NCG Chronic Pulmonary Aspergillosis national service

The National Aspergillosis Centre

Annual Report 2010-2011

Contents

1 General Overview and highlights

This report covers the second full year of this nationally commissioned service. The number of referrals was consistent with the prior year (58 in 2010/11, compared with 63 in 2009/10). Despite 30 deaths during the year, the caseload at the end of the year was 199 patients (not including 6 from Wales), which is up from April 2009 of 90 patients, especially considering there were 50 deaths in the service over the 2 years.

Significant improvements in the service have included the addition of physiotherapy (Philip Langridge), an additional consultant (Dr Pippa Newton), Aspergillus PCR testing, protection from pneumococcal and *Haemophilus* infection through immunisation, systematic quality of life measures, consistency of a single method of measuring Aspergillus IgG, a postal blood service to reduce simple outpatient visits simply to collect blood and improved patient information packs.

Challenges to the service have been the limitation in access to third and fourth line therapies, resulting in an increased number of admissions for IV antifungal therapy, difficulties in clerical staffing, substantial patient complexity requiring high level multi-consultant input, travelling distances for some patients and relatives, antifungal resistance and drug toxicities (notably photosensitivity with voriconazole and neuropathy with itraconazole and voriconazole).

2 Activity

The total referrals, inpatient stays, procedures, death and caseload in 2010/11 were as follows:

Activity Measure / Currency	Month Activity												Contract C	YTD Actual*
	M01 Apr	M02 May	M03 Jun	M04 Jul	M05 Aug	M06 Sep	M07 Oct	M08 Nov	M09 Dec	M10 Jan	M11 Feb	M12 Mar	Y/N	
Referrals	16	19	20	18	16	22	19	22	15	26	30	23	N	246
New Patients testing	4	4	6	4	3	10	7	4	4	5	7	6	Y	58
Follow-up outpatients attendances	70	64	72	101	80	64	89	72	70	108	77	84	N	951
Caseload - band 1	46	50	52	54	58	64	65	69	75	76	77	79	Y	76
Caseload - band 2	80	80	83	85	86	90	89	93	91	91	95	96	Y	96
Caseload - band 3	20	19	18	20	20	19	19	18	18	16	19	18	Y	18
Occupied bed days	64	151	59	39	56	158	76	108	85	102	37	128	Y	1063
Discharges	6	7	4	4	3	5	3	8	8	5	2	11	N	66
Surgical resection	0	0	0	1	0	1	0	0	0	0	0	1	Y	3
Embolisations	1	2	2	0	1	0	1	2	0	0	2	4	Y	15
Deaths	1	6	1	2	0	1	4	2	2	5	2	4	N	30

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

Of the 63 new patients referred from England and Scotland during the year 2010/11 (5 had delayed diagnosis, so not in the figures above), the mean time from referral to being seen was 6 weeks (range 0.25-17 weeks), or 5.5 weeks if the time of being seen of 3

DNAs are not included. Appendix 2 shows the area of residence, date of referral and date of appointment.

Overall, 30 patients died during the year and 3 were presumptively cured with surgery.

3 Service developments and personnel

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

1) Mycology Reference Centre, Manchester.

Key achievements of the Mycology Reference Centre Manchester (MRCM):

- Consolidation of test portfolio
- Expansion of training and educational activities
- Recruitment of a HPC registered Agenda for Change Band 7 Clinical Scientist
- Expansion of training and educational activities

Ongoing experience and consolidation of test portfolio offered for the benefit of CPA patients:

- Aspergillus precipitins
- Aspergillus galactomannan (antigen)
- Expansion of sensitivity testing on Aspergillus to include terbinafine, anidulafungin, caspofungin and micafungin
- Real-time PCR for Aspergillus in respiratory secretions and blood
- Molecular identification of fungi, including unusual *Aspergillus* species.
- Evaluation of automated DNA extraction robots in order to respond to the dramatic increase in PCR assay requests
- Other assays: Real-time PCR for Pneumocystis DNA
- Environmental monitoring of patients's houses for indoor moulds

Commencement of 4 year training programme for two trainee clinical scientists funded by the NHS NW SLA.

In May 2011 the MRCM was awarded a three-year training post under the Department of Health's Modernisation of Scientific Careers scheme. A Band 6 Health Care Scientist has been appointed to this post.

In April 2010 the MRCM, as part of the Manchester Medical Mycology Partnership, successfully passed its CPA accreditation without difficulty.

In 2009 the Manchester Mycology Reference Centre was selected as the single UK participating partner in the European Union Leonardo da Vinci e-learning continuing medical education project and has continued in this role in 2010-2011.

In 2010 the MRCM and the NAC ran two three-day preceptorships for 12 infectious diseases and haematology specialists from the Middle East and South Africa.

In May 2011 the MRCM and NAC ran a highly successful post-graduate workshop for the European Society for Clinical Microbiology and Infectious Diseases entitled: 'Aspergillosis: from allergy to invasive disease'.

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 (3 PAs)
Dr Pippa Newton, Consultant in Infectious Diseases (10 PAs)
Dr William Hope, Senior Lecturer in Infectious Diseases (1PA)
Dr Hana Alachkar, Consultant in Immunology (1 PA)
Dr Ibrahim Hassan, Consultant in Microbiology (1 PA)
Dr Ales Chrdle, Locum Consultant in Infectious Diseases (5 PAs)
Dr Riina Richardson, Consultant in Oral Microbiology & Infectious Diseases (20%)
ST2/3 physician in Infectious Diseases (100%)
Ms Marie Kirwan, Specialist Nurse (20%)
Ms Deborah Kennedy, Specialist Nurse (100%)
Ms Georgina Powell, Specialist Nurse (100%)
Mr Philip Langridge, Senior Specialist Physiotherapist (50%)
Dr Caroline Baxter, Clinical Fellow (100%)
Dr Livingstone Chishimba, Clinical Fellow (100%)
Ms Christine Harris, NAC manager (100%)
Dr Graham Atherton, Senior Clinical Information Architect (Patient engagement) 25%
Ms Joanne Gill, Medical Secretary (60%)
Ms Jennifer Mann, Medical Secretary (100%)
Locum Clerical Assistant cover (100%)

3) Use of validated scores to assess severity of disease and outcomes (QOL)

Quality of Life assessments have now been in operation in the National Aspergillosis Centre for nearly 23 months. In that time 225 separate individuals have filled in at least one St Georges respiratory questionnaire and a total of 744 St Georges questionnaires have been completed.

360 questionnaires were completed in the first year of operation (April 2009 - March 2010) and 384 so far in the part year April 2010 – 21st February 2011. All questionnaires are entered into a webpage based application that calculates scores and enters the results into a database for storage. Four scores are calculated though all entered data is saved; these are St George scores relating to symptoms, impact, activity and the total score calculated from all three.

Evaluation of the correlation of QoL scores with clinical signs took two forms;

1. Correlate baseline clinical test results with initial QoL scores taken on the first visit of each patient to the clinic
2. Correlate subsequent changes in QoL scores recorded at (roughly) 3 monthly intervals with changes an assessment of the patients progress made by nursing staff

Evaluation 1 was partially successful and identified a strong correlation of C-Reactive Protein (CRP) levels with Impact and Total QoL scores. Evaluation 2 was also partially successful and QoL scores accurately identified 48% of patients that improved but only 17% of those that where judged to have deteriorated by clinical staff.

We then set out to improve the accuracy of QoL predictions, compared with clinical assessment. We undertook a large scale retrospective review of case notes with an assessment of 104 patients by a doctor and nurse for each time they visited the clinic and filled out a QoL questionnaire. Patients' condition was rated as 'stable', 'slightly better', 'much better', 'worse' or 'much worse'. The aim was to be able to compare QoL assessment scores with clinical assessment over multiple time points and an overall assessment of the patients' clinical status from the beginning of their time in the clinic to their latest visit. Importantly we focused on recording side-effects of treatment and changes in medication, the effects of either of which could mask an underlying improvement in CPA but interfere with the QoL score and clinical assessment.

The data for this project has taken a considerable amount of time to collect and collate but that process has now been completed. An initial assessment looking only at overall response to treatment and concurrent QoL scores suggested that the first step was to define the clinical assessment 'stable' in terms of QoL score. We had been using a change in QoL score of less than 4 to signify 'stable' but this quickly proved to be too narrow and gave us inaccurate results. Increasing the definition of 'stable' to a change in QoL score of 10 eliminated some of the inaccuracy, but only 31% of the clinical assessments agree.

Different thresholds of accuracy were compared.

1. Highly accurate result - e.g. Clinician states 'slightly better' and the QoL agrees (31%)
2. Moderately accurate - no more than one category out, so stable/slightly better and stable/worse are equivalent, as is slightly better/much better and worse/much worse. (63% of assessments)
3. Dangerously inaccurate - where QoL suggests an improvement and clinician suggests the opposite (8%)

Using this system we 'correctly' identify 75-80% of changes with some degree of accuracy and with a severe inaccuracy rate of only 8%. This is not quite as good as it appears as there are still many examples of a clinical assessment of 'slightly better' or 'worse' that is given a QoL rating of 'stable' which is misleading but may represent the limit of sensitivity of the QoL score system.

It is easy to see how important our QoL score definitions (i.e. our parameters to decide how much change in the QoL score is equivalent to which clinical assessment category) are going to be to the final conclusions of this project and the usefullness of this information in the clinic. We seem to be seeing evidence of broad agreements between

QoL and clinical assessment but there is much yet to do. We have not yet begun to look at the individual QoL score components, the multiple QoL scores and clinical assessments we have for each patient, and the influence of side effects & drug changes.

Professor Ann Caress (Nursing) will be examining the methodology and results in more detail in the next 2-3 months.

4) Long term outpatient antifungal management

a) Intravenous antifungal therapy

A total of 3 patients (including 1 patient from Jersey) received OPD managed IV antifungals during the year 2010/2011. Initial therapy was AmBisome 200mgs 3 times a week. One patient was on AmBisome prior to April 2010. Second line IV therapy is micafungin 200mg 6 times weekly, with oral terbinafine 250mg twice daily (to prevent the emergence of resistance).

- Patient 1 commenced AmBisome® 200mgs 3 times a week from July 2009 and continued treatment until it was discontinued in July 2010 following surgery.
- Patient 2 commenced AmBisome 12 months between July 2008 and June 2009. Treatment failure led to a switch to micafungin 200mgs IV 6 times a week with oral terbinafine from June 2009 to present.
- Patient 3 received AmBisome 200mgs three times weekly for 12 months from March 2008 to February 2009. Drug toxicity led to dose reduction to 200mgs twice per week for 12 months February 2009 to February 2010 when due to worsening renal impairment and clinical failure AmBisome was discontinued, during a hospital admission. Micafungin and terbinafine were commenced May 2010 to present.

b) Medical problems with long term IV access

2 Portacath infections, resulting in removal of the PortaCath, insertion of PICC line and subsequent reinsertment of the Portacath.

5) Postal bloods

The service was enhanced by implementing local collection of blood samples, and transportation to UHSM for analysis using the postal service. This allows easier follow up after antifungal drug modifications, or repeat of prior abnormal tests, without the patient having to visit. We found that this was best undertaken at GP surgeries than in hospitals, as hospitals felt obliged to follow their internal procedures for blood samples and results never arrived back at NAC.

6) Approval process for third or fourth line antifungal therapy

A number of detailed clinical requests were submitted for posaconazole or micafungin therapy. The National Commissioning Group (NCG) Individual Case Panel (ICP) considered each request, and most were denied, based on the limited evidence base for significant improvement with posaconazole and micafungin efficacy for patients with CPA. Unfortunately this leaves many patients with no therapeutic avenues other than supportive care.

