NCG Chronic Pulmonary Aspergillosis national service

The National Aspergillosis Centre

Annual Report 2009-2010

Contents

1 General Overview and highlights

The NAC grew out of a tertiary referral service for patients with allergic and chronic pulmonary aspergillosis. In the 2008/9 year approximately 25 patients with CPA were referred. Introduction of the NAC lead to nearly 3 times this number of CPA referrals (n=66) and at least twice as many again of allergic bronchopulmonary aspergillosis and other Aspergillus disease. This major increase in referred patients, most of whom continue to be seen regularly as these are chronic conditions, has lead to significant changes in service provision. Friday clinics are staffed by 5 - 6 doctors, including 2 clinical fellows supported by NAC and 2 specialist nurses. Immunology input is sought on many patients with a fortnightly visiting consultant in immunology. Clinic stretches to Friday afternoon to accommodate numbers (typically ~50 patients) and to accommodate patients travelling long distances. A new clinic has been set up on Wednesday afternoon (April 2010 onwards), to reduce the pressure on Friday clinic. Inpatient numbers have also been higher than expected, and the appointment of Dr Pippa Newton as a new ID consultant for the NAC has meant that she manages all the inpatients (with limited junior doctor support during the working day unfortunately), with input and crosscover provided by the 2 other consultants. CPA patients are also being seen in the general ID Monday am clinic (Drs Hope and Newton).

Substantial effort has gone into patient engagement, including holding two meetings for patients, a comprehensive 'user' survey and numerous patient interactions between clinics between the specialist nurses and patients and their relatives. The Support for Patient's website and Yahoo patient group as part of the Aspergillus Website were increasingly active through the year, with patients all over the world drawing on experiences in Manchester.

The Mycology Reference Centre laboratory has grown under Professor Richardson's leadership and was re-accredited by the CPA in April 2010, along with the Manchester Medical Microbiology Partnership. Aspergillus serology, direct PCR testing of respiratory samples for *Aspergillus*, molecular identification of fungi from both culture and fixed tissue and environmental sampling for fungi have all been introduced. Additional staff were appointed and 2 additional training Clinical Scientist posts awarded by the Workforce Confederation to start in September 2010.

Innovations in patient care through the year have included introduction of double testing of *Aspergillus* IgG antibodies because of limitations we identified in both tests (as well as transfer of this testing in house and validation), testing and subsequent immunisation and retesting of pneumococcal and *Haemophilus* antibodies as many CPA patients appear to be unprotected against these common pathogens and suffering infections regularly, introduction of *Aspergillus* PCR testing on sputum as it appears to be more sensitive than culture (although there remain laboratory sample handling issues to be resolved), routine testing for mannose binding lectin deficiency and coeliac disease, and evaluation of patient outcome scores. In addition, the response and adverse event rates of posaconazole as both primary and salvage therapy has been evaluated, as our anecdotal experience previously was that this medication was better tolerated and effective, and better than itraconazole and voriconazole. This effort was also necessary as the frequency of

itraconazole resistance has continued to rise, and posaconazole is the most active of the oral azoles. All these innovations have been audited (see below). Most patients were enrolled into our ongoing genetics studies, funded by the Medical Research Council and the Moulton Trust, with the first outputs expected in late 2010.

External professional education about CPA and other respiratory fungal diseases was ongoing throughout the year, primarily by the Director, with other contributions from the specialist nurses. These efforts included training all the SpRs in Respiratory Medicine in Scotland and the West Midlands in the diagnosis and management of CPA, and numerous other national and international talks. In addition, 8 one day Mycology workshops were held on site with >60 attendees to re-introduce medical and BMS staff to the laboratory aspects of fugal diseases. Short news articles on the NAC appeared in the British Thoracic Society news and ARNS magazine for specialist respiratory nurses. The book chapter on Aspergillosis in Harrison's Principles of Internal Medicine, 18th ed (perhaps the world's leading specialist internal medicine textbook) has been updated, as well as a chapter on aspergillosis in Clinical Mycology 2nd Edition.

2 Activity

The total referrals, inpatient stays, procedures and caseload in 2009/10 were as follows:

ACTIVITY	Totals		Regional totals			
	Annual Plan	YTD Actual	No from England*	No from Scotland	No from Wales*	No from Northern Ireland*
Referrals	**40**	67	58	8	1	0
Caseload - band 1#	**33**	44	**44**	**0**	**0**	**0**
Caseload - band 2	**56**	89	**80**	**6**	**3**	**0**
Caseload - band 3	**18**	22	**18**	**3**	**1**	**0**
Total caseload (including Wales)		**155**				
Discharges	**8**	50	47	1	2	0
Surgical resection	**4**	0	0	0	0	0
Embolisations	**9**	8	7	1	0	0
IV Outpatients	**4**	4	4	0	0	0

* The NCG fund patients from England and Scotland only
# Appendix 1 shows the complexity banding criteria

Of the 66 new patients referred from England and Scotland, the mean time from referral to being seen was 4.44 weeks, (range 1-16 weeks). 63 patients accepted their first appointment. Three patients deferred, including a patient admitted to hospital. If these 3 patients are removed (16, 6 and 8 weeks) the mean waiting time was 4.2 weeks.

Overall, 20 patients died during the year.

3 Service developments and personnel

The NAC has completed it first year of operations. The major shifts and improvements in practice and capacity are as follows:

1) Strengthening the Regional Mycology Laboratory, Manchester. The appointment of Professor Malcolm Richardson PhD as Director, his wife Dr Riina Richardson DDS PhD and Dr Marcin Fraczek PhD as molecular biologist, has enabled substantial growth in the test portfolio. Tests that have been adopted, validated and are now routinely run for the benefit of CPA patients include:

- Aspergillus precipitins
- Aspergillus galactomannan (antigen)
- Additional sensitivity testing on Aspergillus for terbinafine and micafungin
- Real-time PCR for Aspergillus
- Molecular identification of fungi, including unusual *Aspergillus* species.

The RMLM decided to change its name the Mycology Reference Centre, Manchester. It has been successful in its bid to the Workforce Confederation to take on an additional 2 trainee clinical scientists. The RMLM successfully passed its CPA accreditation without difficulty.

