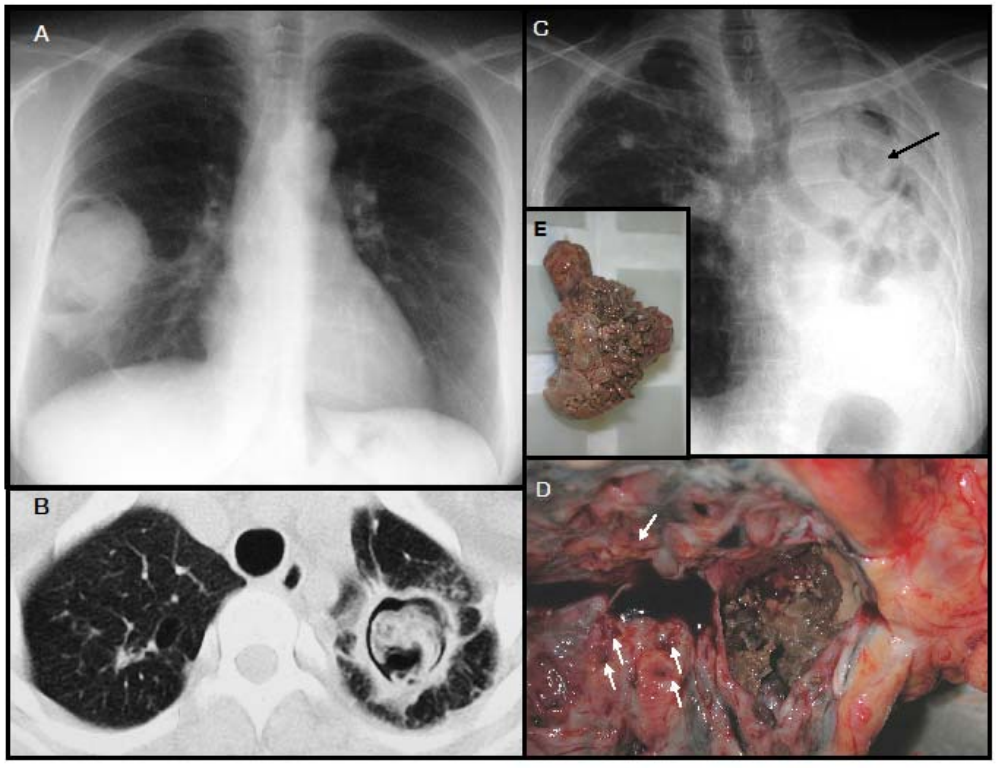
NCG Chronic Pulmonary Aspergillosis national service

The National Aspergillosis Centre

Annual Report 2011-2012



Contents

[Cover figure: Panel A shows the chest radiograph of patient, with a large right sided aspergilloma contained within a pre-existing, presumably congenital, bulla. Panel B shows the thoracic computed tomography scan of both apices of the lung in patient 2 demonstrating a thick walled cavity and surrounding inflammatory reaction, and an irregular aspergilloma within the cavity. This aspergilloma is not completely rounded, as is common in the earlier stages of formation. Panel C shows the chest radiograph of patient 3, with complete fibrotic destruction of the left lung which occurred over 5 years and a large aspergilloma visible in a large cavity in the upper mid zone (arrow) with multiple other empty cavities surrounding this. At autopsy, there were numerous interconnected cavities in the mid and upper parts of the left upper lobe (white arrows), 2 containing aspergillomas, one of which is shown in panels D and E. The actual surface of the aspergilloma is remarkably irregular in contour.]

1 General Overview and highlights

This report covers the third full year of this nationally commissioned service. The number of referrals has slightly increased over the last year; 66 in 2009/10, 58 in 2010/11 and 74 in 2011/12. There was a 50% reduction in deaths to 20 compared to the previous year. A new pathway for 2011/12 introduced 'discharges from service', so that patients who could not attend, derived no benefit from attending including stable patients off therapy or were better off being looked after locally because their disease was far advanced were all reviewed and 41 patients were discharged. This left a total caseload at the end of the year of 223 patients (not including 6 from Wales).