7) Lung transplantation referral

Two patients have been referred for lung transplantation and both are still being assessed. The first patient is awaiting a cardiothoracic opinion to assess whether it is technically feasible to perform a left sided thoractomy due to his extensive pleural disease. If surgery is technically feasible then he might be a candidate for a double lung transplant. The second patient has recently been assessed by an endocrinologist with regards to the management of his adrenal insufficiency in the post-operative period in the event of transplantation. The endocrinologist feels that he can be appropriately managed and he is currently awaiting further review by the transplant team.

Over the last year several large transplant centres worldwide have started to consider patients with CPA for transplantation provided that their cavitary lung disease does not involve the pleura and there is not a large amount of pleural thickening. We transplanted one CF patient with multiple aspergillomas and azole resistant *Aspergillus*, from Dublin in June 2011.

4 Audits

Several audits have been undertaken in 2010/11. Some of these have been completed:

1) Prevalence of peripheral neuropathy in patients on long term triazole antifungal therapy

Dr Carline Baxter

The triazole class of antifungals are the mainstay of treatment for patients with chronic pulmonary aspergillosis (CPA) and are often used as steroid sparing drugs in patients with allergic aspergillosis. Peripheral neuropathy (PN) is a rare but reported side effect of both itraconazole and voriconazole during treatment for invasive aspergillosis but the prevalence in patients receiving long term triazole treatment for chronic and allergic aspergillosis is unknown. This retrospective cohort study describes 314 patients commencing long term triazole therapy in whom 7% developed PN attributable only to their triazole medication. The average onset of symptoms was after 4 months of therapy. The majority of cases were axonal, length dependent neuropathies which recovered after medication was discontinued. However, 2 patients in this study had non progressive but irreversible PN. 44% of the cases were associated with high drug levels in the 3 months prior to symptom onset highlighting the need for therapeutic drug monitoring. This report also describes the first case of posaconazole induced PN. 2 patients were diagnosed with mononeuropathies indicating that the diagnosis of triazole associated PN must include exclusion of other causes using blood tests and formal nerve conduction studies. Patients receiving long term triazoles should be screened for PN symptoms and signs on a regular basis.

Patient details below in the Table.

Now published as: Baxter CG, Marshall A, Roberts M, Felton TW, Denning DW. Prevalence of peripheral neuropathy in patients on long term triazole antifungal therapy. J Antimicrob Chemother 2011;66: 2136-9.

ID	Age	Drug	Dose	Time on drug to symptoms	Drug level	B12/ folate	Glucose	TFTs	IgG	Nerve conduction findings
JL	57	Voriconazole	350mg BD	4 months	0.78	N	N	N	N	moderate length dependent motor and sensory axonal polyneuropathy
JT	53	Itraconazole	200mg BD	2 months	16.9	N	N	N	N	mild length dependent motor and sensory axonal polyneuropathy
WW	66	Posaconazole	200mg BD	3 months	3.26	N	N	N	N	mild length dependent mixed axonal/demyelinating polyneuropathy
PB	61	Itraconazole	200mg BD	6 months	19.1	N	N	N	N	mild length dependent sensory axonal polyneuropathy plus right carpal tunnel syndrome
PY	72	Itraconazole	200mg BD	1 month	17.5	N	N	N	N	acute motor and sensory axonal polyneuropathy
RB	77	Itraconazole Voriconazole	200mg BD 200mg BD	7 months 2 months	21.6 4.32	N	N	N	N	Not done acute motor predominant axonal polyneuropathy
JR	52	Itraconazole Voriconazole	150mg BD 200mg BD	3 months 2 months	>25 2.4	-	N	N	N	Not done mild length dependent sensory axonal polyneuropathy
JH	60	Itraconazole	200mg BD	2 months	12.3	N	N	N	N	mild length dependent sensory axonal polyneuropathy
BB	77	Itraconazole	200mg BD	2 months	8.3	N	N	N	N	length dependent predominant small fibre polyneuropathy
BL	72	Voriconazole	200mg BD	11 months	1.64	N	N	N	Gamma paraprotein , BJP neg	length dependent predominant small fibre polyneuropathy
VE	66	Itraconazole	200mg BD	1 month	13.0	N	N	N	N	mild length dependent sensory axonal polyneuropathy Normal 6 months after cessation of medication
BS	71	Itraconazole	100mg BD	5 months	12.3	N	N	N	N	Left carpal tunnel syndrome
JB	55	Voriconazole	250mg BD	3 months	0.77	N	N	N	N	Bilateral tarsal tunnel syndrome
JG	65	Itraconazole	200mg BD	3 months	17.6	-	N	N	N	no evidence large fibre polyneuropathy 2 months after drug cessation
CR	31	Itraconazole	200mg BD	3 months	20.8	N	N	N	N	no evidence large fibre polyneuropathy 1 month after drug cessation
MH	78	Itraconazole	200mg BD	3 months	19.2	N	N	N	N	no evidence large fibre polyneuropathy 3 months after drug cessation
AH	59	Itraconazole	200mg BD	5 months	17.4	-	N	N	N	Not done, dose reduced and symptoms resolved
PH	60	Itraconazole	200mg BD	8 months	17.5	N	N	-	N	Not done, dose reduced and symptoms resolved
CJ	56	Itraconazole	150mg BD	11 months	23.5	N	N	-	IgA rise	Not done, changed to posaconazole, symptoms resolved
GS	47	Voriconazole	250mg BD	7 months	2.22	-	N	-	N	Not done, changed to posaconazole, symptoms resolved
AR	59	Itraconazole	200mg BD	3 months	9.3	N	N	N	N	Not done, symptoms resolved off treatment
DP	53	Voriconazole	200mg OD	4 months	3.6	N	N	N	N	Not done, symptoms resolved off treatment
HR	74	Itraconazole	200mg BD	2 months	13.4	N	N	-	N	Not done, symptoms resolved off treatment
KD	43	Itraconazole	200mg BD	1 month	7.0	N	N	N	N	Not done, No recovery of symptoms, no progression on voriconazole
HRe	21	Itraconazole	200mg BD	18 months	5.4	N	N	N	N	Not done, No recovery of symptoms, no progression on voriconazole

2) Pulmonary aspergillosis – an alternative diagnosis to lung cancer after positive ^{18}F-FDG positron-emission tomography

Dr Carline Baxter.

^{18}F-FDG PET scans have significantly improved the diagnosis and staging of lung cancer but false positive scans are known to occur due to inflammatory and infectious diseases. Recognition of the conditions leading to false positive scans is important. One or more pulmonary nodules, with or without cavitation, are one of the manifestations of acute and chronic pulmonary aspergillosis. Clinical features of pulmonary aspergillosis are very similar to those of lung cancer. This report highlights pulmonary aspergillosis as an alternative diagnosis to lung cancer in patients with positive ^{18}F-FDG PET scans and the need to strive for pre-surgical histological diagnosis, including Aspergillus serology.

Table of cases below.

Now published as: Baxter CG, Bishop P, Low SE, Baiden-Amissah K, Denning DW. Pulmonary aspergillosis – an alternative diagnosis to lung cancer after positive 18F-FDG positron-emission tomography. **Thorax** 2011;66:638-40.

	SuVmax (g/ml)	Operation	Histology	Aspergillus IgG (mg/L)	Precipitins titre	Total IgE (KIU/l)	Aspergillus IgE (KUa/l)	Diagnosis	Treatment
Case 1	7.2	Wedge resection	Septate fungal hyphae and conidial heads	78	1/2	42	0.5	CPA	Itraconazole
Case 2	8.3	Wedge resection	Hyphal fragments	>200	1/2	8045	36.7	ABPA	Itraconazole
Case 3	4.0	Wedge resection	Fungal hyphae involving adjacent blood vessels	28	1/2	1100	40.5	Subacute IA	Voriconazole
Case 4	3.5	CT guided biopsy	Fungal hyphae admixed with spores	82	1/2	90	<0.4	CPA	Posaconazole
Case 5	2.6	Wedge resection	Branching fungal hyphae	66	1/16	570	8.0	CPA	Itraconazole
Case 6	3.9	CT guided biopsy	Branching Fungal hyphae	94	1/4	140	<0.4	CPA	Itraconazole
Case 7	2.2	Wedge resection	Fungal hyphae admixed with spores	56	Neat	1000	14.9	CPA	Itraconazole
Case 8	7.9	Wedge resection	Branching fungal hyphae	50	Neat	73	<0.4	CPA	Voriconazole
Case 9	9.0	CT guided biopsy	Branching fungal hyphae	76	1/64	62	<0.4	CPA	Itraconazole
Case 10	2.9	Lobectomy	Aspergilloma	_	1/2	61	<0.4	Simple Aspergilloma	Nil

3) Chronic respiratory diseases impact pneumococcal antibody levels and response to pneumococcal vaccine

Mrs Georgina Powell, Julie Morris, David W Denning Hana Alachkar & Ray Borrow

Objective

Streptococcus pneumoniae is a leading cause of infection worldwide. The 23 valent polysaccharide vaccine (PPV) was introduced in 2003. The objective was to establish if patients with chronic respiratory disease have low pneumococcal antibody levels and if they achieve adequate response following PPV.

Methods

Patients attending specialist respiratory clinics routinely had pneumococcal antibody levels tested. Antibody levels to 12 serotypes were compared between 4 groups – chronic pulmonary aspergillosis (CPA) n=156, allergic-bronchopulmonary aspergillosis (ABPA) n=83, bronchiectasis n=36, and asthma/severe asthma with fungal sensitisation (SAFS) n=43, age range 18yrs – 87 yrs. A level of $\geq$0.35µg/ml signified adequate response and patients with low levels to $\geq$6/12 serotypes were given PPV.

Results

127/318 patients were vaccine naïve, with pre-vaccine levels for serotypes 1 and 4 lower than all others ($p<0.05$). 241/318 patients had post-PPV levels, with a significantly lower number having adequate response to serotype 4 compared to other serotypes. 55 patients had pre- and post-vaccine levels with 75% having antibody levels checked within 3 months of PPV (range 1-24 months). CPA patients had poor response to serotypes 1 and 4. ABPA and bronchiectasis patients also showed poor response to serotype 4. The asthma/SAFS group had adequate response to all serotypes. Overall post-PPV antibody levels declined over time (range 1month-16yrs), with increased age indicating poorer response, particularly in the bronchiectasis group.

Conclusions

Poor pre- and post-vaccine levels to serotype 4 are surprising. Decline in protection over time is documented in people >60 yrs and in those with respiratory disease. Good response rates to most serotypes supports the use of PPV for most respiratory patients. Revaccination is not currently recommended, but our data suggests re-testing could be important to check protection, especially in bronchiectasis and increasing age.

4) Comparison of IgG, IgA, IgM and mannose binding levels in patients with different respiratory conditions.

Georgina Powell, Julie Morris, Hana Alachkar & David W Denning

Objective

Immunoglobulins and mannose binding lectin (MBL) are involved in the immune response and protection against infections. The objective was to compare patients with different respiratory conditions to establish if they have different levels of immunoglobulins and MBL.

Methods

Patients attending specialist respiratory clinics had serum immunoglobulin and MBL levels tested as part of routine clinical care. IgG, IgA, IgM and MBL levels were compared between 4 groups – chronic pulmonary aspergillosis (CPA), allergic-bronchopulmonary aspergillosis (ABPA), bronchiectasis, and asthma/severe asthma with fungal sensitisation (SAFS).