The Manchester Mycology Reference Centre has been selected as the single UK participating partner in the European Union Leonardo da Vinci e-learning continuing medical education project (due for completion in 2011)

2) Clinical and administrative personnel
The following staff were appointed or redeployed to contribute to the NAC:
Professor David Denning, Professor of Medicine and Medical Mycology
Dr William Hope, Senior Lecturer in Infectious Diseases
Dr Hana Alachkar, Consultant in Immunology
Dr Ibrahim Hassan, Consultant in Microbiology
Dr Pippa Newton, Consultant in Infectious Diseases
Ms Marie Kirwan, Specialist Nurse
Ms Deborah Carr, Specialist Nurse
Ms Georgina Powell, Specialist Nurse
Dr Caroline Baxter, Clinical Fellow
Dr Timothy Felton, Clinical Fellow
Ms Christine Harris, NAC manager
Dr Graham Atherton, Senior Clinical Information Architect (Patient engagement)
Ms Joanne Gill, Medical Secretary
Ms Natalie Cannon, Clerical Assistant

3) Use of validated scores to assess severity of disease and outcomes (QOL)
The NCG requested an objective measure other than clinical symptoms and Aspergillus antibody titres to assess response to therapy. We therefore worked on quality of life measures. We applied the SF36 and the St Georges Respiratory Questionnaire (SGRQ) to our patients to determine which assessed the severity of their symptoms best and which

best reflected improvement or not. The SGRQ has been fully validated for use in patients with chronic airflow limitation e.g. asthma (Jones 1994), COPD (Jones and Bosh 1997) and bronchiectasis (Wilson, Jones et al. 1997). Several questions related specifically to their respiratory condition. Short Form 36 (SF-36) is a more general survey including questions on e.g. emotional status and general bodily pain. It has been tested and found useful in asthma (Bousquet, Knani et al. 1994).

Both questionnaires were presented to CPA patients to complete on their first attendance at clinic and then at approximately 3 monthly intervals. [Parenthetically we found that electronic direct entry did not work with this patient population, probably because they are not very computer literate, so all questionnaires were administered by hand and scores transcribed.] The patients were strongly encouraged to respond to the questions on their own and not to use prompts from a carer or family member that may have arrived with them. None compliancy was 3%. Both questionnaires were scored using specific computer applications; SF-36 by a proprietary scoring system purchased from QualityMetric (QualityMetric 2010), and SGRQ using an world wide web-based system designed and built in-house with php/MySQL using the freely available manual and scoring system obtained from St. Georges Hospital (Jones 2008). Both systems use strict sets of rules to handle instances when questions were not answered (particularly important for one or two SGRQ questions that are not relevant to some of the patients attending clinic at NAC as they are strongly related to other respiratory conditions).

By 30th April 2010 there had been 387 SGRQ and 324 SF-36 questionnaires completed (NB these scores include the last few weeks when we have stopped using SF-36). Lack of response with the SF-36 questionnaire varied from 0.6% to 4.3% which was better than with the SGRQ. This is consistent SF-36 being a much more generally applicable with much less tendency to ask specific questions that some patients would think were not applicable to themselves.

In December 2009 we carried out a comparison of QOL scores with a series of clinical test results, the NAC banding scale for CPA patients and the 5-point MRC breathlessness scale (Stenton 2008) with the aim of finding any baseline correlations for severity. Both SGRQ and SF-36 showed good correlation with the MRC scale with p-values at 0.001 or better for all components in each QOL apart from SF-36 physical component score (PCS) (p-value = 0.007). The NAC banding correlated well with SGRQ Impact component but no others. Both SGRQ Impact component (p-value = 0.010) and Total score (p-value = 0.018) showed reasonable correlation with C-Reactive Protein levels. Diffusion lung capacity for carbon monoxide (DLCO) correlated reasonably (p-value 0.01) with the SGRQ Activity component.

We have partially assessed each questionnaire for its sensitivity in assessment of improvement or deterioration in clinical status as assessed medically. In February 2010 116 patients had completed more than one SGRQ questionnaire and 106 who had completed more than one SF-36 questionnaire. Of these, SGRQ TOTAL scores showed

- 41 (35%) showed improvement
- 33 (28%) deteriorated

- 42 (36%) showed no change

And SF-36 Mental Component scores showed
- 37 (35%) improved
- 39 (37%) deteriorated
- 39 (37%) showed no change

and SF-36 Physical Component scores showed
- 24 (23%) improved
- 27 (25%) deteriorated
- 55 (52%) showed no change

Comparison of results suggests that SGRQ TOTAL scores seem to have a reasonable correlation with clinical judgment of the patient's health status and are more sensitive than SF-36 with better accuracy. In CPA patients, response to treatment showed a poor correlation between SF-36 scores and clinical assessments of changes in patient's health status since first attending the NAC. The two SF-36 components frequently failed to correlate with each other and neither was a good indicator for clinical improvement or lack of response. SGRQ showed promise as an indicator for improvement in clinical status by successfully identifying 48% of the patients who responded well to treatment but was much less successful in identifying lack of response. All of these results were based on fairly crude assessments of both QOL scores (some responses are based on 2 scores, some 5 scores). Overall QOL score response was taken by comparing the first score with the last taken, ignoring scores taken between these visits.

This dataset is being examined in greater detail to determine whether more global and domain-specific assessment of response at each time point reflects the SGRQ score. The aim of this additional work (primarily a retrospective notes review for specific time-points) it to determine if the score can contribute to the clinical assessment in real-time at the time of clinic, or if it is better used as a retrospective tool.

4) Long term outpatient antifungal management

A total of 5 patients received OPD managed IV antifungals during the year 2009/2010. Initial therapy was AmBisome 200mgs 3 times a week. Four patients were on AmBisome prior to April 2009. Second line IV therapy is micafungin 200mg 6 times weekly, with oral terbinafine 250mg twice daily (to prevent the emergence of resistance).

5) Lung transplantation referral

Three patients were referred for possible lung transplantation.

4 Audits

Several audits have been undertaken in 2009/10. Some of these have been completed:

1) Aspergillus IgG antibodies (Dr Caroline Baxter), presented in Rome at the Advances Against Aspergillosis meeting in February 2009:

A COMPARISON OF THE PRECIPITATION TECHNIQUE AND IMMUNOCAP FIEA FOR MEASUREMENT OF IgG ANTIBODIES TO *ASPERGILLUS FUMIGATUS*

*Caroline Baxter, Andrew Jones, Kevin Webb, Robin Gore, David Denning

Purpose

Aspergillus precipitins are used to aid diagnosis and monitor treatment in aspergillosis. The recent introduction of the ImmunoCAP® fluorescent immuno enzyme assay (FIEA) is a fast, automated method to detect IgG antibodies to *Aspergillus*. A level above 40mg/L has been recommended as indicative of aspergillosis. However, this assay has not been validated for individual patient groups and the clinical significance of levels is not known. This study aimed to compare IgG levels obtained using the ImmunoCAP® FIEA test with the *Aspergillus* precipitin test in patients with Cystic fibrosis (CF), Chronic Pulmonary Aspergillosis (CPA), and Allergic Bronchopulmonary Aspergillosis (ABPA).