Significant improvements in the service have included the addition of an additional consultant (Dr Libby Ratcliffe), introduction of home delivery of oral antifungal agents, and frequent evaluation of gamma IFN production (often low or non-existent) and development of local support groups for patients away from Manchester. Professor Hope has left the service to move to Liverpool University, to head up anti-infective pharmacology. Dr Caroline Baxter (Clinical Fellow) returned to her SpR post and was replaced by Dr Iain page.

Challenges to the service remain the volume of new patients referred requiring expert input, combined both substantial patient complexity and large numbers of follow up patients most requiring high level consultant input, travelling distances for some patients and relatives, a continuing problem with 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 2011/12 were as follows:

Activity Measure / Currency	Month Activity												Contract Currency	Annual Plan †	Year to	
	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		YTD Actual	YTD Plan
Referrals	25	12	18	18	31	22	25	23	21	15	15	25	N	0	250	0
New Patients	7	4	5	9	8	9	6	4	4	7	6	5	Y	65	74	65
Outpatient - Follow-Up Attendances	102	90	90	90	83	109	92	91	86	91	85	125	N	0	1,134	0
Caseload - Band 1	72	70	71	76	79	81	87	86	88	86	89	79	Y	104	79	104
Caseload - Band 2	87	94	95	95	96	95	99	99	104	103	108	124	Y	112	124	112
Caseload - Band 3	19	19	19	19	19	19	18	18	17	17	16	15	Y	21	15	21
Occupied Bed Days	111	163	279	76	61	82	98	174	15	96	144	97	Y	894	1,396	894
Discharges	5	7	9	5	4	6	5	8	3	7	9	9	N	0	77	0
Surgical Resection	1	0	1	2	0	0	0	0	0	1	1	1	Y	6	7	6
Embolisations	0	1	0	3	2	0	0	4	3	0	4	0	Y	20	17	20
Discharges	17	2	1	1	1	5	5	1	3	2	1	2	N	0	41	0
Deaths	3	3	1	2	4	0	0	3	0	1	2	1	N	0	20	0

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

Of the 250 new 'aspergillosis' referrals from England and Scotland during the year 2011/12, 74 (30%) had CPA. There were seven inpatient admission diagnoses/transfers. Among the outpatient referrals, the mean time from referral to being seen was 9.8 weeks (range 0.25-52 weeks), with all 7 appointments longer than 10 weeks related to non-attendance, transport arrangement difficulties, admission to hospital elsewhere, or moving house and an incorrect address. If these seven patients are removed, the mean delay between referral and first visit is 7.9 weeks, longer than the previous year (mean of 5.5 weeks). Appendix 2 shows the area of residence, date of referral and date of appointment.

The introduction of Homecare has forced earlier reappraisal of banding and so there was a relative increase in Band 2 patients. There has been a growth in Band 1 from 72 to 79 patients over the year and a reduction in Band 3 from 19 to 15 patients. Band 2 patients have grown from 87 to 124 patients. These shifts include 20 deaths and 41 discharges from service. 7 patients were presumptively cured with surgery.

Admission days were 1396, substantially more than forecast at 894 (56% 'over-performance'). This excludes 229 days spent in the hospital by CPA patients but not on active antifungal therapy, for other reasons, usually IV antibiotics.

3 Service developments and personnel

The NAC has completed its third 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):

1. Consolidation of test portfolio
2. Expansion of training and educational activities, including training courses and preceptorships, and hosting industrial placements for two University of Salford students
3. Successful bid to host for one year a Consultant Clinical Microbiologist from Sri Lanka under the Department of Health's Medical Training Initiative

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

- Aspergillus precipitins: transfer to a new platform: counterimmunoelectrophoresis
- Aspergillus galactomannan (antigen)
- Ongoing experience regarding sensitivity testing on Aspergillus isolates 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
  - ELISA for Candida mannan antigen
- Environmental monitoring of patients's houses for indoor moulds, including *Aspergillus*

Ongoing 4 year training programme for three trainee clinical scientists funded by the NHS NW SLA.

Ongoing three-year Healthcare Scientist training post under the Department of Health's Modernisation of Scientific Careers scheme.

In April 2012 the MRCM, as part of the Manchester Medical Mycology Partnership, successfully passed a CPA interim accreditation without no non-compliances.

