We stopped routine three-monthly IV treatments some time ago, believing that the risks of frequent elective therapy outweighed the benefits now that people with CF enjoy such better health and will live so much longer. Four elective IV courses annually for over 50 years is an unnecessary risk.

**Drug-induced problems** - In Leeds we keep an updated computer record of your drug allergies/intolerances. Dr Paul Whittaker and Dr Daniel Peckham have done some innovative and high quality research with Liverpool University on the pathology behind drug allergic responses in CF. In general terms as noted above we need to monitor aminoglycoside use as these drugs can also damage the hearing and balance centres. Azithromycin, though reducing lung inflammation, may predispose to other infections. There must always be an appreciation of the balance between the benefits of a drug and its potential side effects.

### New treatments

#### A New Inhaled Therapy

Many of you will have heard of the dry powder inhaled tobramycin - the podhaler - and in Dublin the dry powder inhaled colomycin was unveiled. One capsule twice a day in a disposable inhalation device that fits in a pocket. It is quick, easy and no cleaning. Hopefully, you will soon be able to make a choice of your favoured way of taking inhaled antibiotic therapy - dry powder or nebulised, or switching from one to the other according to the situation at the time, e.g. nebuliser at home, dry powder when away on holidays.

#### Getting the abnormal protein (CFTR) produced in CF to work better

1) In CF the liquid in the airway is too sticky because the cells take in too much sodium and the sodium is followed into the cell by airway surface water, dehydrating the airway surface. If we could block the movement of sodium into the cells more water would remain on the surface, the mucus would be less sticky, and there would be less infection. Drugs that block the excess movement of sodium into the cell are at advanced stages of development.

2) About 10-20% of people with CF have a mutation that just stops the production of the protein that is produced by the non-mutant gene. Trials mostly in the USA, Israel and France have looked at a drug that allows the genetic code to be read despite this “road block” so that a normal protein comes off the assembly line. The results seem promising but not dramatic. We await the full data in a scientific paper.

3) Other exciting studies on the use of “corrector” drugs that stop the cell destroying the abnormal protein made by the CF gene, and “potentiator” drugs that help the protein to work properly when it reaches its working position on the cell surface, continue. In people with the G551D mutation the potentiator drug increases FEV1 by 10%. In people with the more
common delta F508 mutation early interim analysis suggests that about 35% of people in the trial show greater than 5% increase in FEV1 and 19% show greater than 10% increase.

From Mouse to Pig

The conference ended with an excellent update from the Iowa University Hospital on their research with the CF pig - animals having the CF gene and in lung structure much closer to humans than the CF mouse. There are no immediate clinical benefits but their work is increasing our understanding of the basic problem in CF and for sure will lead to new effective therapies in the future.

"New" Infections

As we are more successful at treating common infections in CF such as Staphylococcus and Pseudomonas, so "new" infections come along to fill the gap! We are seeing more people with MRSA infections and with bacterial infections that don't cause disease in the healthy lung, but can cause problems in the CF lung. One of these is the family of bacteria called mycobacteria, e.g., Mycobacteria abscessus, Mycobacteria avium intracellulare. The difficulty for the doctor is to know whether the bug is just sitting in the lung harmlessly or whether it is causing lung damage. Although we do treat some of these infections, we have long discussions first because treatment is for a long time, over a year, and some of the drugs may have important side effects. At the meeting various drug combination treatments and the ways to try and determine if the bacteria are causing real disease, were discussed.

Delegates view the research poster area, and Orla Tinsley who has CF speaks at the Opening Ceremony

Specific Latest News about Improving Treatment:

Ataluren for people with Class 1 CF Causing Mutations:

We know there has been lots of interest in the Ataluren clinical trials from those 8-10% of you that know you are affected by Class 1 CF causing mutations. Results of the large randomised controlled trial of this agent taken by mouth in 232 volunteers aged six years and above with class 1 CF mutations were presented and unfortunately were not as dramatic as hoped. Lung function only improved by 3% compared to the placebo (dummy arm) over 48 weeks of study, and chest infections reduced by 24%. There was no effect on sweat test results. There were some side effects that caused concern, particularly with regard to causing potential problems with kidney function. Further analysis of the study results is needed. We will keep you posted in clinic, and you will be able to follow the results online by putting “ataluren” or “PTC Therapeutics” into your search engine.
**VX770 and VX809 combination for people with delta F508 CF Causing Mutation:**

Approx 70% of people who attend our paediatric and adult CF clinic carry at least one copy of the delta F508 gene, with most of these people having two copies of delta F508. For this group we have interim results of a large clinical trial which are looking promising. 19% of volunteers in the clinical trial experienced a 10% improvement in lung function, and there were also sweat test improvements. You can see a press release regarding this drug on the “Vertex” website. The safety and side effect profile appears good. This drug combination is taken orally twice a day, so will be easy and quick to take. We expect full clinical trial results to be presented in October at the North American CF Conference, and depending on these results a decision will be made as to whether this drug combination can be licensed for clinical use. It is worth you being aware that Vertex Pharmaceuticals (and indeed some other companies) have some other promising products in early development (e.g. VX661) that may be more effective than VX809. This family of agents is looking extremely promising for the future in terms of keeping stable health in the long term, although there is anxiety regarding how expensive these drugs will be, based on how expensive the first drug in this family “VX770/Ivacaftor/Kalydeco” (which are the three different names this drug used specifically for G551D CF mutation goes under) is in the USA where it is already approved for G551D patients. For more details regarding this do look on the CF Trust website.