Method

83 adult patients attending Manchester's National Aspergillosis Centre and 72 patients attending the Manchester Adult Cystic fibrosis Unit (MACFU) gave a blood sample. Serum was analysed by the ImmunoCAP® assay for specific IgG *Aspergillus* and by counterimmunoelectrophoresis (CIE) for *Aspergillus* precipitating antibodies (all *A. fumigatus*). An ImmunoCAP® result of >40mg/L was considered positive and the number of precipitating lines was recorded.

Results

In the non-CF patients there was 93% concordance between a positive IgG result and a positive precipitin result. In contrast there was 49% concordance in the CF patient group. There was a good correlation between IgG level and precipitation titre ($r=0.903$, $p=<0.01$) in the non-CF patients but this was not observed in the CF group ($r=0.199$, $p=0.11$). Of note the maximum level of IgG reported was 200 but precipitation titres in these patients ranged widely from 1/8 to 1/512. 82% of patients with CPA had a raised specific IgG whereas 55% of ABPA patients had a raised specific IgG. Patients with CPA had significantly higher mean IgG levels than patients with non-CF ABPA (mean 102 mg/L, vs mean 44 mg/L $p=<0.01$), but not CF ABPA patients (mean 102mg/L, vs mean 79 $p=0.24$).

Conclusions

The IgG ImmunoCAP® may be a useful alternative to the *Aspergillus* precipitin test when monitoring patients with CPA but once values reach >200mg/L the precipitating antibody titre is more informative. Results correlate well for non-CF ABPA patients so again the ImmunoCAP® may be a suitable alternative for this group of patients. In CF patients there is little correlation between the ImmunoCAP® test and precipitating antibodies. For both ABPA groups neither the precipitin test nor specific IgG was a good predictor of disease.

2) Mannose binding lectin and aspergillosis pulmonary aspergillosis

Mannose binding lectin genotype and serum levels in patients with chronic or allergic pulmonary aspergillosis

Elizabeth Harrison, Abhinav Singh, Nicola Smith, Marcin Fraczek, Caroline B Moore, David W Denning

Several studies suggest mannose binding lectin (MBL) deficiency is associated with various manifestations of aspergillosis. MBL serum levels and function are genetically determined, but levels may vary during inflammation. We address the relative frequency of deficient genotypes, the relationship between serum levels and genotype and both age and disease manifestations in patients with chronic pulmonary aspergillosis (CPA), allergic bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal sensitisation (SAFS). DNA was extracted from blood samples and *MBL2* genotyping was performed using the INNO-LiPA *MBL2* kit. Serum MBL concentrations were determined by ELISA. 115 patients were evaluated, 62 (54%) with CPA, 40 (35%) with ABPA or SAFS and 13 (11%) had both CPA and ABPA. The mean MBL serum level was 1980µg/L, and did not differ between groups. Mean serum MBL levels in subjects with A/O or O/O genotype were lower (507µg/L) compared to A/A genotype (2684µg/L) ($p < 0.0001$) and A/A subjects with CPA had higher levels (3022µg/L) compared with allergic A/A subjects (2164µg/L) ($p = 0.005$). We found 40 subjects with exon 1 genotypes producing the lowest MBL serum levels (A/B, A/C, A/D and O/O). The frequency of A/O and O/O carriers in each population was 40%, 30% and 46% for CPA, allergic and both CPA and ABPA subjects respectively, not different from published normal controls. No single haplotype, genotype or allele was significantly related to any of the aspergillosis phenotypes. Functional homozygote ABPA subjects ($n = 28$) in this study were ~11 years younger than ABPA subjects ($n = 12$) carrying exon 1 defects ($p = 0.011$). Subjects with bronchiectasis had higher MBL serum levels ($p = 0.014$) and was more common in subjects with allergic disease than CPA alone ($p = 0.037$). CPA subjects with more severe disease had higher circulating levels than those with less severe disease ($p = 0.019$). Defective *MBL2* genotypes are not associated with chronic or allergic aspergillosis. Elevated serum MBL levels in CPA patients may mask defective genotype status.

3) <u>Efficacy of posaconazole in CPA</u>
Posaconazole is an Effective Treatment for Chronic Pulmonary Aspergillosis

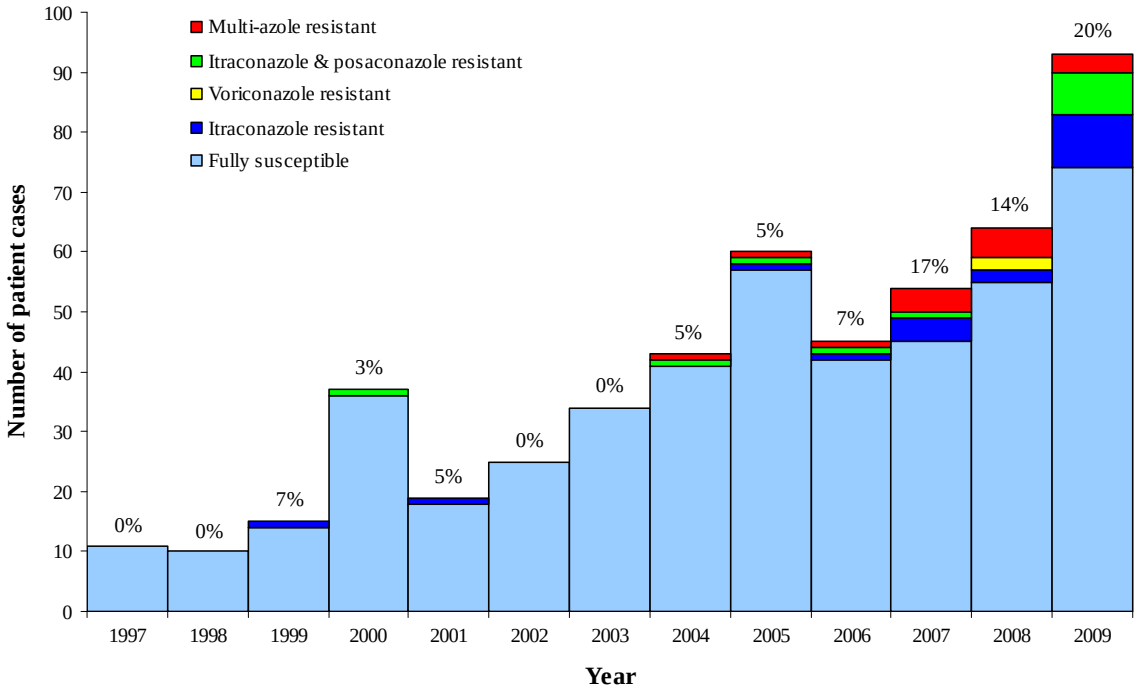
T. FELTON, S. ROBERTS, WW. HOPE, DW. DENNING
National Aspergillosis Centre, Univ. of Manchester, UK
Background: Chronic pulmonary aspergillosis (CPA) is a progressive chronic infection characterized by pulmonary cavitation and presence of antibodies to Aspergillus spp. There are few treatment options. Posaconazole has potent anti-Aspergillus activity. We investigated the utility of posaconazole for CPA.
Methods:A retrospective study was performed. CPA was defined as pulmonary cavitation and antibodies against Aspergillus. Patient demographics, underlying disease, antibody and fungal culture results were recorded. Patients were classified as receiving primary therapy or salvage therapy. A composite clinico-radiological score was used to assess response. A Cox model was used to determine time to clinical stability/improvement and clinical failure/death. Underlying diagnosis, antibody titre to Aspergillus prior to starting posaconazole and posaconazole serum concentrations were assessed as covariates in this model.
Results: There were 79 patients. 21 patients received primary therapy. Initial dosage was