In 2011 the MRCM and the NAC ran one three-day preceptorship for 11 infectious diseases and haematology specialists from the Middle East and South Africa.

Two training visitors in 2011-2012.
Dr Maithili Kavatheka (India) (1 month)
Dr Rital Oladele (Nigeria) (1 month)

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, Professor in Infectious Diseases (1PA)
Dr Hana Alachkar, Consultant in Immunology (1 PA)
Dr Ibrahim Hassan, Consultant in Microbiology (1 PA)
Dr Libby Ratcliffe, Locum Consultant in Infectious Diseases (5 PAs)
Dr Riina Richardson, Consultant in Oral Microbiology & Infectious Diseases (30%)
ST2/3 physician in Infectious Diseases (100%)
Ms Marie Kirwan, Specialist Nurse (50%)
Ms Deborah Kennedy, Specialist Nurse (100%)
Ms Georgina Powell, Specialist Nurse (100%)
Mr Philip Langridge, Senior Specialist Physiotherapist (50%)
Miss Reyenna Sheehan, Specialist Physiotherapist (20%)
Dr Iain Page, 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) National Aspergillosis mulitdisciplinary team meetings (MDT's)
The National Aspergillosis Centre hold a variety of MDT's to improve the management and care of our patients.

Surgical MDT – arranged when sufficient cases are listed for discussion (approximately quarterly).

To discuss cases that may be suitable for surgical resection. Scans and results are reviewed with several of the cardiothoracic surgeons and our team. If patients are suitable they are referred to the cardiothoracic surgeons for further discussion and the patient is informed.

Immunology – held once a month to discuss difficult immunological problems that a number of our patients tend to suffer from. Dr Alachkar assists us with these patients and reviews them in clinic where necessary.

DFS (discharge from service) – held once a month to discuss whether patients are ready to be discharged from service or whether they should be retained for continued care.

NCG/ID MDT – NAC team every Thursday to discuss problems that arise with patients and their management. These range from medication, in-patient stays, referrals, care in the community, GP and hospital physician enquires etc. The team will discuss and decide what action should be taken.

Radiology MDT – Every Thursday with consultant radiologists to discuss difficult CT's, embolisation etc.

4) Home delivery of antifungal agents
After an extensive procurement process, Healhcare at Home was selected to deliver high cost antifungal medicine to patients at home, reducing some clinic visits, improving service to patients, particularly those receiving posaconazole liquid which is expensive to carry and reducing cost to the NCG (no VAT but a delivery cost). The delivery service has been extended to PCT funded patients with other forms of aspergillosis. Over 100 patients have now been switched to home delivery with considerable savings and extremely few problems.

5) Postal bloods and sputum
The postal blood service works well for following up antifungal drug levels between clinics. Three to six bloods are handled each week in this way. Postal sputum has resulted in some broken specimens, and some complaints from laboratory staff. The need arises because Aspergillus PCR on sputum is not available elsewhere in the country and is clearly much more reliable than culture in detecting resistance and clinical failure.

6) Home nursing
Procurement and contract exchange was achieved for home nursing CPA visits, and the first patients selected for this service.

7) Use of validated scores to assess severity of disease and outcomes (QOL)
The NAC has been using the St. George's Respiratory Questionnaire (SGRQ) as a proxy measure of patients well-being as it is widely used for several chronic respiratory diseases. We examined the reliability and validity of SGRQ in CPA and compared with it with the general health survey (SF-36) and MRC dyspnoea score.

Eighty eight CPA patients completed the SGRQ, the SF-36 and the MRC dyspnoea scale. Lung function and BMI were also measured. Pearson correlation, T-Test, ANOVA and their equivalents for non-parametric data; and multivariate linear and binary analysis were used. The SGRQ components (symptoms, activity and domain) and total scores achieved high internal consistency (Cronbach's α 0.77, 0.91, 0.86 and 0.94); and SGRQ components had good inter-correlation ($r \geq 0.41$, $P<0.001$) and correlated well with the total score ($r \geq 0.63$, $P<0.001$). There was high intra class correlation coefficients for the total SGRQ and its dimensions (≥ 0.92). The SGRQ scores showed significant correlation with the MRC dyspnoea scale and SF-36 components; and differentiated between all grades of shortness of breath and different bands of disease severity ($P<0.05$). In addition, patients with greater clinician-rated disease severity had more impairment of health status ($P<0.006$). CPA severity was independently associated with impairment in health status, and COPD co-morbidity affected significantly health status in patients with CPA. We conclude that SGRQ demonstrated significant level of reliability and validity in measuring health status in CPA. (Paper accepted in Chest).
Additional work is ongoing to assess fatigue as an important component of CPA and on the change of SGRQ with antifungal therapy.