**VX-770 for people with Class 3-5 CF Causing Mutations:**

There are a small number of you who have rarer class 3-5 mutations causing your CF. For some of you this means that your CF is towards the milder end. Research was presented at the Dublin conference suggesting that VX770/Ivacaftor/Kalydeco may be effective for people with these mutations too. Further work is needed to see if the clinical benefits for people with these mutations make it worth taking the drug, and we will keep you posted as more information becomes available.

**New Dry Powder Antibiotic Inhalers (e.g. Tobramycin and Colomycin) may be quicker and more convenient for some:**

We often hear from you that you do find nebulised therapy time consuming, particularly when you consider the time it takes you to clean and dry your nebuliser after each use. You tell us that this can be frustrating for many of you who need to take nebulised antibiotics twice a day to treat infections like Pseudomonas. At the conference we heard the latest news about dry powder inhaler forms of Tobramycin (TIP) and Colomycin (Colobreathe). These are quicker to take, don’t need cleaning (as they are disposable, each one lasts for seven days, and then you open a new
inhaler), and are very similar to inhalers used for treating asthma. They seem as effective as the nebulised forms of the drug. Some people may find it causes cough, but we think it may be a case of seeing whether nebuliser or dry powder works best for you. The Tobramycin inhaler is now available and funded for NHS clinical use, whereas Colobreathe is not yet available in the UK, but will probably become an option here in the autumn. We will keep you updated when we see you in clinic.

With improving long term outcomes CF teams need to work harder at supporting parents and young people with CF to make the most of their education in order to achieve their chosen career and life choices without letting CF hold them back: We hope and anticipate that with our current treatments and those treatments just around the corner, a full, active, and fulfilling adult career should be possible for all.

As you know, we are committed to helping you all protect your long term health, and are delighted with the improvements in average lung function, nutritional outcomes, quality of life, and life expectancy, that we are seeing compared to five, 10, and 15 years ago. In the past parents did not have the hope and expectation that their children with CF would be well enough to hold down a job or develop a career, and consequently school, college, apprenticeships, or University etc were not seen as priorities or even options for their children in the future. Having CF has thus limited young people’s ambitions and aspirations. We are very conscious that we do not want this to be the case, and we sincerely want to work with you all to listen carefully to your short term and long term plans and goals and ambitions. We can thus work with you to plan how to support you in keeping your CF under control, so that you can minimise CF getting in the way of the things you want to achieve and enjoy.

**Poster from Leeds Adult CF Centre showing employment experiences of adults with CF attending the Leeds Centre:**

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**CF Health remains stable through the period of transition from paediatric care to adult care in Leeds. Dr Alison Thorpe from the Paediatric Unit presents our experiences with the Transition process to adult CF services in Leeds:**

Many parents express to us their anxiety at the time their son or daughter with CF approaches the age at which transfer occurs to the Adult CF Centre (approximately 17 years of age). As you know we try to minimise this anxiety by discussing the process with you in advance, organising a tour of the adult centre, and making you aware of how closely we work together as adult and paediatric teams, using shared protocols, clinical electronic notes, and performing a careful joint handover clinic. Dr Thorpe from the paediatric unit has undertaken a careful review of the clinical progress of everyone who has transitioned to the Adult Centre over the last 10 years. Encouragingly the results demonstrate that people with CF in Leeds remain stable for the year before and after they transition to adult services.

We all want CF Treatments to continue becoming more effective, but also easier to take and less time-consuming. Clinical Trials of new potentially better treatments are the only way to make this progress, and as you probably know here at Leeds we are one of 30 European CF Society Clinical Trial Network Sites, situated at leading CF Centres across 11 European Countries.
From time to time we may talk to you about clinical trials of new CF treatments that you may wish to be involved with. Whether or not you choose to be involved, we thank you for considering being involved in such studies, as it is the only way that new and better CF treatments can be developed.

A UK study reports that many CF patients have beliefs and concerns that mean they don’t take their nebulised medication regularly:

A total of 59 patients with CF from Wales (mean age 27 years) completed a Beliefs about Medicines questionnaire, and results were compared to how much nebulised treatment they were actually taking. Almost one-third of patients expressed doubts about their personal need for nebuliser therapy, even though the CF team had prescribed it for them. Only 22% of patients said that the full dose was needed for treatment to work. Common issues with nebulizer therapy were that it was an unwelcome reminder of having CF (46%); it disrupted the patient’s life (40%), the concern that therapy would become less effective if used regularly (40%), and being embarrassed by nebulising (25%). A total of 54% said they forgot to nebulise; 41% said they did it only when they felt breathless. Patients who doubted the need for nebuliser therapy were significantly less likely to take them.