400mg BID. Median age was 60 years with 57% males. Emphysema and previous pulmonary tuberculosis infection were the commonest underlying conditions. A Cox model showing stability or improvement was reached in 70% of patients at 6 months and 85% of patients at 1 year. A treatment failure/death rate of 20% at 1 year rising to approximately 35% at two years was observed; 8 patients (10%) had died at 12 months. Covariates were not significant in the Cox model. There was no difference between patients receiving primary and salvage therapy. Adverse reactions (nausea, n=5; rash, n=5; headache, n=1; lethargy, n=1) were observed in 12 patients (15%) leading to withdrawal in 9. Aspergillus spp. was recovered in 22 patients; 4 isolates resistant to posaconazole (MIC > 8mg/L), one emerging during therapy. Treatment failure was observed in all 4 patients.
Conclusions: Posaconazole is a safe and effective treatment for CPA. Prospective comparative studies are required to further define optimal regimens for CPA.

4) Frequency of azole resistance in *A. fumigatus*
Frequency and evolution of triazole resistance in *Aspergillus fumigatus*

A Bueid, SJ Howard, CB Moore, MD Richardson, E Harrison, P Bowyer, DW Denning
University of Manchester, and Mycology Reference Centre Manchester, UK

Background: Resistance to triazole antifungal drugs in *Aspergillus fumigatus* is now a major clinical problem in some locations. Mutations in the target enzyme *cyp51A* appear to be the dominant mechanism of resistance.
Aims: To update the frequency of azole resistance in Manchester, 2008-2009. To obtain the frequency and the distribution of mutations in the *cyp51A* gene.
Method: 230 isolates were investigated phenotypically and genotypically. Susceptibilities were determined using a modified EUCAST microtitre method. Putative breakpoints used were >2mg/L for itraconazole and voriconazole, and >0.5 mg/L for posaconazole. The entire coding region of the *cyp51A* gene from resistant *A. fumigatus* isolate was sequenced in both directions.
Results: Of 230 isolates, 64 (28%) were azole resistant. In 2008 and 2009, 14% and 20% of patients had resistant isolates respectively. During this period 62 of 64 (97%) were itraconazole resistant, 2 of 64 (3%) were only voriconazole resistant and 78% cases were multi-azole resistant. 43% of resistant isolates did not carry a *cyp51A* mutation. However, a novel finding is that two patients had one isolate each with a *Cyp51A* A284T mutation (alanine to threonine substitution) conferring reduced susceptibility to itraconazole, voriconazole and posaconazole. Isolates with G54R, P216L and G448S mutations were all associated with itraconazole and posaconazole resistance, whilst remaining susceptible to voriconazole. We found isolates with five different amino acid substitutions at position M220, namely I, K, V, R and W, of which M220R and M220W have not been previously reported. All alterations at codon 220 are associated with itraconazole and posaconazole resistance, but have variable voriconazole MICs (typically raised).
Conclusion: Azole resistance is common, continues to evolve, and many isolates do not have a *cyp51A* mutation. Non-cyp51A mutation mechanisms are increasing in frequency.



5) Occurrence, management and outcome of peripheral neuropathy related to azole use.
Dr Carline Baxter. (incomplete)

6) Positive PET scans in chronic pulmonary aspergillosis mistaken for lung carcinoma
Dr Carline Baxter. (incomplete)

7) Comparison of pneumococcal serotype-specific antibody response in CPA, compared with other aspergillosis conditions, and response to immunisation
Mrs Georgina Powell (incomplete)

5 Patient engagement

Patient involvement

The National Aspergillosis Centre was launched at Wythenshawe Hospital on May 1st 2009 with a meeting that was chaired by Dr Geoffrey Scott, Chairman of the Fungal Research Trust, and included an introductory talk Prof Denning, a review of bronchial artery embolisation by Dr Ray Ashleigh, a discussion of therapeutic drug monitoring by Dr William Hope and an overview of the National Commission Group's aims and operations by Andrew Bibby. Two patients recounted their experiences in a powerful way. This was followed by a series of short research presentations.

Prior to the launch meeting, patients were invited to a specially convened meeting of their own held in the morning before the launch. This was well attended with 18 patients attending with their carers. This meeting was well attended with 18 patients attending with their carers. After a short introduction there was a wide ranging debate into what advantages the new centre would have for patients, how we could improve our service to patients and a series of suggestions from patients were noted. This was independently

facilitated by Nick Montague (Chairman of the Children's Adventure Farm Trust Charity). A list (effectively an 'action list') of all proposals (14 in all) was drawn up (Appendix 2). Most of these points have been gradually implemented. Progress reports were sent out to all patients after a few months and further feedback requested, but communication was difficult and it was felt that several of the actions required specialist help.

Specialist nurses also provide the resources to implement several of the suggestions made by patients in the first meeting e.g. they provide a contact number available to all NAC patients during working hours and an answerfone for messages out of normal hours.

User survey (January 2010)
13 questions. 60% return rate, 71 patients responded (Appendix 3).
Satisfaction rates exceeded 90% (>95% in most cases) for quality of care, waiting times.
Communication, information and support were given 100% satisfaction ratings.
Despite these high ratings there was still a need expressed for more information & communication, with 12% wanting more information on first visit to the clinic and 47% expressing interest in attending a patients information meeting, 38% in a patient support meeting. 100% were happy to participate in research.
The only major criticism was that the car park was too expensive.

On-line materials
The Aspergillosis for Patients website was running at an average of 27,000 hits per month in the six months prior to the launch of the National Aspergillosis Centre. We used the launch of the centre to launch a new website dedicated to patients (www.aspergillus.org.uk/newpatients/) which set out to try to follow the thought processes of a newly diagnosed patient, taking them every step of the way through diagnosis, treatment, long term care & prognosis alongside an extensive support group and online Question & Answer forum. Six months after launch we were getting 53,000 hits per month, 12 months after launch we got 66,000 hits in March 2010 – demand is still growing.