Results
Patients results were analysed for IgG (n=290), IgA (n=295), IgM (n=292) and for MBL (n=264). 5 patients had IgG levels <5.5mg/L, none with asthma/SAFS. CPA patients had significantly higher levels of IgG (geometric mean–GM, 13g/L,range 3.3-35.2,p<0.001), IgA (GM 3.0 g/L, range 1-10, p<0.001), and MBL (median 1.93mg/L, range <0.05 - >0.4, p=0.030) than the others, with no significant difference in IgM levels. Immunoglobulin levels were compared to MBL levels and in relation to age. 51/177 (28.8%) patients had MBL levels <0.5mg/L

Conclusions
Higher IgG, IgA and MBL levels for CPA patients were expected, as part of the immune response against chronic infection. The same was expected in the bronchiectasis group, however, they had high IgG and IgA but low MBL.
For CPA patients the immune response against pathogens is CD4+TH-1 lymphocyte mediated, as opposed to CD4+TH-2 response in ABPA, SAFS and asthma. These patients are more likely to have received oral corticosteroids than CPA patients, possibly accounting for lower serum IgG and IgA levels.
Comparison with MBL (excluding those with baseline <0.5) showed correlation between higher MBL levels and higher IgG (p=0.004) and IgA (p=0.05) levels, CPA patients had significantly higher levels. There was no correlation between immunoglobulin levels and age, age is not associated with changes in immunoglobulin levels.

5) <u>The Prevalence of Coeliac Disease among Patients with Chronic Pulmonary Aspergillosis</u>
<u>Yousef Gargani (medical student)</u>
Some patients with chronic pulmonary aspergillosis (CPA) also have coeliac disease (CD). The prevalence of CD amongst the UK population is varies from 0.8% to 1.9%, with an undiagnosed prevalence of around 1%. Of 167 patients attending the CPA clinic, 4 (2.4%) already had a diagnosis of CD (95% CI 0.94% to 6.00%). After screening 111 CPA patients, 1 patient had an abnormal anti-tTG result and likely had CD, and none were IgA deficient. The minimum prevalence of CD in the UK CPA population is 3% (95% CI 1.3% to 6.8%), which justifies active screening; especially as weight loss is a common features of both diseases. Additional data would confirm or refute a possible association, given the width of the confidence interval.

6) <u>Multifocal pulmonary cavities with aspergillomas - an unusual variant of chronic pulmonary aspergillosis</u>
Matthew Pendleton (medical student)
Not quite complete

7) New cutaneous reactions to posaconazole and review of cutaneous reactions to triazole antifungal agents

Dr Timothy Felton (paper in draft form)

Background: Posaconazole is a new second-generation triazole with excellent anti-Aspergillus activity and an extended spectrum. We describe new cutaneous adverse events related to its use.

Methods: We treated 79 patients with chronic pulmonary aspergillosis and 4 (5%) developed significant cutaneous reactions. Three patients developed acneiform facial and upper trunk reactions in 2 to 20 days after commencing oral posaconazole. One discontinued therapy. One patient developed a severe exacerbation of psoriasis within 3 weeks of starting posaconazole and stopped therapy. All patients had posaconazole levels >2.0 mg/L. Reactions resolved on stopping therapy in 2 patients, and continued in those not stopping.

Conclusion: Posaconazole is a new useful agent for the long term treatment of aspergillosis, but cutaneous reactions limit its use in some patients.

8) Bronchoscopy sampling, culture technique and real-time PCR for Aspergillus affect diagnostic yield

Marcin Fraczek

Background: Fungal culture methods for respiratory specimens have never been formally compared. Real time PCR for *Aspergillus* spp. has recently been introduced in Europe, Africa and Canada. We compared 2 culture methods and PCR on multiple sputum and bronchoscopy samples from 3 patients with aspergillosis.

Method: We bronchoscoped 3 patients: ABPA, prior IA and COPD and Aspergillus bronchitis. We compared 1) the UK standard method for processing respiratory cultures (BSOP57) (modified to plate 10uL instead of 1uL) with 2) high volume culture of one third of the specimen (range 20µL – 2.3mL, avg 0.5mL) on Sabouraud dextrose agar (30˚C) and 3) real time PCR (MycAssay Aspergillus) preceded by DNA extraction using the MycXtra kit. The sensitivity of this assay is <1 genome, following a >10% extraction efficiency. Sputum samples were obtained before and after the bronchoscopy procedure. Material obtained was split into 'highly mucoid' material and more liquid material, if possible. Approximately equal volumes of material (33% each) were used for the PCR and 2 culture methods.

Results: 21 samples were processed for Aspergillus. All (100%) were *Aspergillus* negative by routine culture and 14 of 21 (67%) negative by high volume culture. Only 2 (10%) were negative by PCR, 3 were below clinical cutoff (Ct <36) and 16 (76%) positive (Ct values 28.9-35.7). Of the 6 sputum samples (2 split), all were positive by PCR and 5 of 8 (63%) were positive by high volume culture (1-6 CFU). BAL samples were all *Aspergillus* culture negative, and 8 of 10 samples (80%) were PCR positive. In 2 patients the highest PCR yield was the initial bronchoscopy trap aspiration (often discarded as contains lignocaine), but not in one patient; hyphae and Charcot-Leyden crystals were visible in this sample from patient with ABPA and 19 CFU were grown in high volume culture.

Sample	n	Aspergillus positive samples (%)		
		Aspergillus culture		MycAssay Aspergillus real time PCR
		Routine	High volume	
Pre-bronch sputum	4	0	4 (100)	4 (100)
Post-bronch sputum	4	0	1 (25)	4 (100)
First trap aspiration	3	0	2 (67)	3 (100)
First BAL (10-20mL)	5	0	0	4 (80)
Second BAL (10-50mL	5	0	0	4 (80)

Conclusion: The UK standard method for culture is grossly sub-optimal for *Aspergillus* spp. and needs revision. Improved culture methods may be of value for sputum but are inferior to real time PCR using the MycXtra DNA extraction system and MycAssay Aspergillus assay. Bronchoscopy sampling has considerable variability in diagnostic yield; sputum may be superior.

9) Efficacy and safety of voriconazole and posaconazole as second line therapy in ABPA and SAFS

Dr Livingstone Chishimba (paper submitted)

Background and Objectives; Allergic bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal sensitisation (SAFS) are progressive allergic fungal lung diseases. Current treatment with itraconazole (itra) is associated with a 40% failure rate and adverse events (AEs). Very little is known about the response rates or appropriateness of treatment with voriconazole (vori) or posaconazole (posa). This study assessed the effect of vori or posa as second and third line therapy.

Methods: We conducted a retrospective audit of 27 adult asthmatic patients who fulfilled diagnostic criteria for either ABPA or SAFS. All patients had previously received itraconazole. Vori (300-600 mg/day) or posa (800 mg/day) (adjusted by TDM) was given for at least 6 months if tolerated. Clinical, radiological and immunological evaluation was used to assess response. We defined response as improvement in symptoms and either fungal serology or radiological abnormalities. The rates of clinical response or failure and their adverse effects (AEs) after 3, 6, and 12 mos of treatment were analyzed. Co-existing diagnoses, *Aspergillus* antibody titre, vori and posa levels and lung function were used as co-variates.

Results: There were 27 patients, ABPA (n = 22) or SAFS (n = 5), 11 males, median age = 59 yrs. All patients had failed itra (n=11) or developed AEs (n=12), low serum concs (n=2) or itra resistance (n=2). There were 34 courses of therapy analysed, 25 with vori and 9 with posa; only 2 posa courses were not preceded by vori (resistance).

Clinical response to voriconazole was observed in 17/25 (68%) at 3 mos, 15/20 (75%) at 6 mos and 12/16 (75%) at 12 mos, compared to 7/9 (78%) at 3, 6 and 12 mos for posa. 6/25 (24%) vori pts had AEs requiring discontinuation before 6mo compared to 0/9 posa patients. Vori AEs included GI upset (7), skin photosensitivity (11), blistering (4), visual light flashes (10), insomnia (2), visual hallucinations (2), depression (1), adrenal suppression (2), peripheral neuropathy (4), eye irritation (2), vivid dreams (1), dizziness (1) and headache (1) but most of them were transient and mild. Posa AEs included insomnia (2), GI upset and mild liver impairment. Among those who discontinued, 4 relapsed (one at 3 mo, 3 at 12 months).

Conclusion: Both voriconazole and posaconazole are safe and effective treatment options as second line therapy for SAFS and ABPA. Larger prospective studies are required.

The clinical response data presented in the paper submitted is shown as follows:

		Clinical outcome of courses of therapy (%)		
		3 months	6 months	12 months
ABPA				
Voriconazole	Improved	13/20 (65)	11/15 (73)	9/13 (69)
	Stable	2/20 (10)	2/15 (13)	2/13 (15)
	Failure	1/20 (5)	0/15	2/13 (15)
	Discontinued (AEs)	4/20 (20)	2/15 (13)	0/13
Posaconazole	Improved	7/9 (78)	7/9 (78)	7/9 (78)
	Stable	2/9 (22)	2/9 (22)	0/9
	Failure	0/9	0/9	2/9 (22)
	Discontinued (AEs)	0/9	0/9	0/9
SAFS				
Voriconazole	Improved	4/5 (80)	4/5 (80)	3/4 (75)
	Stable	1/5 (20)	1/5 (20)	1/5 (20)
	Failure	0/5	0/5	0/5
	Discontinued (AEs)	0/5	0/5	0/5

Confidential: For Review O

10) Audit of IV Ambisome Therapy
Pippa Newton and Chris Harris

Nine chronic pulmonary aspergillosis (CPA) patients (5 females and 4 males) aged between 47 and 74 years (mean 61 years) at the time of their first dose of Ambisome have had more than one course of IV Ambisome therapy as an inpatient at UHSM. Six of these patients live within the Northwest region. Two patients have had at least one further course of IV Ambisome in their local hospital.

Four patients have had repeated courses of IV Ambisome therapy as an inpatient (two courses of treatment {n=3}, three courses of treatment {n=1}) and 5 patients had both IV Ambisome course /s in hospital followed by long-term treatment in the community (one

course of IV Ambisome initially {n = 3}, two courses of IV Ambisome initially {n=2} prior to long-term treatment).

Repeated courses of Ambisome

The dose of IV Ambisome given for inpatient courses ranged between 2.53 – 4.62 mg/Kg daily (mean 3.03 mg / Kg) with the daily dosage ranging between 100 – 250 mg a day (n = 16). The duration of IV Ambisome therapy courses varied between 3 to 36 days (three days was used to teach the patient intermittent IV Ambisome administration; mean was 20.3 days, median was 21 days). Eight courses of IV Ambisome were accompanied by the use of IV or oral antibiotic therapy. In two cases, gamma interferon replacement therapy was also started whilst on IV Ambisome. The interval between IV courses varied between 2 – 60 months (median 3 months and mean 11.28 months; the patient with a 60 month time delay between courses had his last course locally 60 months ago and at UHSM 68 months ago).

Triggers for the use of IV Ambisome courses (total courses = 16) were primarily a deterioration in their chest symptoms and / or radiology (n = 10; such as increased sputum {n=2}, worsening cough {n=10}, haemoptysis {n=7}, shortness of breath {n=9}, radiology {n=1}) and constitutional symptoms / general health (n = 9; lethargy {n=6}, weight loss{n=8}, poor appetite {n=4}).

Five out of nine (56%) patients noted an improvement in their chest symptoms following IV Ambisome with two patients having improvements on two separate occasions. Four out of nine (44%) patients had improvements in their constitutional symptoms following IV Ambisome with two patients experiencing improvements on two different occasions. One patient was noted to have improved clinically but there was no written documentation regarding in what way he had improved. One patient has not been seen following his last course of Ambisome and hence an assessment of his response to treatment has not yet been made. There was only one course of IV Ambisome (out of 16 (6%)) where the patient did not notice any improvement in her symptoms following treatment. This patient did later respond both clinically (improvement in chest and constitutional symptoms) and immunologically to a subsequent course of IV Ambisome.