So: if this chimes with you and you are not sure about the point of taking your nebulisers please be honest with us in clinic so we can have a realistic chat about the pros and cons of taking your nebulised treatment.

Final Thoughts

There is much that looks promising! I know many of you tell us you won’t believe about progress until you have the new treatments in your hands, but there is a lot of change for the better just around the corner. We have already come a long way from the 1950s when there were no adult CF clinics and little in the way of antibiotics or pancreatic enzymes. As a paediatrician I can see childhood CF symptoms becoming less and less common over the next 10 years, which is a fantastic prospect. Just keep going with the treatments we have now, and keep listening out for the new developments.

Professor Stuart Elborn (President of the European CF Society) describes the progress of CF research over the last year. From a CF perspective the increasing numbers of delegates attending the conference from across the world is a good demonstration of the improvements in clinical care and new treatments.

Christine Etherington (Associate Specialist)

There were 360 posters at the Conference covering a wide range of issues/topics. I have decided to report what I feel were in my opinion the ‘top ten’ posters which I hope you will also find of interest. If you have any questions regarding any of the information please feel free to discuss it at your next clinic visit.

1) Simultaneous liver and pancreas transplantation in patients with CF

This was a poster from the liver transplant team at King’s College Hospital in London. Significant liver involvement affects only a small number of patients with CF and those with end stage liver disease require liver transplantation. The authors reported outcomes in two patients who were also diabetic and dependent on Insulin and pancreatic enzyme replacement. As you know the pancreas has two main functions - one to provide the hormone Insulin to control blood sugar levels and secondly to produce pancreatic enzymes to allow absorption of food. Both patients received liver and pancreas organ transplantation. Their nutritional status improved significantly and at 8-14 months post transplantation neither patient required any further Insulin injections and their need for
enzymes was either completely abolished or significantly reduced. This procedure has only been carried out in a few centres with just a few reports to date but I am hopeful that it may become more widely available in the future.

2) Dry powder formulation of inhaled Colomycin (Colobreathe®) compared to nebulised TOBI®

As you may be aware a dry powder inhaled form of nebulised Tobramycin has become available recently (TIP) and we will hopefully be able to switch patients who are currently nebulising TOBI to this inhaled version soon. The alternative drug patients nebulise if they grow Pseudomonas is Colomycin (prescribed as Promixin if given through the I-neb device). The company that manufacture the intravenous preparation of Colomycin (Forest Laboratories) have manufactured a dry powder formulation to inhale and they reported results on the safety and effectiveness of Colobreathe® versus TOBI® in a large multicentre study.

The study involved 380 subjects over six years of age from 66 different CF centres and the primary outcome measure was to show non-inferiority i.e. no difference between Colobreathe® and TOBI®

The results showed that Colobreathe® was as effective as TOBI in terms of change in lung function after 24 weeks and well tolerated. In terms of quality of life assessments patients favoured Colobreathe® which only requires inhalation of one capsule in the morning and evening.

3) Anti-inflammatory effects of Amitriptyline in patients with CF

Studies on CF mice have shown high amounts of ceramides in the lung, trachea and gut. Ceramides are lipids (fat molecules) involved in the structure of cell membranes and also are involved in the inflammatory response to Pseudomonas. Drugs that can inhibit ceramide formation are currently being investigated in CF. Amitriptyline (an anti-depressant) has been shown to inhibit the release of ceramide. This was a Phase 2 double blind study comparing Amitriptyline versus placebo (dummy medicine) for 28 days. A significant improvement was seen in FEV1 of between 6.3 and 8.5% in those taking Amitriptyline. In addition, a decrease in amounts of ceramide, reduction in Pseudomonas and reduction in inflammatory markers were seen.

These data confirm the findings of previous studies and support the notion of a positive anti-inflammatory effect of Amitriptyline in CF. Further phase 3 (larger studies of drug effectiveness) studies are eagerly awaited.

4) The use of Alteplase in Port-a-Caths that do not bleed back

This poster from the Manchester Adult CF Centre reported the use of a medication called Alteplase in patients with an indwelling access device (Port) where either the port never bled back or had bled back but then stopped. Alteplase is a medication which is used to break down blood clots in conditions such as a heart attack, stroke or clot in the lung (pulmonary embolus).

Nine out of the ten patients whose ports did not bleed back were given 2mg of Alteplase - seven (78%) bled back, two continued not to bleed (22%). The final port had Alteplase and was very stiff to flush and although it did not bleed back after the medication it was easier to flush. In some of patients more than one dose of the medication was given (on subsequent admissions).

The function of being able to withdraw blood from a port instead of a separate needle is much more favourable and less traumatic and the use of this medication should be given serious consideration. We will look into this further with our CF pharmacists but of course must bear in mind that these drugs have potential side effects and are not without any risk

5) Why do adult patients with CF attend their GP? A specialist CF centre’s perspective

There is little known about how often and the reasons why patients with CF visit their GP. Patients are usually reluctant to see their GP as they feel they do not have the specialist knowledge of CF that the CF centre team have. The poster presented the results of a questionnaire given out to patients from the adult CF centre in Cork, Ireland.