The Aspergillus Support group (http://uk.groups.yahoo.com/group/AspergillusSupport) is a mutual support email group that has been in existence since 1998. At the beginning of 2009 there were roughly 750 members of that group whereas 12 months later numbers are about to break through 900 i.e. the group growth rate has doubled. Many of the new members are UK based who have learned of the group via information given out in the clinic at NAC. A significant part of the 'chat' in the group now consists of people referring to the NAC and patients attending the NAC establishing supportive relationships.

Use of the Q & A phorum has increased hugely over the last 15 months. In the last 6 months prior to the launch of the NAC and new website there were an average of 6,600 hits on that section per month. This section was reorganised and made more widely available to search engines for the new launch and as a result quickly attracted 180,000 hits per month after 6 months, 800,000 after 12 months settling back to a steady 140,000

each month now. Much of this activity is probably caused by users searching for existing questions & answers.

Patients meeting Rome

The Fungal Research Trust funded a meeting directed at patients that took place in Rome on 3rd February 2010. Eight invited speakers prominent in a specific field of aspergillosis and antifungal therapy delivered talks about their subject to a lay audience on subjects not often accessible by patients. The meeting was successful with 26 people attending. In conversations afterwards patients felt that the meeting had proven very worthwhile. It was anticipated that the majority of people interested in listening to these talks would not be able to make it to Rome due to ill health & its effect on flying so the FRT also funded video recording of each talk. These videos & slides are available on the Aspergillosis for Patients website (http://www.aspergillus.org.uk/newpatients/romemeeting.php) and more recently on the popular download service at iTunes (www.itunes.com). Page access statistics show us that the videos have been collectively viewed over 1,200 times up to the end of April 2010 and slides from the meeting downloaded 1,100 times.

6 Research outputs, other published research summary

Publications 2009

A) CPA related publications

Howard SJ, Cerar D, Anderson MJ, Albarrag A, Fisher MC, Pasqualotto AC, Laverdiere M, Arendrup MC, Perlin DS, Denning DW. Frequency and evolution of Azole resistance in *Aspergillus fumigatus* associated with treatment failure. Emerg Infect Dis. 2009 Jul;15(7):1068-76.

Verweij PE, Howard SJ, Melchers WJ, Denning DW. Azole-resistance in *Aspergillus*: proposed nomenclature and breakpoints. Drug Resist Updates. 2009 Dec;12(6):141-7.

Lestner JM, Roberts SA, Moore CB, Howard SJ, Denning DW, Hope WW. Toxicodynamics of itraconazole: implications for therapeutic drug monitoring. Clin Infect Dis. 2009 Sep 15;49(6):928-30.

Hope WW. Toxicodynamics of the azoles: a focus on hepatotoxicity, a clinical primer for physicians, also published www.doctorfungus.org

Howard S.J., Hope W.W. Therapeutic Drug Monitoring for invasive aspergillosis in Ed. Pasqualotto "Aspergillosis: from diagnosis to prevention" (Springer), 2009 [Book chapter]

B) Publications made possible in part by NCG support of the Mycology Reference Centre Manchester

Siikala E, Richardson M, Pfaller MA, Diekema DJ, Messer SA, Perheentupa J, Saxén H, Rautemaa R. *Candida albicans* isolates from APECED patients show decreased susceptibility to miconazole. Int J Antimicrob Agents. 2009

Dec;34(6):607-9.

Richardson M, Rautemaa R. How the host fights against Candida infections. Front Biosci (Schol Ed). 2009 Jun 1;1:246-57.

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Uittamo J, Siikala E, Salaspuro M, Rautemaa R. Chronic candidosis and oral cancer in APECED-patients: production of carcinogenic acetaldehyde from glucose and ethanol by Candida albicans. Int J Cancer, 2009, 3:754-6.

Levon J, Myllymaa K, Kouri V-P, Rautemaa R, Kinnari T, Myllymaa S, Konttinen Y T. Patterned macro-array plates in comparison of bacterial adhesion resistance of tantalum, titanium and chromium compared to diamond-like carbon. J Biomed Mater Res Part A, 2009, 92:1606-13.

Nieminen MT, Uittamo J, Salaspuro M and Rautemaa R. Acetaldehyde production from ethanol and glucose by non- *Candida albicans* yeasts in vitro. Oral Oncol 2009 Dec;45(12):e245-8.

Husebye ES, Perheentupa J, Rautemaa R and Kämpe O. Clinical manifestations and management of patients with autoimmune polyendocrine syndrome type I. J Intern Med, invited manuscript, 2009, 265:514-29.

Richardson M. The ecology of the Zygomycetes and its impact on environmental exposure. Clin Microbiol Infect. 2009 Oct;15 Suppl 5:2-9.

Anttila VJ, Nihtinen A, Kuutamo T, Richardson M. Air quality monitoring of HEPA-filtered hospital rooms by particulate counting. J Hosp Infect. 2009; 71: 387-8.

Rusanen P, Siikala E, Uittamo J, Richardson M, Rautemaa R. A novel method for sampling the microbiota from the oral mucosa. Clin Oral Investig. 2009; 13: 243-6.

Suihko ML, Priha O, Alakomi HL, Thompson P, Mälarstig B, Stott R, Richardson M. Detection and molecular characterization of filamentous actinobacteria and thermoactinomycetes present in water-damaged building materials. Indoor Air. 2009 Jun;19(3):268-77.

Richardson MD, Hope W. Aspergillus. In: Clinical Mycology, 2nd Edition. Eds: EJ Anaissie, MR McGinnis, MA Pfaller. Churchill Livingstone, New York, 2009, p271.

Other publications from the group are shown in Appendix 4.

Poster presentation of key importance

Another key output was the demonstration of the direct detection of azole resistance from culture negative respiratory samples. This was presented at a late breaker in April 2010 Vienna at the European Conference on Clinical Microbiology and Infectious Diseases. This is the abstract text.

Direct detection of triazole resistance in *A. fumigatus* from airway secretions
Stephen Park, Marcin Fraczek, Marie Kirwan, Sarah Follett, Kate Radej, Adrian Moody, David S. Perlin, David W. Denning.