Three out of six (50%) patients with sufficient immunological data available to assess their immunological response showed an immunological response (fall in serology marker) to IV Ambisome therapy.

Only three patients had quality of life data using the St George's questionnaire prior to and following their IV Ambisome course (follow up ranged between 4 – 13 months, mean 8 months; one patient only had one follow-up questionnaire). All three patients had an improvement in their total score (range of best responses was 3 – 19.9; mean was 10.1), in their symptoms (range of best response was 14.7 – 20.2; mean was 17.8) and impact on daily life (range of best response was 5.4 - 27.3; mean was14.7). One patient had an improvement in their activity (best response was 14.1 points) whilst the other two patients noticed a deterioration (range was 6.1 - 6.6 points).

IV Ambisome course followed by long-term treatment

For intermittent treatment the usual regimen was to give IV Ambisome three times a week. The dosage used varied between 2.53 – 6.7 mg/Kg (mean 4 mg / Kg) with the highest dose of 6.7 mg / Kg given to a patient who had a multi-azole resistant *Aspergillus* infection who was clinically failing on 5.4 mg / Kg of IV Ambisome three times a week. The dose of IV Ambisome given for intermittent treatment varied between 180 – 250 mg of IV Ambisome three times a week. The duration of intermittent treatment varied between 4 – 24 months (mean 11.2 months).

Intermittent therapy was generally given to patients who had no other oral options available due to either intolerance and /or resistance apart from one lady who had a major deterioration on itraconazole prior to receiving IV Ambisome. (She later tried voriconazole but was intolerant to this). The intermittent course of treatment was started within one month of their last course of IV Ambisome given as an inpatient (n=5).

All five patients (100%) showed improvement in their symptoms (chest symptoms {n=1}, constitutional symptoms / general health {n=4}) on intermittent IV Ambisome therapy and one out of the three (33%) patients with follow-up immunological data showed an immunological improvement. Of the five patients who had intermittent IV Ambisome, one patient stopped treatment after a pneumonectomy and the other four patients later failed this treatment. One patient has subsequently died of end stage respiratory disease.

11) Development of a radiological score for prospective studies of CPA

Dr Timothy Felton (in validation phase)

Radiological imaging of the chest is a key component when assessing patients with Chronic Pulmonary Aspergillosis (CPA). Computerised tomography (CT) of the thorax is used, not only, as part of the diagnostic criteria for CPA but also to monitor for response or progression of CPA over time. In collaboration with Dr Melanie Greaves, Consultant Thoracic Radiologist, we are developing a scoring system to allow objective assessment of individual patients CT scans. The scoring system is a modification of an existing scoring system that has been validated for use in patients with Cystic Fibrosis (CF). The CF scoring system was chosen because of there are a number of similarities between the two diseases including presence of chronic suppurative infection, progressive parencymal damage, presence of bronchiectasis etc. The CPA scoring system contains 12 domains with a potential score of between 0 and 3. During the first half of 2011 we aim to assess the intra- and inter-observer variability of the score. Following this we will trial the score in a small retrospective, cohort of patients with serial CT scans where the clinical and serological outcome is known to assess correlation between the score and other indicators of disease activity.

12) Aspergillus bronchitis

Dr Ales Chrdle

A retrospective chart review of patients with possible Aspergillus bronchitis was conducted. Many highly symptomatic patients, unresponsive to antibiotics, with either

positive respiratory cultures or elevated Aspergillus IgG antibody titres were identified. Few patients have been described previously with Aspergillus (Aspergillary) bronchitis, unless immunocompromised. We reviewed all the records of patients referred who could fulfil the criteria for Aspergillus bronchitis to define the typical and atypical phenotypes of Aspergillus bronchitis. Patients with persistent symptoms or bronchial obstruction with laboratory testing consistent with Aspergillus infection, who did not fulfill criteria for allergic, chronic or invasive pulmonary aspergillosis were analysed. Patients with an elevated Aspergillus IgG or precipitating antibody to *Aspergillus* spp. and a positive culture or Aspergillus PCR, were regard as having typical Aspergillus bronchitis. Those with fewer positive criteria were also analysed and compared with the typical group. 28 patients' notes were examined. 17 fulfilled the criteria selected for review. 14 were women and the mean age was 57 years (range 39-76). 16 had a productive cough and 8 voluminous tenacious sputum. 8 had MRC dyspnoea scores of 4-5. 7 had recurrent chest infections, and 4 significant fatigue. 3 had lost weight and 2 had had haemoptysis. 12 of 14 patients had bronchiectasis on CT scan. Bacterial co-infection was common, but un-responsive to antibiotics. 13 grew *A. fumigatus*, 3. *A. niger* and 1 *A. terreus*. 12 of 17 had elevated Aspergillus IgG (47-137mg/L, mean 89.2) (Phadia) and 5 had elevated Aspergillus precipitins, 4 with a normal Aspergillus IgG (Phadia). 7 had a major response to antifungal therapy, 5 some improvement and 3 failed antifungal therapy (2 had no treatment). Of 8 patients who discontinued therapy, 5 relapsed and 3 remained well. 9 had mannose binding lectin levels <1.0mg/L.

5 Patient engagement

Patient involvement

Following on from the initial meeting for patients held on the opening day of the National Aspergillosis Centre (May 2009) we initiated regular meetings for patients. Starting in June 2010 there has been a meeting on the first Thursday of the month every month with a speaker on a topic of general interest

Talks have been presented including the following topics:

- providing feedback on research carried out at the clinic
- the difficulties of funding antifungals
- the practicalities of taking antifungals, side effects
- a 'virtual clinic' taking us through a typical visit to the clinic
- what is research and how do we do it?
- the management of mould in our environment to limit our exposure
- diet and aspergillosis/respiratory problems
- Active breathing techniques.

Each meeting finishes off with an opportunity for informal chatting between staff & patients/carers. The primary aim is to provide support for patients and an opportunity for patients to socialise with each other outside of the clinical setting.

The meeting is well attended with 23 - 35 attending including 5 staff, and we ensure that the widest possible number of people can participate by providing a live stream of the

event broadcast via the internet (watched by 18 - 30 people) and a recording of the internet stream which is regularly watched by another 50 - 60 people each month.

For those patients without internet access we provide a summary of the meeting in the form of a newsletter given out at each clinic and write up detailed notes & slides to be available on request or by download from the dedicated website at www.nacpatients.org.uk (as many who do not have direct access to the internet can get documents downloaded and printed out by a carer or relative).

On the 2-3rd October 2010 we were invited to present a day at the 'From Another Kingdom' exhibition at the Royal Botanical Gardens Edinburgh. Close to 200 members of the public watched a series of presentations given by NAC members of staff on different aspects of mould and yeast infections. A major focus of the weekend took place on the morning of the 3rd when we held a meeting for patients. The format was very similar to our meetings in Manchester and was an opportunity for our Scottish patients & carers to participate. The main speaker was Elizabeth Smith who raised over £4,000 for the Fungal Research Trust in memory of her daughter Steph by holding a sponsored walk. The route was the entire length of the West Highland Way (100miles). Elizabeth spoke very emotively about her daughter and of their efforts to raise the profile of Aspergillosis in Scotland. In a subsequent discussion hosted by Graham Atherton we covered topics which including practical problems caused by use of antifungal drugs & steroids and refinements we could make to our service so that people who are remote to the centre in Manchester can be supported as well as possible.

23 patients and their carers attended with 6 members of staff. There was a unanimous vote that we should run more meetings in Scotland in the future.

User survey (January 2011)
Over 99% of patients (n= 146) surveyed were either very satisfied or satisfied with the care they received from the doctors and specialist nurses. Full details in Appendix 3.

On-line materials
The Aspergillosis for Patients website was running at an average of 57,861 hits per month in 2010 compared with 27,000 hits in the six months prior to the launch of the National Aspergillosis Centre. The newly launched website dedicated to patients (www.aspergillus.org.uk/newpatients/) takes new patients and their carers through every step of the way of diagnosis, treatment, long term care & prognosis. This information portal sits alongside an extensive support group and online Question & Answer forum.

The Aspergillus Support group (http://uk.groups.yahoo.com/group/AspergillusSupport) is a mutual support email group that has been in existence since 1998. There are over 900 members, worldwide. 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.

The Q & A phorum is increasingly popular. In 2010, there was an average of 133,408 hits per month, with a peak figure of 187,757 (September) and has increased hugely over the last 15 months. This compares with an average of 6,600 hits on that section per month prior to the launch of the NAC. Much of this activity is probably caused by users searching for existing questions & answers.

Patients meeting Rome

The Fungal Research Trust-funded meeting in Rome on 3rd February 2010 video recordings are still being viewed on-line on the Aspergillosis for Patients website (http://www.aspergillus.org.uk/newpatients/romemeeting.php) and at iTunes (www.itunes.com). Over the 12 months up to January 2011 the pages on which the videos are presented were viewed a total of 7,174 times. Slides accompanying the videos were downloaded more than 10,000 times. The talks are also presented as podcasts - the downloadable format for the iPlayer - and this page was accessed 10,094 times. The same podcasts are also available via third parties such as iTunes and they have achieved high popularity amongst similar podcasts but we have no way of counting downloads.

6 Research outputs, other published research summary

Publications 2010

A) CPA related publications

Felton TW, Baxter C, Moore CB, Roberts SA, Hope WW, Denning DW. Efficacy and safety of posaconazole for chronic pulmonary aspergillosis. Clin Infect Dis. 2010 Dec 15;51(12):1383-91.

Bueid A, Howard SJ, Moore CB, Richardson MD, Harrison E, Bowyer P, Denning DW. Azole antifungal resistance in *Aspergillus fumigatus*: 2008 and 2009. J Antimicrob Chemother. 2010 Oct;65(10):2116-8.

Smith NL, Denning DW. Underlying conditions in chronic pulmonary aspergillosis, including simple aspergilloma. Eur Respir J. 2010 Jul 1.epub

Lestner JM, Denning DW. Tremor: a newly described adverse event with long-term itraconazole therapy. J Neurol Neurosurg Psychiatry. 2010 Mar;81(3):327-9.

Clinical reviews in UpToDate (available in most hospital libraries):
http://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-chronic-pulmonary-aspergillosis

http://www.uptodate.com/contents/treatment-of-chronic-pulmonary-aspergillosis (in revision)

B) Findings affecting clinical practice

1. Higher slightly rate of coeliac disease in CPA from baseline, justifies a single screening assay, because of the issues of weight loss in CPA patients.

2. Antifungal resistance running at a sufficiently high rate that more strenuous methods of collection of respiratory samples for culture. Cultures are however

substantially inferior to commercial PCR in sensitivity, so double samples are now routinely collected.

3. Positive Aspergillus PCR on antifungal therapy signals probably represent clinical failure, and this is potentially helpful, but needs fully auditing.

4. Direct detection of triazole resistance in *A. fumigatus* from airway secretions in culture negative PCR positive samples allows resistance to be detected much more frequently. This needs further clinical evaluation, planned over the coming year.

5. Higher serum mannose binding lectin were associated with bronchiectasis, worse respiratory status and more severe CPA, suggesting that excess inflammatory response is damaging. MBL levels are routinely done at first visit.