8) Applications to the NCG for third or fourth line antifungal therapy
Ten Individual Case Panel (ICP) applications were made in 2010-2011. Of these, 5 were for posaconazole (2 approved), 3 for micafungin intravenously (2 approved) and 2 for AmBisome (both approved). The applications were assessed by a highly experienced part clinical panel on the basis of a detailed summary of each patients medical details, antifungal experiences and likelihood of benefit. In particular the ICP assessed the evidence base for any given therapy (which is currently not very strong for most treatments, partly because most measures of successful therapy are not quantifiable) and whether the patient in question was likely to have an exceptional clinical benefit. Often this is a tough judgement call.

9) Lung transplantation referral
No CPA patient referred for lung transplantation has been accepted onto the program as yet.

4 Audits
1. Time to appointment
Most patients were booked for an appointment within 6-8 weeks. However, some appointments were longer due to distance of patient and arranging journeys to the hospital and the patients were in agreement with this. Others rescheduled or did not attend and were rebooked when slots became available.

Obviously if urgent cases were booked in this would also push back routine appointments. Adhoc clinics were added in where appropriate.

Several audits have been undertaken in 2011/12. Some of these have been completed:

2. Long term posaconazole
All posaconazole cases have now been re-evaluated as requested.

5 Patient engagement
We have held 12 meetings attended by patients and their carers:
2011
April (Diagnostics Services)
May (Expert Patients Program)
June (Lung Function)
July (Antifungal Resistance)
August (Genetic susceptibility to Aspergillus infection)
September (Involving patients in research)
October (Pulmonary Embolisation)
November (Clinical Q & A)
December (Christmas Quiz 2011)
2012
January (Photosensitivity)
February (Quality of Life analysis)
March (Refining Diagnostic Techniques)
Meetings have been attended by roughly 11% of our patients in total, currently running at 10 – 12 per meeting.
These presentations are presented live online and are recorded so that people who cannot visit the NAC for a meeting are able to directly involve themselves in the meeting and are able to listen to the content of each meeting at another time. To date the meeting has been watched live **1551** times (Ustream metrics) and the recordings viewed **4903** times. Our Patients Support Meeting was a finalist in the Nursing Times Awards 2011, recognising the uniqueness of our approach.

Our annual survey of patients opinions (based on 108 patients asked) of our service has identified approximately 30% of patients that don't attend meetings or are able to attend/watch recordings online (they have no computer and/or internet access) but who would like to attend a meeting if it were in a different place or time. To start addressing this problem we have started setting up local support groups run by a patient or carer volunteer that meet every few months. The aim is to provide social support and information via our leaflets and website (leaders of groups have access to the internet). In one case Graham Atherton has attended via videolink for an hour of discussion. We have 4 groups (Liverpool, West Midlands, East Midlands and London) that are reaching 15 – 20 patients with more groups being added whenever we get a new volunteer.
Another benefit of local groups is that we encourage advertising of the groups in local GP surgeries & hospitals and have acquired new participants in this way as well as increased

awareness in the local medical communities. In several cases we have been able to engage a local respiratory nurse to contact the group leader and attend meetings.

6 Research outputs, other published research summary

Publications 2011

a) Findings affecting clinical practice

1. PET positive nodules which resemble carcinoma of the lung may be caused by Aspergillus, and so a new disease entity of Aspergillus nodule has entered the medical terminology, under the umbrella of chronic pulmonary aspergillosis. Once resected (if single), the long term outcome is not known, and will be the subject of a future audit.