Despite being seen every three months at
their CF centre, 92% of patients had attended their GP at least once in the previous year with 45% attending at least three times. The majority (86%) attended for their annual influenza vaccination with 45% attending for renewal of their prescriptions. 18% attended for advice regarding contraception, 10% for a CF exacerbation and 6% for treatment of mood problems. In total 66% felt their GP had a good knowledge of CF.

The majority of patients (86%) preferred to attend the CF Unit for management of a suspected respiratory exacerbation and this preference was independent of the distance needed to travel to the CF Unit (up to a distance of 140km).

CF patients thus rely on their GP mainly for annual influenza vaccination and for issues relating to sexual and mental health. We need to ensure that GPs involved in Primary Care receive adequate support and CF education.

6) Canine detection of Pseudomonas aeruginosa

This was perhaps the most ‘fun’ and different poster presented at the Conference. Two dogs (foxhound cross and retriever cross) were professionally trained to detect blood, narcotics and explosives. As part of this they were trained to detect (sniff out) volatile organic compounds (VOC’s) of Pseudomonas. They first had to be challenged with compounds (acting as control) which were not Pseudomonas (such as Staphylococcus, Aspergillus) and following this were further challenged to a combination of compounds with and without Pseudomonas.

With 338 challenges, dog one successfully detected Pseudomonas in all cases and had only three false positives (detected Pseudomonas when not present). Dog two had nine false positives and one false negative. Overall the mean specificity for detecting Pseudomonas was 92%

Phase 3 clinical trials are now being planned to detect the VOC’s of Pseudomonas directly from patient sputum and captured breath. Don’t worry; however, we are not quite at the stage of dogs sniffing your breath when you arrive for your clinic visit!!

7) Survey of contraceptive practices in women attending a large CF centre

I had to include one of my posters in the top ten! This was a review of our EMIS computer records of contraceptive use in our patients and myself and Sarah Huntington, pharmacist presented the data in Dublin.

With the improved survival it is vital that effective contraception and sexual health choices are made in order to plan effectively for a pregnancy and to reduce the risk of unplanned pregnancies. We analysed data from 150 women attending our Unit. Out of the 150 women, 90 were using some form of contraception, and 60 were not. Out of the 60, 28 had a valid reason (currently pregnant, post-menopausal, no partner, fertility issues etc) but 32 (21%) were not using any contraception and thus at risk of an unplanned pregnancy. This figure of 21% is lower than that reported in previous series. The commonest form of contraception used was the combined pill followed by condoms, depot injection, implant and coil. A small number of women had tubal ligation, partner vasectomy or hysterectomy. The majority of women had received advice regarding contraception from their GP and only 17% from members of the CF team.

Documentation of contraceptive choice is thus an essential part of reproductive health counselling. The study highlights the need for more training in CF teams on the full range of contraceptive methods available and also for contraception specific guidelines and protocols for women with CF. If you have any issues or questions regarding contraception please discuss at your next visit or contact me sooner if required.

8) Factors that increase depression in adults with CF

The life expectancy in CF continues to improve with the latest data from UK registry showing a median survival of 41.4 years. Higher rates of anxiety and depression have been associated with increasing age.

This study from the Brompton Hospital in London evaluated the prevalence of depression and anxiety in 326 adults attending their
centre. Patients completed a questionnaire during an out-patient visit. The total number with depression was 41 (13%) and anxiety 127 (35%). They looked at factors that may be associated with this such as measures of health, employment and education. The results showed a significant association between depression and increasing age, lower lung function and being unemployed. A much larger percentage of females had higher levels of anxiety.

The authors commented that this incidence of depression was surprisingly low in a large population of adult patients. Women with CF are at greater risk of having issues with anxiety. (If you have any concerns regarding any symptoms you might be feeling you must discuss this with a member of the team in Leeds.)

9) The use of statins (widely used cholesterol lowering drugs) to modulate virulence of Pseudomonas aeruginosa

Statins are a class of drugs which are used to lower cholesterol levels but they have also been found to have anti-inflammatory and anti-microbial properties. This study from researchers in Ireland looked at the effects of three statins (Simvastatin, Lovastatin and Mevastatin) on virulence factors of Pseudomonas, the main pathogen in CF associated with increased morbidity and mortality.

The statins were found to reduce motility (movement) and biofilm formation (the jelly-like film that colonies of Pseudomonas produce to protect themselves from your immune system and antibiotics) of Pseudomonas. These are crucial factors involved in the colonisation and persistence of this pathogen in the lungs of CF patients.

These early results suggest the potential for their use in the development of treatment strategies against Pseudomonas.

10) Increased proportion of CF patients with normal FEV1 over an 11 years nationwide study

This was a study from Belgium looking at the number of patients over an 11 year period with a normal FEV1 - defined as FEV1 greater than or equal to 85% predicted. A normal FEV1 does not exclude early lung disease in patients with CF. Their population increased from 566 in 1998 to 1087 in 2008. The number of adults increased from 38% to 50% and the number with a normal FEV1 during this period increased from 28% to 43% and was more likely to occur in males. During this period the number of patients with an abnormal sweat test (chloride level >60) fell from 97 to 84% with a fall in the number with the delta F508 (commonest) mutation.