6. Poor pneumococcal and *Haemophilus influenzae* B antibody responses are frequent. These are therefore evaluated at first visit and immunisation given if low, to prevent as many admissions and antibiotic courses as possible. The efficacy of immunisation in each patient is checked, and immunisation repeated with an alternate vaccine, if persistently low.

7 Statutory reports

MRSA
3 of our patients isolated MRSA - 2 from swabs - (one already known to be colonised - had a previous PEG site MRSA infection) and the other intermittently grew MRSA from swabs. The third grew MRSA from a sputum sample taken in clinic.

C. difficile infection
None

HIRS
8 incident reports

SUI
None

8 Financial position

Expenditure 2010 - 2011
The original plan for 2010/11 was set at £5.87m and included £3.47m of drug costs.

During 10-11 the NCG contract operated as a block varied only in relation to drugs expenditure which was treated as a direct pass through. The fixed and variable nature of the contract in year has meant that despite underperformance in activity the main contract achieved and consistent with the lower than plan activity drug expenditure was less than anticipated at £2.2m generating £1.29m underperformance against plan.

Overall the total cost of the service in 2010-11 was £4.6m against a plan of £4.8m.

The following illustrates the out-turn position against current the contract currencies forming the block element of the contract.

Activity Type	Original Plan		Actual Outturn	
	Activity	Cost £'s	Activity	Cost £'s
Referrals	**80**	**£120,800**	**64**	**£96,640**
Band 1	95	£201,020	79	£167,164
Band 2	155	£580,630	96	£359,616
Band 3	37	£173,900	18	£84,600
Total Banded	**287**	**£955,550**	**193**	**£611,380**
Surgical Resections	5	£56,020	3	£33,612
Embolisation	15	£17,745	15	£17,745
Occupied Bed Days	516	£139,836	1063	£288,073
Infrastructure Costs		£751,174		£751,174
Overhead allocation		£357,197		£357,199
Total		£2,398,322		£2,155,823

Financial Forecast 2011/12

During 11-12 the NCG contract will move to a more marginal basis. A block will be in place for the fixed infrastructure costs with marginal rates applied to activity and drugs expenditure continuing to operate as a direct pass through.

The contract is set at £5.1m and includes a fixed element of £1.4m, £2.3m drugs and the balance attributable to achievement of agreed patient numbers and activity levels.

9 Future developments

Progress on developments planned for 2009/10

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 – Test reformatted and training planed for March 2010 for introduction in 2010.
- 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. No progress on keyhole cavernostomy, as the ideal first patient, has not been identified.

- Introduction of a partially validated outcome score into clinic practice, with continued evaluation of its utility. QoL evaluation delayed by long term sickness of one the NAC specialist burses. Evaluation in progress.
- Introduction of Prevanar 13 pneumococcal vaccine, instead of Pneumovax or Prevanar 7, into routine practice with a clinical evaluation of its impact. Audit completed and poster presented. Paper in preparation regarding Pneumovax and a second one on Prevanar 7 and 13 to be prepared.
- Addition of a dedicated (50%) senior physiotherapist to the NAC. Appointed and making an important contribution.
- 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. Numerous requests made, two funded.
- 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

  Considerable background work done and discussions with industry on an RCT for itraconazole failures in early development.

<u>Developments planned for 2010/11</u>

Numerous advancements in the service are planned for 2010/11. Some are straightforward, others more complex. They include:

- Implementing home delivery of expensive antifungal so minimising VAT.
- Rolling out home nursing to a small number of distant patients to minimise the travelling burden and increase the data inputs, to optimise their care. This needs agreement with the NCG in both concept and detail.
- An audit and additional testing for gammaIFN production deficiency. An increasing number of patients have been identified with profound defects in gamma IFN deficiency. This may need assessment in all patients, or a genetic assay, or both.
- Detailed audit of the utility of PCR testing in respiratory specimens in CPA patients as a marker of antifungal failure
- Implementation of direct detection of resistance to antifungals from PCR positive, culture negative specimens.
- Implementation of METS[1] as a measure of respiratory distress, alongside walking distance and MRC dyspnoea scores.
- Trial of posaconazole for patients who have exhausted other treatment options and stand to benefit substantially from antifungal therapy (pending NCSG approval).
- Detailed discussions between the NCG and the NAC concerning patients for whom little more can be done have resulted in a discharge process from service.

[1] Myers J, Bader D, Madhavan R, Froelicher V. Validation of a specific activity questionnaire to estimate exercise tolerance in patients referred for exercisetesting. Am Heart J. 2001 Dec;142(6):1041-6.

- Proposal for a prospective study of posaconazole for CPA to Merck
- Relaying genetic results back to patients, as we better understand the genetic basis for chronic and allergic aspergillosis. [These are the initial results of our 3 year prospective genetic study funded by the Medical research Council and NIHR].

- **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

Referral to appointment time audit - April 2010 – March 2011

NATIONAL ASPERGILLOSIS CENTRE

Referral to appointment time audit - April 2010 – March 2011

C Harris

MONTH	INITIALS	IDENTIFIER	DATE REFERRED	APPOINTMENT DATE*	WAITING TIME	POSTCODE	AREA	COMMENTS
APRIL	JB	4156420	03/03/2010	09/04/2010	4 weeks	KY12 7RS	Scotland	
	CB	4156421	03/03/2010	09/04/2010	4 weeks	KY11 4BJ	Scotland	
	SL	4159209	26/03/2010	23/04/2010	4 weeks	NG13 8RY	Nottingham	
	CH	4160682	22/03/2010	30/04/2010	2 weeks	DE4 2GJ	Derbyshire	
MAY	IP	1172047	19/04/2010	24/05/2010	4 weeks	CW8 1PQ	Northwich	
	MD	4162192	25/03/2010	26/05/2010	8 weeks	OL4 4PR	Oldham	
	RD	1687529	28/04/2010	28/05/2010	4 weeks	M34 2QA	Manchester	
	BMcI	4157268	25/03/2010	21/05/2010	8 weeks	LE15 6NS	Leicester	
JUNE	JS	4167379	18/05/2010	18/06/2010	4 weeks	CV33 9TS	Warwickshire	
	AS	1358872	28/04/2010	30/06/2010	8 weeks	M6 8RN	Salford	
	BH	1778048	23/06/2010	25/06/2010	2 days - urgent	SK17 9SG	Derbyshire	
	AK	4159219	08/03/2010	21/06/2010	14 weeks	ST1 5JB	Stoke on Trent	DNA 19/4/10
	HP	4169992	08/06/2010	25/06/2010	3 weeks	DE73 5NU	Derby	
	EM	4165557	28/04/2010	04/06/2010	5 weeks	L9 9BA	Liverpool	
JULY	HW	4168995	03/06/2010	09/07/2010	4 weeks	L9 1AD	Liverpool	
	HD	4171394	24/06/2010	02/07/2010	2 weeks	LL59 5LF	Wales	

	BG	4129454		30/07/2010	6 weeks	BB4 7RH	Rossendale	Transition to CPA
	BMcC	4153380	08/02/2010	15/03/2010	4 weeks	EH53 SHA	Scotland	
AUG	SM	4174223	29/06/2010	13/08/2010	6 weeks	LL16 5AG	Wales	
	BH	594433	07/06/2010	06/08/2010	8 weeks	M19 1SH	Manchester	
	BJ	4165889	05/07/2010	20/08/2010	6 weeks	CW10 9PG	Middlewich	Ward referral
	EJ	4174217	06/07/2010	23/08/2010	6 weeks	B69 1QB	Oldbury	
SEPT	AD	4174221	06/07/2010	06/09/2011	8 weeks	OL6 8SJ	Ashton - Lyne	
	DMcB	4145557	05/06/2010	03/09/2010	8 weeks	B14 4DJ	Birmingham	
	NS	1684385	06/07/2010	03/09/2010	8 weeks	SK12 1LZ	Stockport	
	RK	4171152	25/06/2010	09/08/2010	6 weeks	LA13 9QT	Cumbria	
	AN	4176714	08/07/2010	24/09/2010	10 weeks	CM19 4PT	Essex	
	BW	4174226	06/07/2010	03/09/2010	8 weeks		France	now UK resident
	TB	4160690	23/03/2010	14/05/2010	7 weeks	BB6 6JA	Accrington	
	CR	4182203	13/09/2010	17/09/2010	4 days	LL14 2PS	Wales	urgent referral
OCT	KB	4179432	04/08/2010	11/10/2010	8 weeks	WN1 3UY	Wigan	
	JB	24665	03/09/2010	11/10/2010	5 weeks	M33 4FH	Trafford	
	WD	4162185	13/04/2010	24/05/2010	4 weeks	BB1 9QT	Blackburn	
	SS	1927095	24/09/2010	01/10/2010	2 weeks	BL1 6BU	Blackburn	
	MW	4184423	28/09/2010	08/10/2010	1 week	DE24 8PG	Derby	
	DB	4176717	26/07/2010	01/10/2010	8 weeks	LS27 9AF	Leeds	
	CM	4184517	18/08/2010	29/10/2010	9 weeks	M38 9UH	Worsley	
NOV	LC	4184532	03/09/2010	12/11/2010	9 weeks	CW12 1SD	Congleton	
	BS	4180181	17/09/2010	26/11/2010	8 weeks	PR8 4SY	Southport	
	JH	4184543	19/09/2010	22/11/2010	8 weeks	FY5 4FP	Cleveleys	

	MA	4184521	07/09/2010	01/11/2010	8 weeks	BL1 5LG	Bolton	
DEC	CA	4193102	18/11/2010	10/12/2010	3 weeks	BN14 7QH	West Sussex	
	WT	4189306	06/10/2010	10/12/2010	8 weeks	BL4 8QD	Bolton	
	RB	4194089	29/11/2010	17/12/2010	3 weeks	PR9 8ND	Southport	
	GJ	4179421	03/08/2010	13/12/2010	17 weeks	BD13 3QT		DNA 04/10/10
JAN	NC	4098777	25/10/2010	29/11/2010	4 weeks	BL7 9LB	Bolton	
	BP	4147481	18/11/2010	29/11/2010	2 weeks	CW1 4DN	Crewe	Ward referral
	AC	4191643	18/11/2010	20/11/2010	2 days	LE1 7DQ	Leicester	urgent ward referral
	IM	4194019	29/11/2010	07/01/2011	5 weeks	ML9 3RF	Scotland	
	JS	4194084	29/11/2010	21/01/2011	8 weeks		Wales	
FEB	JH	4197523	02/12/2010	04/02/2010	8 weeks	LE11 4UY	Loughborough	
	LD	4070398	25/10/2010	18/02/2011	15 weeks	M40 5FQ	Manchester	DNA 24/12/10
	VH	4197520	17/12/2010	04/02/2011	7 weeks	OX16 1XG	Oxon	
	MF	4201143	07/01/2011	04/02/2011	4 weeks	SE8 4LY	London	
	KF	4197296	13/12/2010	18/02/2011	9 weeks	WN5 7EQ	Wigan	
	BF	1476701	06/01/2011	21/02/2011	6 weeks	SK8 6PB	Stockport	
	DJ	4165563	21/04/2010	14/06/2010	7 weeks	BB9 8DP	Burnley	
MARCH	MT	4204174	17/01/2011	25/03/2011	5 weeks	SS13 2BN	Essex	
	RC	4205674	18/01/2011	21/03/2011	8 weeks	OL16 4PW	Rochdale	
	ET	4200810	22/01/2011	28/03/2011	8 weeks	M11 1BE	Manchester	
	JJ	4199340	06/01/2011	18/03/2011	9 weeks	SW8 3BN	London	
	RF	4203310	14/02/2011	17/02/2011	3 days	CV32 7QE	Warwickshire	Transfer from Warwick
	ND	4187040	30/10/2010	24/11/2010	2 weeks	M43 7HF	Manchester	Ward referral/Transition to CPA

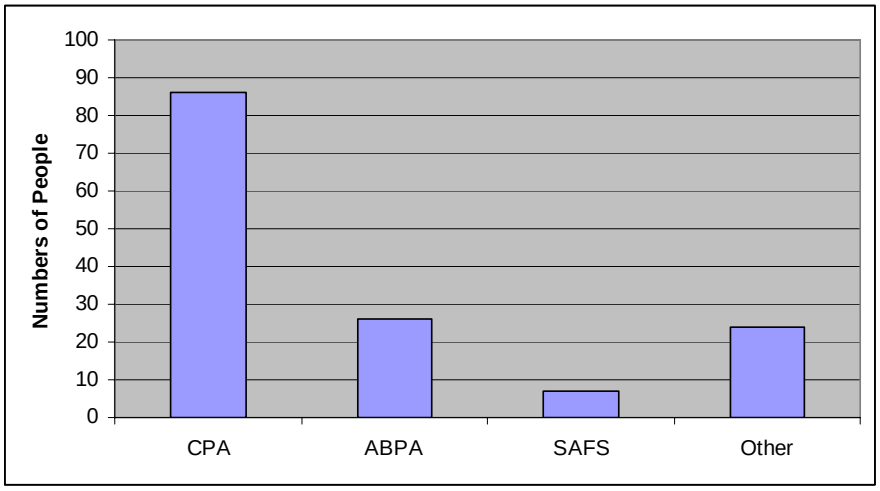
* The month seen is not always the month they are determined to have CPA, because of missing diagnostic data.