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

3. 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. Breakpoints for posaconazole were established across Europe and novel mechanisms of azole resistance described from one of our CPA patients. The ability of biofilms (including aspergillomas) to resist antifungal therapy was shown in a biofilm model.

4. The role of therapeutic azole drug monitoring was further supported.

5. Peripheral neuropathy is a major problem for a minority of patients on long term azoles. This has now been highlighted and described properly.

6. The global burden of CPA following TB has been estimated and using various assumptions, some of which need validation, the annual new caseload worldwide is estimated to be ~375,000 and the 5 year period prevalence about 1,200,000 patients, assuming a 15% annual mortality or surgical cure rate. This work is being expanded to estimate the burden of disease in Uganda and Kenya.

7. In abstract form, we described the remarkable frequency of gamma interferon production deficits in about 2 thirds of CPA patients, some with profound defects. Additional work is ongoing to better understand this. Some of it may be genetically determined, as we have also found about 7 significant genetic polymorphisms associated with CPA.

B) CPA related publications

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.

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

Denning DW, Park S, Lass-Florl C, Fraczek MG, Kirwan M, Gore R, Smith J, Bueid A, Moore CB, Bowyer P, Perlin DS. High-frequency triazole resistance found In nonculturable Aspergillus fumigatus from lungs of patients with chronic fungal disease. Clin Infect Dis 2011; 52: 1123-9.

Albarrag AM, Anderson MJ, Howard SJ, Robson GD, Warn PA, Sanglard D, Denning DW. Interrogation of related clinical pan-azole-resistant *Aspergillus fumigatus* strains: G138C, Y431C, and G434C single nucleotide polymorphisms in cyp51A, upregulation of cyp51A, and integration and activation of transposon Atf1 in the cyp51A promoter. Antimicrob Agents Chemother 2011; 55: 5113-21.

Arendrup MC, Cuenca-Estrella M, Donnelly JP, Hope W, Lass-Flörl C, Rodriguez-Tudela JL; European committee on antimicrobial susceptibility testing - subcommittee on antifungal susceptibility testing (EUCAST-AFST). EUCAST technical note on posaconazole. Clin Microbiol Infect 2011; 17: E16-7.

Rajendran R, Mowat E, McCulloch E, Lappin DF, Jones B, Lang S, Majithiya JB, Warn P, Williams C, Ramage G. Azole resistance of *Aspergillus fumigatus* biofilms is partly associated with efflux pump activity. Antimicrob Agents Chemother 2011 May;55(5):2092-7.

Gargani Y, Bishop P, Denning DW. Too many mouldy joints - marijuana and chronic pulmonary aspergillosis. Mediterr J Hematol Infect Dis. 2011; 3: e2011005.

Purcell J, McKenna J, Critten P, Denning DW, Hassan IA. Mixed mould species in laboratory cultures of respiratory specimens: how should they be reported, and what are the indications for susceptibility testing? J Clin Pathol. 2011; 64: 543-5.

Troke PF, Hockey HP, Hope WW. Observational study of the clinical efficacy of voriconazole and its relationship to plasma concentrations in patients. Antimicrob Agents Chemother 2011; 55: 4782-8.

Denning DW, Pleuvry A, Cole DC. Global burden of chronic pulmonary aspergillosis as a sequel to pulmonary tuberculosis. Bull WHO 2011; 89: 864-72.

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

Denning DW. Aspergillosis. Harrison's Principles of Internal Medicine. 18th ed. McGraw-Hill, New York, 2011. pp1655-60.

3) CPA abstracts presented

Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC 51st) 2011

084: A2-583 - Pharmacodynamics of Voriconazole (VCZ) in a Novel Dynamic in vitro Model of invasive Pulmonary Aspergillosis (IPA): Implications for in vitro Susceptibility Breakpoints and Targets for therapeutic Drug Monitoring (TDM)