It is encouraging to see that with patients getting older lung function is improving and we have seen a similar pattern in our adult Unit. Indeed data I presented as part of changes in bone density (osteopenia and osteoporosis) looking at patients between 2000 and 2011 showed that average FEV1 increased from 47 to 65% predicted and BMI from 20.2 to 21.8. Most importantly the numbers of adult patients with chronic Pseudomonas infection fell from 89% to 50%. So with good care patients are on the whole showing improvements in clinical health status which is extremely encouraging.
Prompt treatment improves lung function, especially when combined with physiotherapy and airway clearance. Overall, it is very difficult to study different treatments for exacerbations, particularly the length of antibiotic therapy, as people who feel well don’t want to be given more than 14 days, and people used to having 14 days don’t want to be given less.

Emerging Dilemmas (Adult Focus)

A Canadian presentation found 16% alcohol abuse, 4% drug abuse and 5% cigarette use among adult patients and suggested risky behaviours were related to a life limiting illness.

A study from an Irish psychologist looked at people’s feelings regarding living with B. cepacia and suggested the patients feel they have: (a) lost identity, they are defined by the bug; (b) feel condemned; (c) feel they are cepacia.

The Registry Session

There was an interesting presentation on benchmarking from the USA. This group looked at the five best performing centres and aimed to identify areas of practice that could be worked on elsewhere.

Benchmarking is difficult and evaluation criteria are hard to determine but some interesting conclusions were:

- Centres performing well on nutrition tend to also achieve better lung function results. Centres achieving good lung function in children do not necessarily achieve good lung function in adolescents or adults.
- Centre performance is not consistent over time, the best centres are not the same year on year. (We cannot sit on our laurels!)
- Many variables influence poorer outcomes, e.g. social class, more women patients, but more intensive care (more clinic visits, more respiratory function tests, more airway cultures, more oral corticosteroids, more IV antibiotics, more inhaled antibiotics, more pulmozyme/DNase) was found in the best performing centres. More aggressive management = better outcomes.

Overall conclusions, better centres have high expectations for care delivered, good management, early intervention, consensus of opinions, clearly defined criteria for diagnosis and treatment, patients know when to contact centre, active involvement of subspecialists, well organised hospital visits, small declines in weight prompting immediate action.

Kate Williams (Research Registrar)

As usual the European CF Conference was a fantastic opportunity to meet other health care professionals from around the world and learn from their experiences. For me it was also my first opportunity to try Guinness (which was not quite such a pleasant experience).

A large number of sessions I attended this year focused on the importance of supporting individuals with CF, particularly with regard to managing the large burden of treatment that many of you experience. The Glasgow CF team took this a bit further and managed to persuade six members of their team (Physiotherapists, doctors and nurses) to try and manage the “average treatment of a CF patient” for a mere three weeks. This treatment package included inhaled therapies, oral medications, exercise and physiotherapy. Electronic monitoring equipment was used to assess how well they did. It may not surprise you to know that physios were the best at taking nebs and exercising.

At the end of three weeks all those that participated had a better appreciation of the difficulties faced. They plan to use this information to develop a training plan for Health Care Professionals who work in CF units.

Another study that caught my eye (for entirely different reasons) was “Canine detection of Pseudomonas aeruginosa (PA) volatile organic compounds.” Two dogs were trained to sniff out pseudomonas! Bess, a two year old foxhound cross and Buddy, a one year old retriever cross, were trained for five months using the same techniques used for training sniffer dogs for the detection of narcotics and explosives. At the end of training both dogs were tested on their ability to detect pseudomonas in the presence of 20 other bacterial or fungal species. Bess was able to successfully identify PA in all combinations and only had three false positives. They are now hoping to move onto trials to see if the dogs can detect pseudomonas directly from sputum and patients’ breath. (It isn’t entirely clear how this would be useful in real life!)
A few of you will already be familiar with Prucalopride, a new drug for treating difficult constipation. We now have a number of patients taking it, the majority with good effect, so we decided to share our experiences. I gave a short presentation on our experiences and with the help of our pharmacists Nicola and Sarah produced a poster too. After the presentation I was asked a lot of questions by doctors from North America who are keen to start to use it themselves.

Last summer over 160 of you completed a short questionnaire asking about your experiences of education and employment. The preliminary results of this are now available and were presented at this meeting. Overall many of you felt that CF had had a significant negative effect on your schooling and employment yet in complete contrast many felt that it had no effect at all. We are still analysing the data and I will send out the full results when available.

As I’m sure you know I’ve been looking at the problem of arthritis in CF. I hope to present the results of my studies at next year’s conference and will tell you all about it then.

Laura Cassidy, Laurie Cave, Alison Morton, Helen White, Sue Wolfe  (Dietitians) Body Composition

There were a number of posters looking at different methods of assessing body composition. In infants and children the easiest and most commonly used methods we use to assess nutritional status are head circumference, weight, height, and more recently body mass index (BMI). These measurements are the plotted on the appropriate percentile charts in order to look at nutritional status and growth progress. In adults nutritional status is assessed by BMI [Weight (kg)/Height (m)2]. We aim to optimise BMI at 22kg/m² for adult females and 23kg/m² for adult males.