Appendix 3
Patient user survey Jan/Feb 2011.

Patient Survey Jan-Feb 2011. Friday clinic only

*** distributed/ 146 respondents

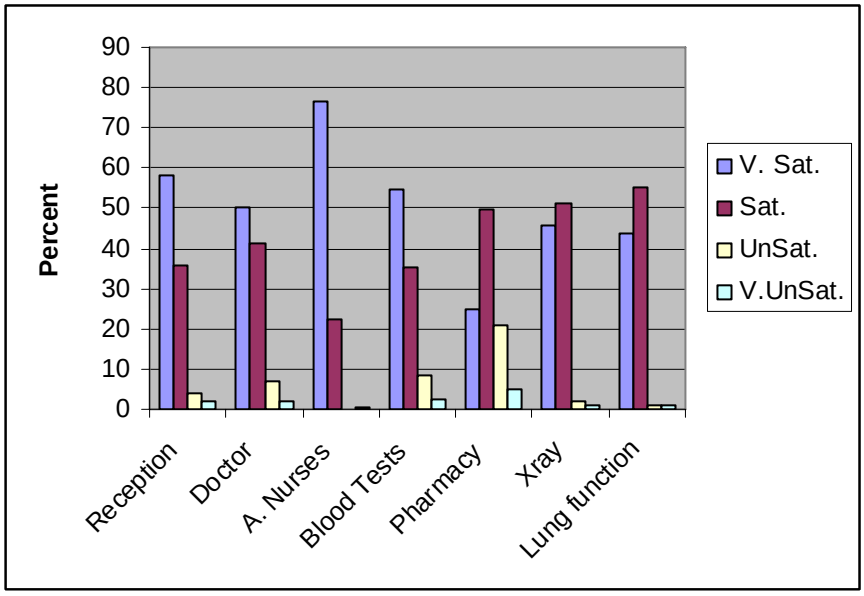
Proportion of the different categories of illnesses treated



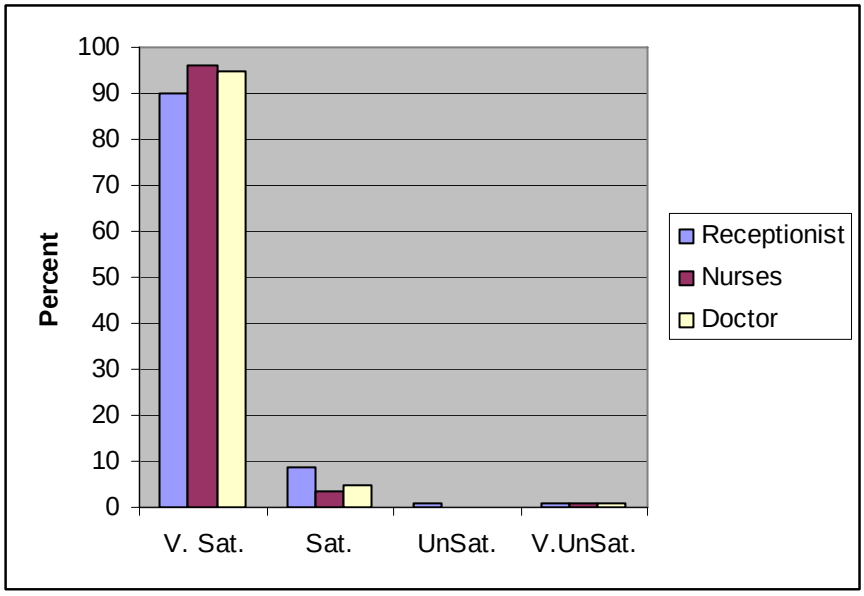
1. Is this your first visit to the National Aspergillosis Centre?

Yes = 5
No = 141 (97%)

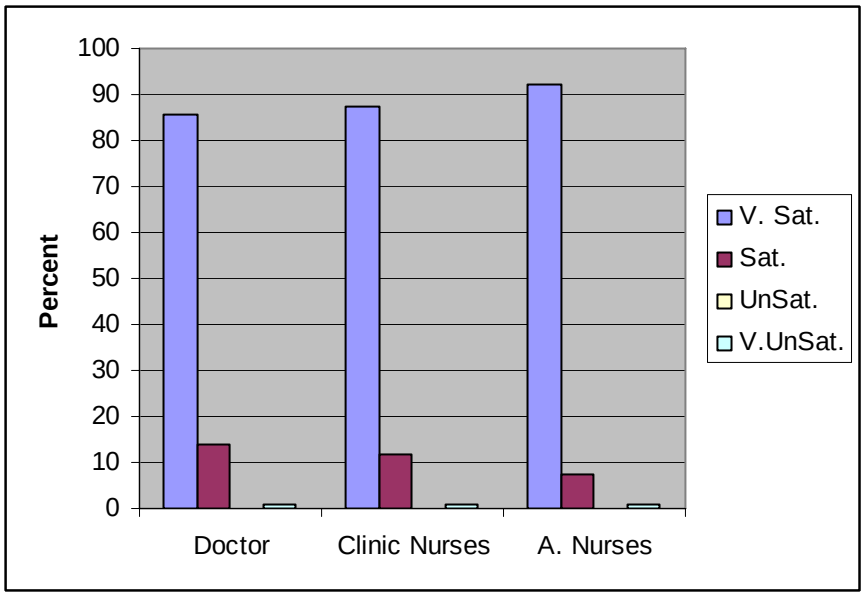
2. How did you feel about the time you had to wait for the following: -



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



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



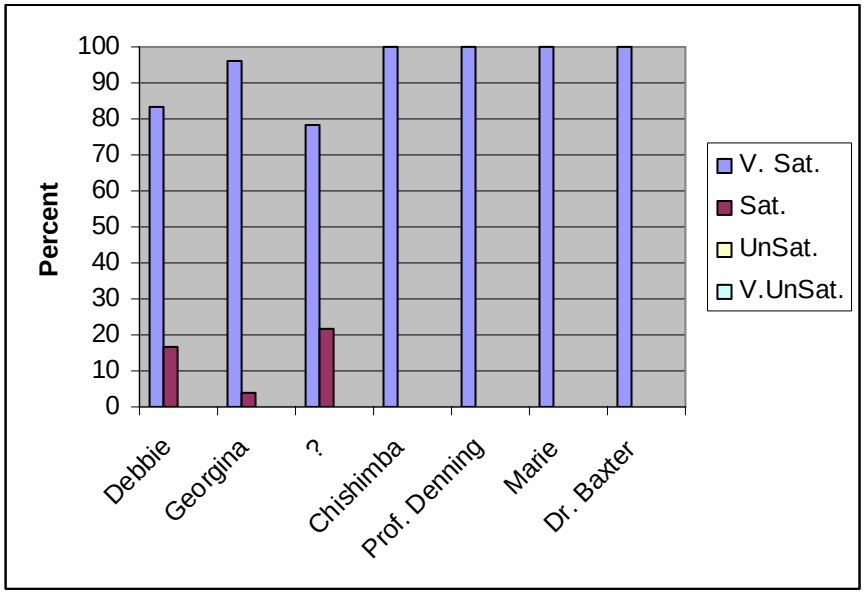
5. How satisfied are you with communication with the NAC staff?

Very Satisified = 108 (75%)
Satisfied = 36 (25%)
Unsatisfied = 0
Very Unsatisfied = 0

6. Have you been contacted by a member of the NAC team after or in between clinic visits?

Yes = 65 (45%)
No = 79 (55%)

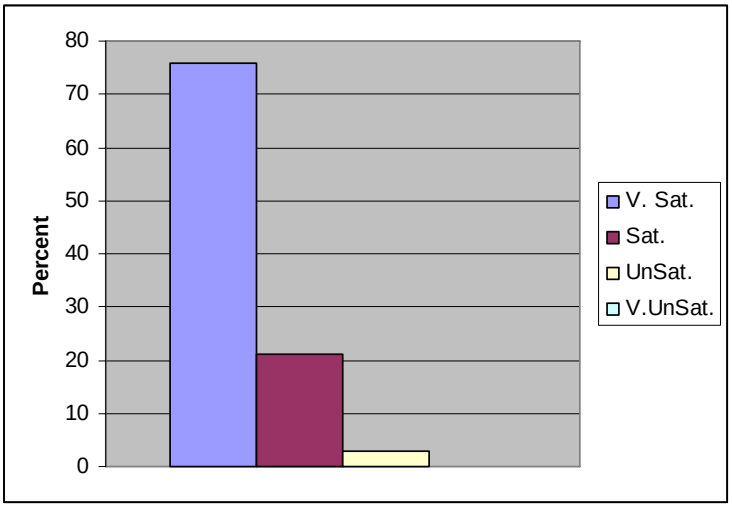
If yes how satisfied were you with this support?



7. Have you been contacted by one of the specialist nurses or have you contacted one of the specialist nurses in-between clinic visits?

Yes = 66 (45%)
No = 81 (55%)

If yes how satisfied were you with this support?



Comments: "Could not ask for better." "Very good." "Found all help received wonderful." "Internet access to patient meetings useful." "Uncertain-different message from consultant." "Always prompt, friendly and helpful." "I have found everyone to be extremely polite and helpful."

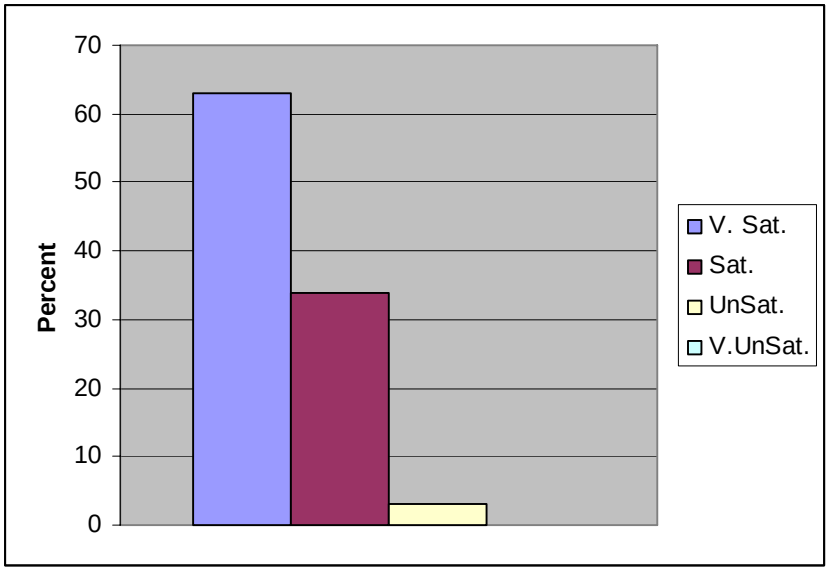
8. A new physiotherapy service has started, what do you think your needs are from this service?