Objectives
Aspergillus fumigatus causes significant morbidity in immunocompromised patients, asthma, cystic fibrosis and chronic pulmonary aspergillosis (CPA). Culture positive rates in invasive disease and CPA are typically ~30%. Rates of culture positivity in allergic aspergillosis (ABPA) are typically ~60%. Increasing rates of azole resistance, determined by MIC on positive cultures, have been noted since 2004. Culture negative cases do not currently allow susceptibility to be determined.
Methods
Patients were recruited from the National Aspergillosis Centre, Manchester if they provided a fresh sputum sample. Samples were split for microscopy and fungal culture or PCR. DNA extraction was performed with the MycXtra kit and real-time PCR using the MycAssay Aspergillus assay. Only those samples that were PCR positive, culture negative were subjected to a nested PCR approach. The CYP51A gene was amplified using Invitrogen Platinum Taq polymerase in two fragments. Fragment 1 (876bp) covered the promoter tandem repeat region to codon 98. The second amplicon (748bp) covered codons 54 to 266. PCR products were cleaned up and each was used as a template to probe with molecular beacon assays for known azole resistance SNPs.
Results
30 patients were PCR positive and culture negative for *Aspergillus* species. No G54 or M138 mutations were found. Four samples had M220 mutations. Sixteen of 29 (52%) had both a tandem repeat (TR) with an H98L mutation. Of particular interest, two samples had a M220 mutation with a TR+ H98L mutation and the TR was found without the H98L mutation in 3 and the H98L mutation without the tandem repeat in 2. One sample did not amplify fragment 2. Overall, therefore 18 of 30 (60%) samples had evidence of azole resistance. Amongst these patients, 6/8 (75%) had ABPA, 11/20 (55%) had CPA and 1/2 (50%) had bronchiectasis with documented aspergillosis. Four had never received triazole therapy and two had known pan-azole resistant CPA (M220K and unknown mechanism). Four were taking itraconazole (2 clearly failing Rx, one non-compliant, one worsening after response, three were taking voriconazole (2 clearly failed Rx, one stable with toxicity) and 5 were taking posaconazole (3 responders, 2 primary Rx).
Conclusions
Using a commercial real-time assay for *Aspergillus*, residual DNA can be used directly to determine azole resistance in *A. fumigatus*. In this small single centre sample, it would appear that resistance is common.

7 Statutory reports
No MRSA cases were reported for the 2 wards to which the CPA patients were admitted.

One patient developed *C. difficile* diarrhoea, without evidence of pseudomembranous colitis.
There were six HIRS reported 2009/2010.
There no Severe Untoward Incidents reported.

8 Financial expenditure 2009 - 2010

The original financial forecast for 2009/10 predicted a total cost to the NCG of £4.4m (for England and Scotland only). The estimate was revised upwards after the level of activity increased, particularly in the first 2 quarters of 2009/10. At the close of the year, new patients accessing the service had risen to 66, with a total of 151 being treated by the centre. As a result of the increased activity levels, drug costs exceeded the original plan by £786k at £3,764k. The overall cost of the service in 2009/10 was £5.4m.

9 Future developments and direction

At the end of 2009/10 financial year, there were 149 patients with CPA under the care of the NAC. This is anticipated to grow to about 200 by the end of the 2010/11 year. Key developments in 2010/11 will be:

- Introduction of direct azole resistance testing from samples, if cultures are negative
- Increased surgical activity, possibly including a 'key-hole cavernostomy' procedure in patients with large fungal balls, not fit for resection, and with demonstrated or at high risk of antifungal resistance development.
- Introduction of a partially validated outcome score into clinic practice, with continued evaluation of its utility.
- Introduction of Prevanar 13 pneumococcal vaccine, instead of Pneumovax or Prevanar 7, into routine practice with a clinical evaluation of its impact.
- Addition of a dedicated (50%) senior physiotherapist to the NAC
- Individual patient requests for posaconazole and long-term IV antifungal therapy, on a case by case basis, and continued audit of their efficacy and tolerance.
- Development of clinical protocols including applications for peer review funding to support clinical trials from NIHR and industry
    - Optimal primary therapy regimens
    - Intrapulmonary pharmacokinetics
    - Strategies to prevent emergence of resistance
    - Optimal salvage regimens

Appendix 1

Categorisation of complexity (Banding)

Stage 1

- Ambulant and independent
- No evidence of antifungal resistance
- No treatment or treatment with itraconazole capsules

Stage 2

- Significant impairment of respiratory function, sufficient to impair activities of daily living, but ambulant
  and/or
- Concurrent anti-mycobacaterial treatment
  and/or
- Failed or developed toxicity to itraconazole capsules
  and
- No evidence of azole antifungal resistance

Stage 3

- Antifungal azole resistance documented
  and/or
- Long term nebulised or IV antibiotic treatment required (bronchiectasis, Pseudomonas colonisation)
  and/or
- Wheelchair bound
  and/or
- HIV infected
  and/or
- Severe hepatic disease

Appendix 2

Summary of matters discussed at the Aspergillus patients meeting on 1st May 2009

1 Aspergillus website

1.1 Patients' Area
A number of people felt that it would be good to have a clearer link to the patients' section of the site and generally to have a patients' section which was more "user friendly" in design and language and not as medical. Clearly some were getting bogged down in all the complex science and found it daunting and confusing.

1.2 Good news needed
There was no good news on the website and this was much needed. People said they often became more and more despondent, the more they read.

Recommendation: Make the patients' section of the website more positive and include some case studies of patients who had been treated and were doing well or had recovered. Two female patients in the room immediately volunteered to have their story told on the website.

1.3 Managing the disease
It was felt that there should be more advice on practical aspects of managing the disease – a separate area on the website which dealt with this.

1.4 Side effects of drugs
This is a major issue. Patients had a lot of information which they could communicate to others and help them.

Recommendation : Create a specific area on the patients' website to cover this and add individual patients experiences i.e. a Yellow Card System.

1.5 Chest Clinic Survey
Apparently there was a recent survey in the Chest Clinic. It was suggested that the results from this should be posted on the website.

1.6 "Website is brilliant"
Graham was complemented on the website by a number of people.

1.7 Practical day to day points
Better communication of practical points (e.g. who is best to go to for travel insurance) was needed – again, a separate area on the website or an online forum where people could post their experiences.

2 Information

2.1 Treatment in emergencies

A number of patients explained that they had visited their local A & E or GP with problems such as coughing blood and they were met with a lack of knowledge of Aspergillus and how to treat it. This was clearly a significant issue for several.

Recommendation : Give the patients a card which explained their condition, the symptoms presented and the treatment, if any, which they should be given from a non specialist unit such as A & E, plus a link to the Asp website relevant sections. This suggestion was greeted with a very positive response.

2.2 Information for visiting patients

Patients wanted "hard copy" information which they could take away and read rather than searching on the internet for information, which tended to be difficult, complicated and often quite depressing.

Recommendation : Have easy to understand leaflets and information available in the clinic and give every patient a pack with these in and any other relevant information. Avoid unnecessary medical language.

3 Education

3.1 Chest physicians across the UK needed to be educated about what Asp was and how to identify the symptoms.

4 Communication

4.1 Helpline

People felt (especially the non internet patients which was 4 from the group of approx 20+) that they had no way of asking for help & advice between appointments and felt isolated and this led to worry and concern.

Recommendation : Set up a telephone helpline with an ansafone at the very least and people could call and leave their question and they would be called back.

5 Charity - marketing and fundraising

Get something going re the charity and publicising it – make it more like other charities with a commercial feel. Were there any celebrities who had suffered with Asp?