These traditional methods of assessing nutritional status are not able to determine body composition. For example, using BMI an individual who has a large amount of muscle mass may be wrongly categorised as being “overweight”. Body composition assessment is able to assess how much of the body weight is made up of lean tissue (mainly muscle), fat, mineral (mainly bone) and water. This information is useful to us so that we can ensure that infants, children and adults with CF gain healthy muscular weight and not just increase their body fat. Muscle strength is enhanced if nutritional support, either normal eating or tube feeding, is accompanied by exercise programmes (as advised by our physiotherapists).

There are various ways of assessing body composition, the best of which is by Dual Energy X-ray Absorptiometry (DXA). We routinely recommend DXA scans for all people with CF over the age of ten years. This was started over ten years ago in the Paediatric Unit and over fifteen years ago in the Adult Unit to assess bone mineral density. The DXA scan result also reports total body fat and fat free mass (lean tissue and water). The posters at the conference reported the accuracy of alternative simpler methods of assessing body composition that may be used more frequently than we perform DXA scans.

One poster from Italy compared the accuracy of using skin fold thickness (measured using callipers which nip the skin) with DXA. They also compared Bioelectrical Impedance (BIA), measured by placing sensors on the body, with DXA. They found that neither of these measurements were as accurate as DXA and therefore should be used with caution. A poster from Germany found that patients with a better BMI and body composition as assessed by BIA had better exercise tolerance. Another poster from Wales compared BMI and lean body mass (measured by BIA) and concluded that BMI is not able to determine loss of lean body mass. BMI may remain good because of a high percentage of fat in the body. The final poster from England suggested that hand grip strength could be used to assess muscle function, but concluded that further research should be done before it is widely used.

In conclusion, body composition analysis is a useful method of assessing the quality of weight gain and allows us to aim to tailor advice to improve muscle mass. Dual energy X-ray absorptiometry is the most accurate method to use, but is usually only performed every one to three years. There are simpler, cheaper methods that are being investigated, which could enable more regular assessment of body composition.
In Leeds we will continue to use DXA and await further results before considering other methods on a more regular basis.

**Gastrointestinal Transit Time, Constipation and Distal Intestinal Obstruction Syndrome (DIOS)**

People with CF often suffer from gastrointestinal problems including constipation, abdominal pain and distal intestinal obstruction syndrome (*a severe bowel blockage*). One study used radiopaque markers to look at how quickly the stomach empties and how quickly food passed through the intestine. They found that passage through the small intestine was delayed in patients with CF particularly in the last part of the small intestine. The sluggish nature of the bowel may contribute to constipation and DIOS. This type of investigation may be unsuitable for routine use. A study from the Liverpool Adult CF Unit reported on the use of ultrasound measurements at the bedside to assess gastric emptying over a two hour period. They found there was a delay in gastric emptying in those patients who need pancreatic enzyme supplements. Ultrasound measurement of gastric emptying can be easily performed and may help to provide additional information about gastric emptying.

Treatment of constipation in people with CF can be difficult as there are many reasons why it occurs. Laxative treatment is the most common treatment and there are a variety of laxatives that can be used. However, in some patients conventional laxative therapy may fail. The Leeds Adult Unit reported the use of a new drug Prucalapride which has been approved by the National Institute for Clinical Excellence (*NICE*) for the treatment of severe constipation in females. We have limited experience but the use of Prucalapride has provided symptomatic benefit and reduced the need for additional therapy in patients.

**Taste and Smell in Cystic Fibrosis**

We have been aware for many years that good nutrition is very important in CF as it helps to maintain good lung function. Poor nutrition results in poor growth, reduced respiratory muscle function, decreased exercise tolerance and increased risk of infection. A study from Germany looked at taste and smell in patients with CF compared to people without CF. They found that disorders of taste and smell were more common in people with CF and suggested that this may affect enjoyment of food and possibly food intake. People with CF with a good sense of smell had more stable weight and height. They suggested smelling and taste disorders should be assessed in routine clinical practice. I particularly liked this poster as it used a Sino-Nasal-Outcome Test (*SNOT!!*)

**Cystic Fibrosis Related Liver Disease**

There was a very interesting symposium on CF liver disease (*CFLD*). Approximately 5% of patients can develop advanced CFLD during the first ten years of life. There is a lot of work going on in this area, as there are still many things that are not known about CFLD. It is clear that regular screening for CFLD is necessary so it can be detected early. We are doing this at Leeds with routine liver ultrasound scans and liver function tests.

There is even more evidence emerging about the possible protective role of ursodeoxycholic acid (*URSO*). We have been using URSO and taurine for over 20 years in Leeds and feel this is the main reason why we do not have any patients under the age of 10 years with advanced CFLD.

Several animal models of CF have been developed and are currently being used to increase our understanding of CFLD and help identify new treatments.