Comments: "Don't know about it." "Breathing, standing steady, exercises to keep muscles strong when mobility is restricted." "Need advice for home/physio." "Perhaps how to move stubborn sputum (in practice)." "Help with mobility." "Review breathing exercises." "At present none." "Would benefit gratly but nothin available ear to where I live." "Help with postural drainage techniques." "Helpful." "Good care." "Chest exercises." "Some advice on moving, working, breathing." "Would be greatful for advice on exercises for muscles." "Good idea to have physiotherapist in the team." "I would benefit from this service." "Newsletter detailing physio presentation to patient group was useful. Advice on coping with breath-lessons would be helpful." "Physio could help my condition." "Non, due to distance from home." "Do via BLF active." "Advice re physio." "A reminder a chest clearence might be helpful." "Too far away." "Clearing sputum from lung." "None at the moment, already been seen by physio at leigh for postural drainage and exercise advice." "Chest explanations." "None-recieved specialist sercive elsewhere." "Beneficial." "I will need their service good idea." "I already have access to physio through my primary hospital."

9. A consultant Immunologist attends the clinic twice a month, if you have seen the Immunologist have you any comments about this service?

Comments: "Interesting to find out new things." "Not seen the consultant as yet." "Very good." "Good, helpful." "Was good, changed meds." "Good care." "I have a better understanding after asking the immunologist questions." "Satisfied with this service." "Very good/We were very satisfied." "Very satisfied." "Still having to travel to Hope to see her." "Advantageous/informative." "I have an immunologist, have seen your immunologist and she was fine."

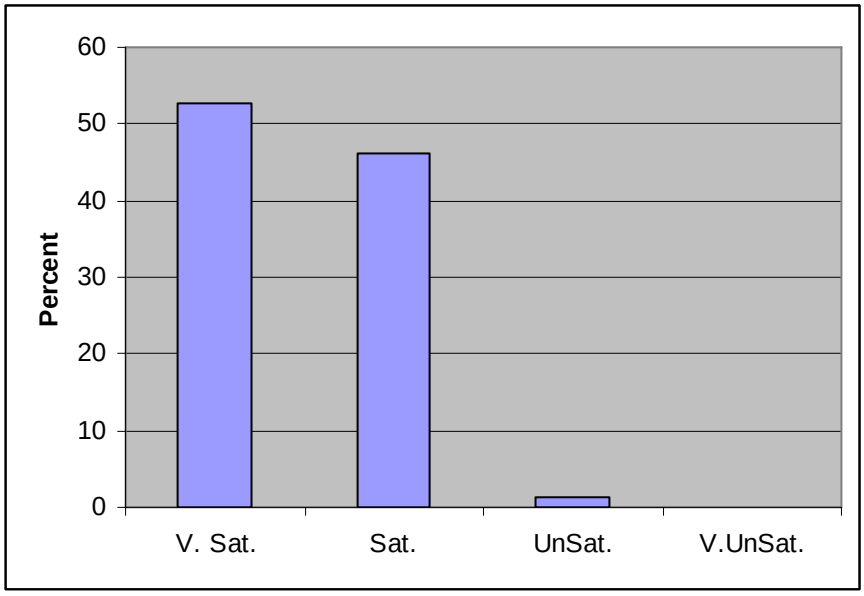
10. How satisfied are you with information you received about your condition?



11. Have you visited the Aspergillus website?

Yes = 76 (53%)
No = 68 (47%)

If you have, how satisfied are you with the Aspergillus website?



If you have not visited the website is there a reason why?: "No computer." "Not available." "Unaware." "Did not know about it." "However does not answer questions I have." "Rely on information received from medical staff." "Do not have access" "Work away from

home." "1st visit." "Tried a few times, Not been able to access it." "Had no information." "Forgot." "Not on internet."

12. We are in the process of developing the information that is sent out to the patients prior to their first visit?

What do you think is important to include?: "Treatment may be long term but it will help." "Any improvement." "Up to date information." "Side effects of drugs." "All relevant information." "Aspergillus booklet." "Patient and relative perspective." "Breathing techniques, posture, things to do to improve/maintain quality of life." "Who is available to talk to at clinic." "Comments form other patients and info leaflets." "Brief on what to expect." "Waitning time, Name of doctor to be seen." "Information given was explicit." "Write down any questions-it is easy to forget." "Information on meetings;other patients." "An idea of how long the first may take." "Where you can park with wheelchairs." "Plan of what happens at the clinic." "Research." "More info on aspergillus and its origins." "Test results." "Is train station nearby? Taxis available and costs." "Perhaps a link to the website-although the accounts of patients experiences might be distressing." "Map condition info URL to website." "Precise definition of prognosis and clear future if potential problems." "Information about the condition, the service and directions." "What to expect at the clinic. Quite overwhelming first visit." "Direction to hospital." "Information about condition, the treatment available and prognosis." "FAQ and pamphlet of condition including symptoms etc." "New treatments." "Clinic location/facilities/parking costs and proximity/discuss waiting times/cafe facilities." "Information on actual aspergillus/aspergillosis and how it affects them as individuals." "Information on what to expect such as possibly having to give blood, x-rays, septum tests." "The treatment will increase the frequency of asthma attacks." "Lifestyle issues related to disease e.g. diet, exercise, contra-indications." "Website;After support group." "Symptoms."

13. We have been holding monthly patient meetings here in Manchester and one in Edinburgh,

Have you attended a patient's meeting?

Yes = 22 (15%)
No = 122 (85%)

If yes, have you any comments about the patient meeting/s?: "Very good." "Very informative and useful." "Very informative." "Always good to attend when I can." "I Live too far away." "Distance a factor when attending." "Would be interested but have little spare time." "Too far for me to travel." "Very helpful." "Attended 'local' meeting in Edinburgh and found it very informative." "Sorry I live too far away to attend." "Informative." "Could internet useage be made better." "Interseting." "Did not know about it." "Very helpful and can talk to staff informally." "Was not informed about them."

14. Over the last few months the presentations from the patient's meetings have been recorded and put on the Aspergillus website. Have you viewed any of the presentations?

Yes = 31 (23%)
No = 107 (77%)

If yes have you any comments?: "Very helpful." "My daughter will." "No new information." "Good." "Will look at this." "Sound getting better." "Will have a look." "Lots of information." "Very interesting meetings." "I would like to access the presentations online, but can't. Perhaps my broadband connection is too slow?" "Intend to view the next one." "Very informative." "Sound is low." "However I do intend to view." "Not aware of them." "Hard to see powerpoint."

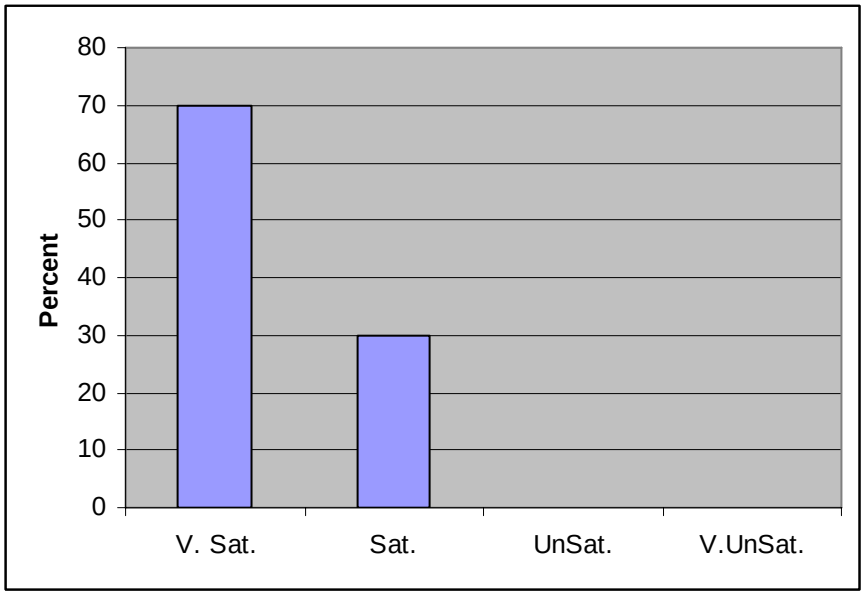
15. It has been possible for patients and carers, if they were not able to attend a meeting, to view the patient's meetings live over the internet. Have you watched a meeting live over the internet?

Yes = 10 (7%)
No = 128 (93%)

16. Do you travel to clinic by hospital transport?

Yes = 10 (7%)
No = 134 (93%)

If you travel by hospital transport how do you find this service?

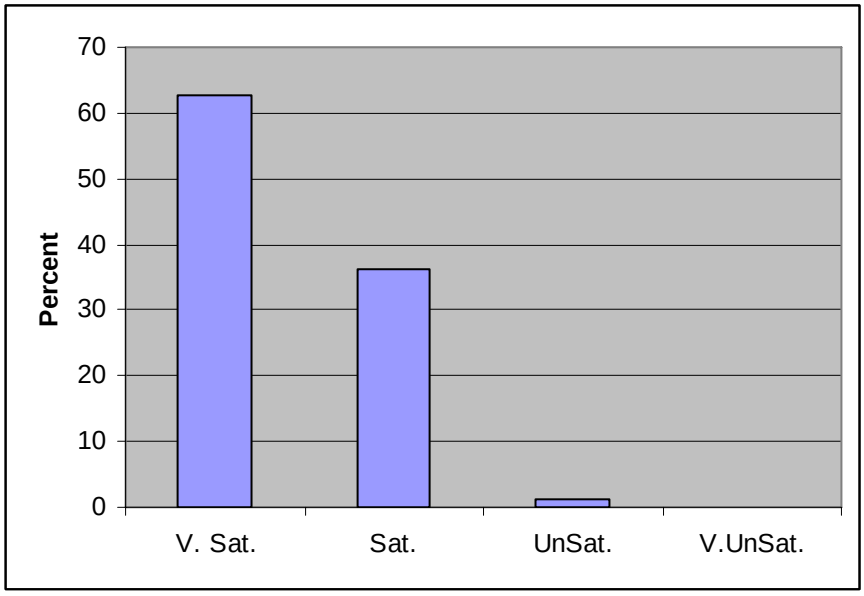


Could you please provide us with the first part of your postcode?:
L32,WN1,BL4,SK15,SK11,OL7,WN6,OL1,M20,GL6,SK16,M34,M38,WA7,M22,BB4,M22,M43,WN6,WN5,FK8,RM16,CV35,DE5,M18,LA4,WN5,M12,CB6,FY3,LL65,EH48,WA15,M19,SK16,SY3,LS27,LL1,ML3,M28,SK3,EH44,M29,SK16,M6,SP8,WN7,WN7,M73,M33,DE4,M14,OX16,BL4,WN6,M23,

17. Are you generally happy to participate in clinical research?

Yes = 133 (93%)
No = 10 (7%)

If you already have, were you happy with the procedures and consent process?