6 Health & Safety

Concern was expressed about the lack of warnings about risk areas – e.g. garden compost. One patient felt that he had contacted the disease directly from a compost bin.

Recommendation : Liaise with the Health & Safety Executive and councils to introduce warning signage in risk areas.

7 More meetings

The feeling of the group was very positive towards continuing the meetings, although some could not do this due to distance. They left their email addresses at the end together with an indication as to whether they could join a "core" patient group ongoing.

Could it be organised so that people could dial into the meeting and listen to what was going on and also contribute? Needs investigating.

Nick Montague
01/05/2009

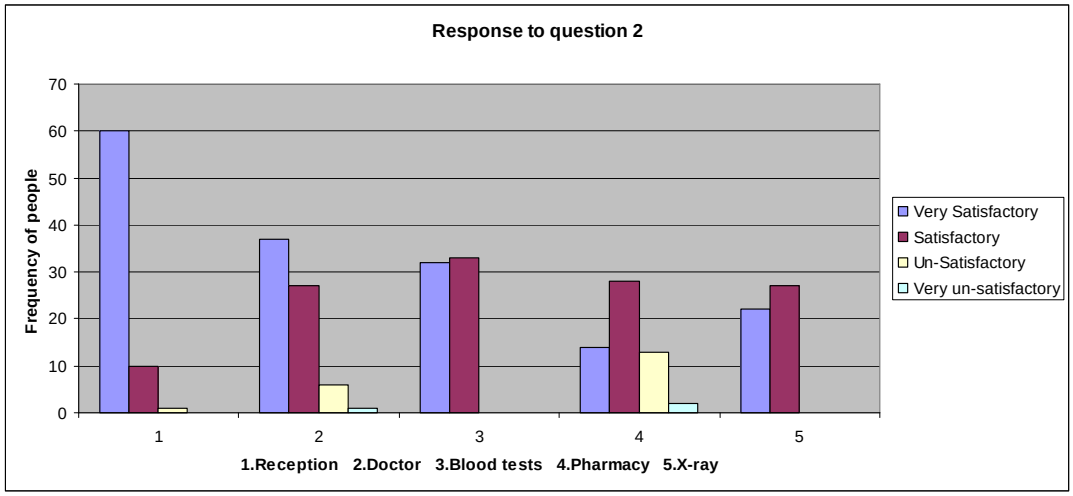
Appendix 3
Patient user survey Jan/Feb 2010.

Friday clinic only.

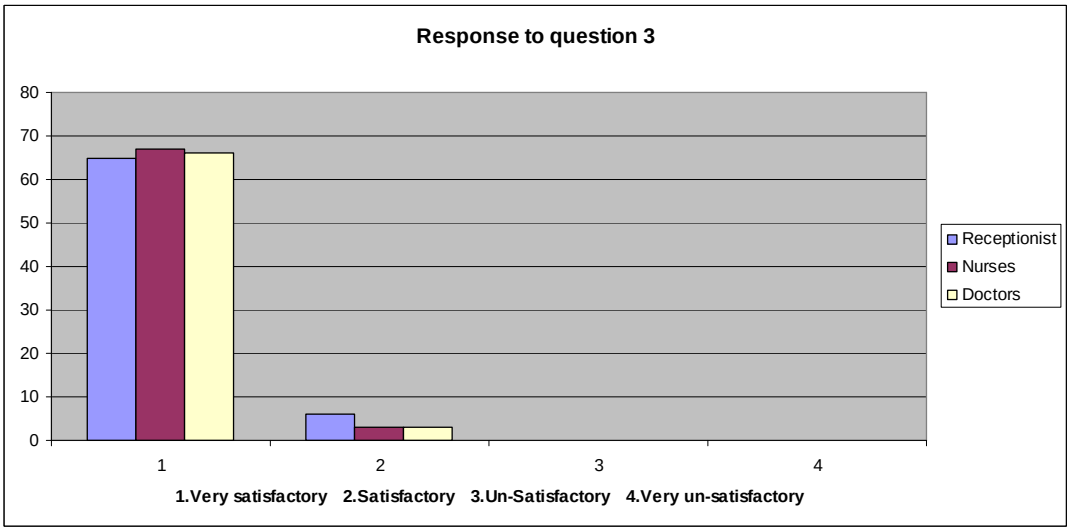
71 respondents (60% response rate). Administered by hand in clinic.

1. Is this your first visit to the National Aspergillosis Centre (NAC)
   Yes = 1
   No = 70 (99%)

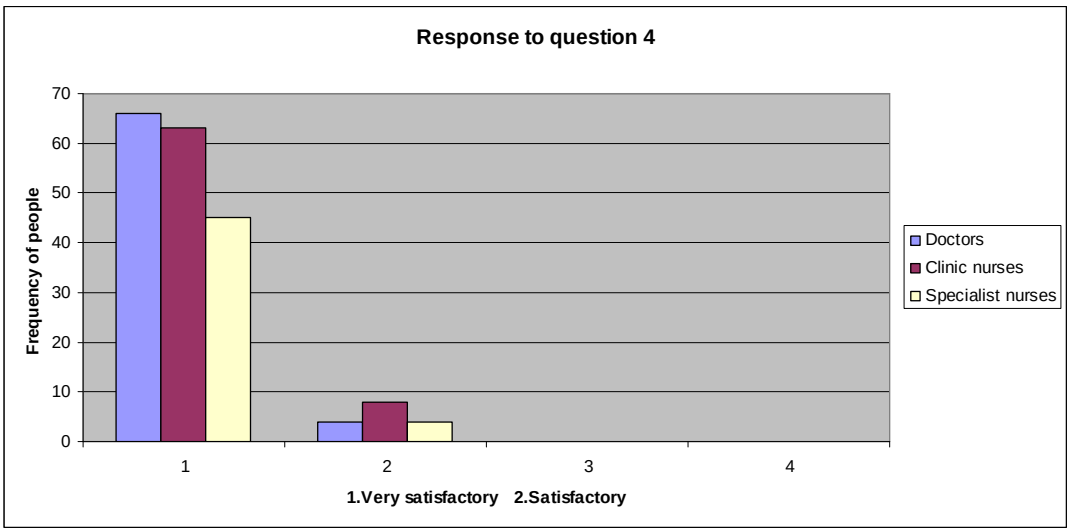
2. How did you feel about the time you had to wait for the following?