**European Cystic Fibrosis Nutrition Group**

**Motivational Interviewing**

In this separate symposium two interesting presentations were given which have nutritional implications. Work examining the use of motivational interviewing (*MI*) demonstrated that within a regional centre in Birmingham using this technique can have clear benefits in moving patients through decisions to undertake nasogastric tube feeding, gastrostomy placement and improve diabetic control. The techniques identify that for all of us there are pros and cons to changing behaviour. In MI the pros and cons are discussed and your
confidence to achieve goals is explored before you set the goals that are the most important to you. Success is then more likely.

**Liver and Pancreas Transplantation**

Exciting work from King’s college, London, was presented on a new approach in transplantation. Patients requiring liver transplantation have recently been transplanted with liver and pancreas simultaneously. This has had two main nutritional benefits for patients; firstly that pancreatic enzyme replacement therapy with fat containing foods has no longer been required and secondly, those who were diabetic at the time of transplantation no longer need to take insulin. For patients it has been the second factor that has been the most important benefit.

Nicola Shaw & Sarah Huntington  
(Pharmacists)  
A Pharmacists Perspective

We were really lucky that both of us could attend the conference in Dublin and were there not only to learn as much as we could but also to support and be a part of the CF Pharmacists Meeting. This was the first time CF pharmacists had been allocated a full morning to host a meeting and we were very excited as there were pharmacists attending from the UK, Europe, US and Australia! The aim of the meeting was to identify different approaches to therapy and to share current practice. The first topic we discussed was the treatment of DIOS (distal intestinal obstruction syndrome or severe constipation). It was reassuring to know that our practice in Leeds is similar to other units in the UK. Keith, the pharmacist from St Bartholomew’s Hospital in London, then discussed giving antibiotics via the nebuliser that are not especially designed to be given this way. Examples are meropenem and amikacin that are licensed as intravenous products. Even though they are not licensed to be given via a nebuliser, many units are administering them this way and from this limited data we know they are safe and effective. However, we are going to work together to collect information to expand the knowledge base we have. Professor Robert Kuhn, from the US, also gave us a very interesting presentation, via teleconference, on their use of continuous antibiotic infusions in CF patients.

Then it was our turn.....

Nicola: I spoke about the best way to monitor intravenous tobramycin. Most of you will have had at least once course of intravenous tobramycin and some of you will have had much more. Tobramycin is a very useful antibiotic but there is a fine balance between getting enough into your blood stream to kill the Pseudomonas and causing some unwanted side effects such as changes in hearing and kidney function. At the moment current practice is to take a ‘tobramycin blood level’ just before your 2nd dose is due however there have been developments in computer software that can look how individuals handle tobramycin. It means we can choose a dose of tobramycin that is perfect for you!

We are very interested in this computer software and would like to look at in more detail so watch this space............

Sarah: I followed Nicola by speaking about the contraception work myself and Dr Etherington did last year. A big thank you to all those patients who helped us with this! This is the largest contraception audit to date in females with CF. We found that although the majority of you who require contraception are using it, one in five females are not. The project surprised us with the number of different brands and forms of contraception that are now available! Each of these has different advantages/disadvantages and it is therefore really important to discuss your contraceptive choices with both your GP/Family Planning Clinic and us. There is also very little CF specific guidelines or patient information on contraception so this is something we would like to work on in the future.

Other than the pharmacists meeting we also attended lots of other presentations and read with interest the many posters that were on display. Of particular interest to us were the final updates from the clinical trials on inhaled mannitol (Bronchitol®), nebulised aztreonam (Cayston®) and tobramycin dry powder inhaler (Tobramycin Podhaler®). Clinical trial data was also discussed on the dry powder formulation of inhaled colistimethate sodium (Colobreathe®). This should be launched in the UK by the end of the year. The good news is that it is only one capsule to be inhaled twice a day!
This year I had the opportunity to attend the (European CF Conference ECFC) in Dublin. We were well looked after by the CF Association Ireland (CFAI), whose members presented a big part of the programme.

Jill and I attended the International CF Nurse Specialist Group meeting which was a day of varied speakers covering different topics including transition, fertility, pregnancy, and renal disease. The information that I found really interesting was around Acute Kidney Injury in CF.

A short presentation was given by Dr. Liam Plant, a Nephrologist who works in Cork. He showed a commonly used diagram of the CF body and affected organs and was horrified that the precious kidneys didn’t feature on this! He spoke about the perception that the kidneys are not affected by CF being dated.

In recent years there have been increased reports of renal disease in CF. Contributing nephrotoxic factors are: chronic and acute bacterial infections, excessive and prolonged antibiotic use, especially of aminoglycosides (tobramycin). CF related diabetes and immunosuppressive drugs post transplant can also be potentially damaging.

Dr. Plant spoke about recent research to detect early kidney injury using kidney injury marker (KIM 1 and KIM 2). Paul Whitaker and Nicola Shaw will be leading this study at our Unit.

We do monitor renal function closely on all our patients’ and also follow guidelines of safe Tobramycin dosing and monitoring assay levels. You can help by drinking plenty of fluids (non alcoholic!), especially during IV therapy. Also providing a urine specimen on admission gives us a baseline assessment of how your kidneys are.