Comments: "Happy to participate in clinical trials if it fits my working life." "Although a participant I have not received any feedback on results." "It would be useful to get more feedback on research outcomes-the feedback from the flu questionnaire last winter was excellent." "In general very good." "The delay at the pharmacy is excessive, would it be possible for repeat prescriptions to be available so that they could be collected by my wife whilst i await a consultation." "Would like to know more about the process and what the objectives are."

Any further general comments: "I would like more information on the long term affects of my illness and what the doctors are trying to achieve." "As I have no computer I find it hard to keep in touch with what is going on, like websites etc." "I am happy with the care and treatment I'm recieving." "The docs are wonderful and so are the nurses. God bless this hospital. Many, many thanks." "Always wait a long time for blood." "To wait longer than an hour for blood tests is unacceptable." "Very happy with all staff" "Very satisfied with all aspects of care." "Pleased with service and help." "Timing is a huge problem. We only have a limited time due to husbands work commitments. We ask for an early appointment, but timings are not adhered to. The doctor seen today was very supportive." "I would certainly be dead without this clinic. The staff are caring and attentive, we have never had a 'bad' day. Brilliant-thankyou." "Staff very good-

waiting time too long." "Could the timing of the visit to the chemist department after a doctors appointment be made to occur simultaeneously. The patient being processed in conjunction with, someone else able to get the prescription at the same time-to greatly increase speed. (Halve it)." "Have had TB, not aspergillosis." "An exemplary service. I would like more information on staying well." "Waiting time delays between appointment time and seeing the specialist are far too long. (Over 3 hours on one recent occasion)." "Bloods and other info should where possible be taken prior to seeing the doctor so info is up to date." "My home hospital should carry out such a survey.""Service in general is good." "All in all I am very impressed with the clinic." "I feel very cared for by all I meet." "I am very satisfies with my treatment to date. Very friendly and competent staff-doctors, nurses and receptionists." "Well run clinic. I don't come here to discuss aspergillosis, for another reason. I stil recieve good care every time." "The clinic is a great support system, for the patient/family involved and after many years of feeling ill, I now feel in good hands." "I have found the service I recieve from all staff involved in the clinic to be very helpful. I was actually very surprised at the friendliness and helpfulness of everyone involved and feel the standard of care and sharing of information is excellent. It is a relief to attend a clinic which gives the patient confidence in their treatment and an understanding of their medical condition." "Fantastic service." "Patients need to be more informed about their condition and how they can help themselves. Not enough information is given regarding lifestyle and how they can get involved based on their background." "I feel very valued as a patient, all the staff make me feel at ease." "We waited 2 hours to see doctor, the consultation took 10 minutes. the general impression is one of lack of organization and too many patients and not enough doctors."

Appendix 4

Publications from the Manchester Fungal Diseases Group (2010)

1: Uittamo J, Nieminen MT, Kaihovaara P, Bowyer P, Salaspuro M, Rautemaa R. Xylitol inhibits carcinogenic acetaldehyde production by *Candida* species. Int J Cancer. 2010 Dec 10. [Epub ahead of print] PubMed PMID: 21154745.

2: Seppänen L, Lemberg KK, Lauhio A, Lindqvist C, Rautemaa R. Is Dental Treatment of an Infected Tooth a Risk Factor for Locally Invasive Spread of Infection? J Oral Maxillofac Surg. 2010 Oct 13. [Epub ahead of print] PubMed PMID: 20950917.

3: Siikala E, Rautemaa R, Richardson M, Saxen H, Bowyer P, Sanglard D. Persistent *Candida albicans* colonization and molecular mechanisms of azole resistance in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) patients. J Antimicrob Chemother. 2010 Dec;65(12):2505-13. Epub 2010 Sep 28. PubMed PMID: 20876623.

4: Seppänen L, Rautemaa R, Lindqvist C, Lauhio A. Changing clinical features of odontogenic maxillofacial infections. Clin Oral Investig. 2010 Aug;14(4):459-65. Epub 2009 May 16. PubMed PMID: 19449042.

5: Levon J, Myllymaa K, Kouri VP, Rautemaa R, Kinnari T, Myllymaa S, Konttinen YT, Lappalainen R. Patterned macroarray plates in comparison of bacterial adhesion inhibition of tantalum, titanium, and chromium compared with diamond-like carbon. J Biomed Mater Res A. 2010 Mar 15;92(4):1606-13. PubMed PMID: 19437436.

6: Cosgrove L, McGeechan PL, Handley PS, Robson GD. Effect of biostimulation and bioaugmentation on degradation of polyurethane buried in soil. Appl Environ Microbiol. 2010 Feb;76(3):810-9. Epub 2009 Nov 30. PubMed PMID: 19948849; PubMed Central PMCID: PMC2813001.

7: Allen G, Bromley M, Kaye SJ, Keszenman-Pereyra D, Zucchi TD, Price J, Birch M, Oliver JD, Turner G. Functional analysis of a mitochondrial phosphopantetheinyl transferase (PPTase) gene pptB in *Aspergillus fumigatus*. Fungal Genet Biol. 2010 Dec 30. [Epub ahead of print] PubMed PMID: 21195204.

8: Segal BH, Cornely O, Bromley M. Proceedings from the 4th Advances Against Aspergillosis Conference. Med Mycol. 2010 Nov 26. [Epub ahead of print] PubMed PMID: 21108577.

9: Carr PD, Tuckwell D, Hey PM, Simon L, d'Enfert C, Birch M, Oliver JD, Bromley MJ. The transposon impala is activated by low temperatures: use of a controlled transposition system to identify genes critical for viability of *Aspergillus fumigatus*. Eukaryot Cell. 2010 Mar;9(3):438-48. Epub 2010 Jan 22. PubMed PMID:

20097738; PubMed Central PMCID: PMC2837977.

10: Zhao Y, Park S, Warn P, Shrief R, Harrison E, Perlin DS. Detection of *Aspergillus fumigatus* in a rat model of invasive pulmonary aspergillosis by real-time nucleic acid sequence-based amplification. J Clin Microbiol. 2010 Apr;48(4):1378-83. Epub 2010 Feb 3. PubMed PMID: 20129972; PubMed Central PMCID: PMC2849568.

11: Lansley SM, Searles RG, Hoi A, Thomas C, Moneta H, Herrick SE, Thompson PJ, Newman M, Sterrett GF, Prêle CM, Mutsaers SE. Mesothelial cell differentiation into osteoblast- and adipose-like cells. J Cell Mol Med. 2010 Nov 10. doi: 10.1111/j.1582-4934.2010.01212.x. [Epub ahead of print] PubMed PMID: 21070599.

12: Jiang X, Tsitsiou E, Herrick SE, Lindsay MA. MicroRNAs and the regulation of fibrosis. FEBS J. 2010 May;277(9):2015-21. Review. PubMed PMID: 20412055; PubMed Central PMCID: PMC2963651.

13: Howard SJ, Arendrup MC. Acquired antifungal drug resistance in *Aspergillus fumigatus*: epidemiology and detection. Med Mycol. 2010 Aug 26. [Epub ahead of print] PubMed PMID: 20795765.

14: Piper L, Smith PB, Hornik CP, Cheifetz IM, Barrett JS, Moorthy G, Hope WW, Wade KC, Cohen-Wolkowiez M, Benjamin DK Jr. Fluconazole Loading Dose Pharmacokinetics and Safety in Infants. Pediatr Infect Dis J. 2010 Nov 16. [Epub ahead of print] PubMed PMID: 21085048.

15: Hope WW, Petraitis V, Petraitiene R, Aghamolla T, Bacher J, Walsh TJ. The initial 96 hours of invasive pulmonary aspergillosis: histopathology, comparative kinetics of galactomannan and (1->3) β-d-glucan and consequences of delayed antifungal therapy. Antimicrob Agents Chemother. 2010 Nov;54(11):4879-86. Epub 2010 Aug 16. PubMed PMID: 20713673; PubMed Central PMCID: PMC2976140.

16: Lestner JM, Howard SJ, Goodwin J, Gregson L, Majithiya J, Walsh TJ, Jensen GM, Hope WW. Pharmacokinetics and pharmacodynamics of amphotericin B deoxycholate, liposomal amphotericin B, and amphotericin B lipid complex in an in vitro model of invasive pulmonary aspergillosis. Antimicrob Agents Chemother. 2010 Aug;54(8):3432-41. Epub 2010 May 3. PubMed PMID: 20439615; PubMed Central PMCID: PMC2916353.

17: Hope WW, Smith PB, Arrieta A, Buell DN, Roy M, Kaibara A, Walsh TJ, Cohen-Wolkowiez M, Benjamin DK Jr. Population pharmacokinetics of micafungin inneonates and young infants. Antimicrob Agents Chemother. 2010 Jun;54(6):2633-7. Epub 2010 Mar 22. PubMed PMID: 20308367; PubMed Central PMCID: PMC2876406.

18: Roberts JA, Hope WW, Lipman J. Therapeutic drug monitoring of beta-lactams for critically ill patients: unwarranted or essential? Int J Antimicrob Agents. 2010 May;35(5):419-20. Epub 2010 Mar 1. PubMed PMID: 20189777.

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22: Puttikamonkul S, Willger SD, Grahl N, Perfect JR, Movahed N, Bothner B, Park S, Paderu P, Perlin DS, Cramer RA Jr. Trehalose 6-phosphate phosphatase is required for cell wall integrity and fungal virulence but not trehalose biosynthesis in the human fungal pathogen *Aspergillus fumigatus*. Mol Microbiol. 2010 Jun 9. [Epub ahead of print] PubMed PMID: 20545865; PubMed Central PMCID: PMC2954268.

23: Zhang YQ, Gamarra S, Garcia-Effron G, Park S, Perlin DS, Rao R. Requirement for ergosterol in V-ATPase function underlies antifungal activity of azole drugs. PLoS Pathog. 2010 Jun 3;6(6):e1000939. PubMed PMID: 20532216; PubMed Central PMCID: PMC2880581.

24: Rodriguez-Tudela JL, Gomez-Lopez A, Arendrup MC, Garcia-Effron G, Perlin DS, Lass-Flörl C, Cuenca-Estrella M. Comparison of caspofungin MICs by means of EUCAST method EDef 7.1 using two different concentrations of glucose. Antimicrob Agents Chemother. 2010 Jul;54(7):3056-7. Epub 2010 May 17. PubMed PMID: 20479199; PubMed Central PMCID: PMC2897297.

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in cynomolgus macaques. Infect Immun. 2010 Jul;78(7):2946-55. Epub 2010 Apr 12. PubMed PMID: 20385751; PubMed Central PMCID: PMC2897392.

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32. Renata G.K. Leuschner, Tobin P. Robinson, Marta Hugas, Pier Sandro Cocconcelli, Florence Richard-Forget, Günter Klein, Tine R. Licht, Christophe Nguyen-The, Amparo Querol, Malcolm Richardson, Juan E. Suarez, Ulf Thrane, Just M. Vlak, Atte von Wright. Qualified presumption of safety (QPS): a generic risk assessment approach for biological agents notified to the European Food Safety Authority (EFSA) Trends in Food Science & Technology, Volume 21, Issue 9, September 2010, Pages 425-435 (IF: 4.051)

33. Nihtinen A, Anttila VJ, Richardson M, Ruutu T, Juvonen E, Meri T, Volin L. Factors influencing the performance level of Candida mannan antigen testing in allogeneic stem cell transplant recipients not receiving fluconazole prophylaxis. Transpl Infect Dis. 2010 Dec 22. doi: 10.1111/j.1399-3062.2010.00593.x. [Epub ahead of print]

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