3. How satisfied are you with the courtesy shown to you by



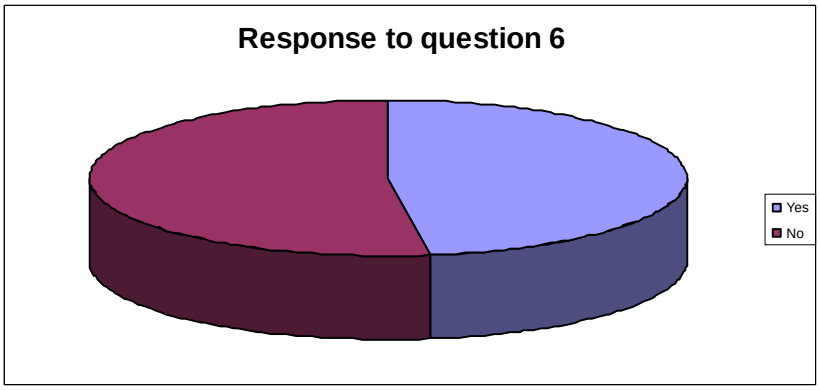
4. How satisfied are you with the quality of care received from



5. How satisfied are you with the communication with the NAC staff?

Very satisfied = 54 (76%)
Satisfied = 16
Unsatisfactory = 0
Very unsatisfactory = 0

6. Have you had any telephone support from a Doctor or Nurse after or in between clinic visits?



Comments: 1.Excellent 2.Very helpful and informative 3.Always helpful 4.My Doctor arranged new dosage so ver impressed. - 1.Very Good. 2.Good when I managed to speak to someone. 3. very helpful. 4.Good. 5. I do get very good 6. I do get very good support from Dr Gore - my local chest specialist at Chorley/Preston Hospital. 7.Very good. 8. took 3 days to get a response. 9.First class. 10.Fine - 1. Very helpful. 2. Very good. - 1.Very good. 2.Good.

7. How satisfied are you with information you received about your condition?

Very satisfied = 50 (70%)
Satisfied = 21

Unsatisfactory = 0
Very unsatisfactory = 0

8. Have you visited the Aspergillus website?
Yes = 46 (65%)
No = 25

If you have, how satisfied are you with the Aspergillus website?
Very satisfied = 50 (70%)
Satisfied = 21
Unsatisfactory = 0
Very unsatisfactory = 0

Comments: 1. Did not know it was available. 2. Unaware or possibly forgotten I had been told about it. 3. No internet connection. 4. Not got round to it yet. 5. All information provided by the doctor to our satisfaction. - 1. Did not know there was one. - 1. Did not know there was one. 2. Do not have the facility.

9. Would you have liked more information about the clinic sent to you prior to your first visit?
Yes = 8 (12%)
No = 60

Comments: 1. General information about Aspergillus. 2. What would be likely to happen during the first appointment, also directions, I found it easily enough without internet but it maybe helpful for those who can't access the internet and are travelling a long distance. - 1. I was not told what my diagnosis was before my first visit. 2. Info on doctors and clinic times etc. Also number of patients treated.

10. We are considering holding a patient information meeting here in Manchester. Would you be interested in attending a patient information meeting?
Yes = 33 (47%)
No = 37

Comments: 1. I live too far away to attend a meeting. 2. The contributions made by patients at the last meeting were very interesting. 3. Too far to travel. 4. Travelling from Scotland at 9am is dependent on others bringing me to Manchester, so it would be difficult to say in advance. - 1. If I'm Available 2.Travel distance is a barrier 3.At clinic attendance days. 4.Please make it on a Thursday/Friday - 1. Depends on time and date.

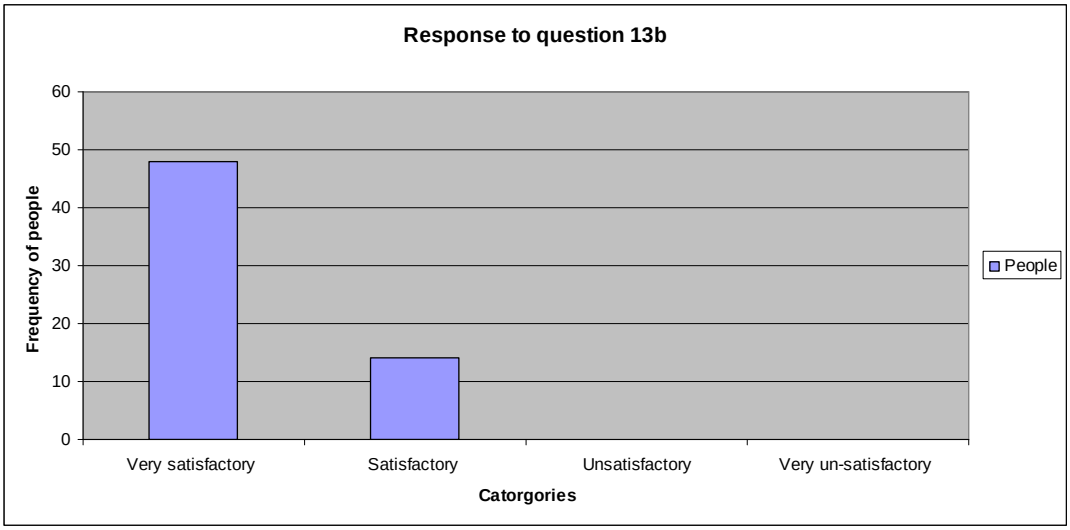
11. Would you be interested in attending an informal patient support meeting?
Yes = 25 (38%)
No = 45

Comments: 1. Due to distance, could only attend if this were on a clinic day, or held at the same time as the patient information meeting. - 1. If I'm Available 2.As in 10 about.

12. Do you travel to clinic by hospital transport?
Yes = 3 (4%) 2 of 2 satisfactory
No = 88

13. Are you generally happy to participate in clinical research?
Yes = 71 (100%)
No = 0

If you already did participate, were you happy with the procedures and consent?



Comments: 1. Very happy with the North West Centre 2. Quick, efficient procedures. Detailed information given by consultant. - 1.I attended, but was not suitable. -

Additional comments: 1. Any help I can give towards research I will provide further information and it is not a problem. Thank you. 2. I have been severely impressed by the care of attention I have received from both nurses and doctors. I feel that staff have "kept track" of things well, they have saved enough time to discuss, I ask questions and they have been very courteous and friendly. 3. Very happy with the clinic. Always get a lot of time with the consultant whop goes through the medical jargon simply and this helps me to understand my condition. 4.FAB HOSPITAL 5. I was given information about my diet by the specialist nurse when I attended clinic, this was VERY useful. 6. Professor Denning has improved my quality of life. Very impressed with everything. - 1. NAC are going from strength to strength. 2. I have visited many hospitals- this is the best/most civilized of them all (spacious, nicely decorated, aquarium/artwork, etc). Also the volunteer service for coffee and snacks is much appreciated. All the staff I have dealt with were very pleasant and helpful - well done! 3.I think the centre provides excellent care. - 1.The care I received here was Excellent. Thank you. 2. Car Park too expensive.

Appendix 4

Other publications from the group

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