This year I was fortunate to obtain sponsorship from Calea to attend the European Conference in Dublin. This was the second conference that I have attended, the first one being five years ago, and it was a good opportunity to meet other people working within Cystic Fibrosis care and to find out what is happening in other CF units in the UK and in other countries around the world. I was pleased to find that we are still very much up to date and that the standard of care and the facilities we have in Leeds are much better than many patients receive.

There were so many interesting presentations to attend that it was sometimes difficult to decide which would be the most relevant and which I would benefit from the most, and that sometimes meant rushing from one auditorium to another to hear different speakers. There were a lot of interesting nursing and psychosocial posters submitted and it was interesting to be able to discuss them with the authors and to attend the ePoster sessions. Unfortunately the nursing presentations were limited but the ones that were available raised some interesting issues.

Helping people with Cystic Fibrosis to improve adherence was a recurring topic of discussion in the nursing sessions. Studies have demonstrated that an increased treatment burden correlates with poor adherence to therapy.

We are all aware that the complex CF treatment requires an increase in time and effort by the patient and that a large number of people experience difficulty with treatment adherence. It is important to identify the barriers that people face e.g. lack of time, forgetfulness and unwillingness to take treatment in public. There was much discussion about the ways of minimising the treatment burden without compromising health and encouraging people to be honest about what treatment they do or do not take. So I’m sure we will be hearing more about this in the future.

Two sessions that I particularly enjoyed:

1) **Benchmarking in the USA**

Aims:
- To evaluate the degree of variation across different centres with regards to processes used and outcomes.
- To determine currently attained level of success
• To continue to learn from those centres who reach a high level of success in outcomes, and to determine how they got there.

We have to know how to determine the best outcomes?

We can’t really do randomised controlled trials for many things.

We currently evaluate success using lung function (FEV1) and BMI

We continue to audit our practice.

Difficulties in comparing:

• Centres which have excellent lung function results are not necessarily the best for nutritional status.

• Some centres may have the highest BMI results, but this doesn’t necessarily mean that they have the lowest proportion of patients with nutritional failure.

• Centres aren’t always consistent over time.

• We need to adjust for case mix also as socio-economic status can have an effect.

Factors influencing outcomes in Cystic Fibrosis include:

• More clinic visits

• More and longer courses of IV antibiotics

• More non-quinolone antibiotics

• More inhaled antibiotics in young people

• More DNAse (pulmozyme)

The current aim in USA is for a benchmarking team to visit high performing centres as a project in order to determine how to reach highest levels of success for all. In the UK we already have the CF registry and can compare easily how our centres are performing alongside others. However, it is always important to continue to be open to learning from other centres which may be more successful in certain areas, and obviously always strive to be better, even in areas where we are doing well.

2) How to manage complex Infections in CF:

a. MRSA

Questions:

• Do we aim to eradicate in colonized healthy subjects? Is there a benefit?

• Do we target known MRSA with every CF exacerbation?

Chronic Infection:

There are very little data. Thoughts include:

• Combination antibiotic treatment

• Cycles of treatment as with chronic Pseudomonas

b. Achromobacter Xylosoxidans

This is suggested as rapidly emerging with a prevalence of 5-18%. It has been associated with:

• Possibly causing serious and early decline in lung function

• High resistance to antibiotics

• High cross infection risks

Although some studies have shown no negative effects, others feel it may be as important as Pseudomonas Aeruginosa.

Treatment

• Very difficult as it is often multi-resistant

c. Managing Non-tuberculous Mycobacteria (NTM)

Facts

• Increased prevalence of NTM has been shown with an annual prevalence increase from 20 to 47:100,000

• Peak seems to be in childhood rather than later

• It can cause annual decline in FEV1 of 2.5%

• NTM can only bind to damaged epithelium and mucus plugs.

• Associated with water, hot tubs, soil, gastro-oesophageal reflux, shower heads
• Chronic use of macrolides such as Azithromycin may be associated with increased risk of NTM
• Allergic Broncho-Pulmonary Aspergillosis (ABPA) may be associated with lower immunity to NTM
• Vitamin D deficiency may also reduce immunity to NTM

Diagnostic difficulties:
• Symptoms are often overlapping with other infections
• Radiological findings are often non-specific

Screening
• How often should we send sputum sample and should we have a holiday from prophylactic antibiotics in order to try to increase yield of culture?

When to treat:
• If patient is symptomatic
• If we have smear positive culture, and high bacterial load

Treatment aims are to eradicate, prevent progression and symptom relief.

Rosemary Ball (Physiotherapist)

The conference this year was full of exciting developments.
A big focus during the meeting was presenting more information on the importance of exercise and its role in maintaining the lung function of all those people with CF, children and adults.

There was also research to show how the level of general activity within a person’s day has a significant effect on lung function. This means that as well as getting involved in enjoyable sporting activities it is also good to look at how much time you spend just sitting during the day and ways you can incorporate activity into normal daily life.

There are European working parties investigating both of these issues further and we look forward to the results of their work.