A. R. Jeans, S. J. Howard, Z. Al-Nakeeb, J. Goodwin, L. Gregson, P. A. Warn, W. W. Hope.

Background: VCZ is a first-line agent for IPA. Isolates of Aspergillus fumigatus with elevated VCZ MICs are increasingly seen. In vitro susceptibility breakpoints have not been defined.
Methods: A novel dynamic in vitro model of the human alveolus was used. Human-like VCZ concentration-time profiles were generated using pumps. Four strains of Aspergillus fumigatus with CLSI MICs 0.5-16 mg/L and defined resistance mechanisms were studied. Conidia were inoculated into the alveolar compartment. Fungal growth and the antifungal effect of VCZ were estimated using circulating galactomannan (GM) concentrations. VCZ was injected into the circuit every 12 hours. Treatment was initiated 6 hours post inoculation and continued for 48 hours. A mathematical PK-PD model was fitted to the data and used to link AUC:MIC with GM. The VCZ AUC:MIC and trough concentration:MIC that suppressed fungal growth were determined. The implications for humans were explored using a VCZ population PK model fitted to patient data and Monte Carlo simulations.
Results: Fungal growth was progressively inhibited with higher drug exposures. Strains with higher MICs required proportionally greater drug exposures to achieve a comparable antifungal effect. The AUC:MIC and trough:MIC associated with suppression of GM were 60 and 2, respectively. Monte Carlo simulations suggested that 64% of simulated patients receiving standard IV therapy would have adequate drug exposure if infected by a strain with an MIC of 1 mg/L. Adequate exposure would be achieved in only 28% if the MIC increased to 2 mg/L. Target attainment was unacceptably low for strains with higher MICs. The overall fractional target attainment rate was 89%.
Conclusions: Aspergillus fumigatus with VCZ CLSI MICs $\geq$ 2 mg/L should be classified as resistant. Resistance mechanisms can be overcome with elevated drug exposures, but these are likely to be associated with clinical toxicity. A trough:MIC of 2 is a potential target for TDM.

All presented at Abstracts from 5th Advances Against Aspergillosis, January 2012, Istanbul

144: Chronic pulmonary aspergillosis severity and health status worsening; data from the National Aspergillosis Centre, Manchester, UK.

K Al-shair, GT Atherton, S Whiteside, DW Denning

Purpose:cChronic pulmonary aspergillosis (CPA) is a leading cause of illness with a high mortality rate. We aimed to investigate the association of CPA severity with health status

deterioration or improvement in patients with CPA. We also compared the discriminative ability of a respiratory disease-specific instrument (the St. George's Respiratory Questionnaire (SGRQ)) to a widely used generic instrument the health survey SF-36.
Method: To rate disease severity, we used our National Aspergillosis Centre criteria for banding CPA patients (band 1 = mild), (band 2 = moderate), (band 3 = severe). Health status was assessed using the respiratory specific scale St. George's Respiratory Questionnaire (SGRQ) (1-100, 100 poor) and a generic scale the health survey SF-36 which its two summary scores, a physical component summary (PCS) and mental component summary (MCS) score were calculate. Differences in means for continuous variables between CPA severity grades were examined using analysis of variance (ANOVA) and the non-parametric equivalent (Kruskal-Wallis). Differences in means for continuous variables between CPA grades 1 versus 3 were examined using independent sample T-Test and Mann-Whitney test. Binary logistic regression was also used.
Results: We examined 128 patients where 35 (27%), 72 (56%) and 21 (17%) had mild, moderate and severe CPA respectively. Using total SGRQ score and its activity and impact domains only, worse health status was consistently associated with increasing severity of CPA where patients with severe CPA has worse health status than patients with mild or moderate disease (P = 0.02, 0.049 and 0.03 respectively). A stronger correlation was observed comparing only mild CPA versus severe CPA; we found patients with severe CPA had worse health status as measured by the total SGRQ, SGRQ activity and impact domains p=0.015, 0.02 and 0.017 respectively.
We did not find statistically significant difference in the mean score of SF-36 PCS and SF-36 MCS between different stages of CPA. However, patients with severe CPA had higher scores of SF-36 PCS only comparing to patients with mild disease (p= 0.055). No statistically significant difference was seen between patients for SGRQ symptoms domain and SF-36 MCS.
Binary logistic regression analysis using mild versus moderate/severe CPA showed that patients with disease severity suffered more health deterioration represented by total SGRQ score and its activity domain, and SF-36 PCS only after controlling for age, FEV1% and FVC% (OR 1.06, 95% CI 1 – 1.03, p = 0.04; OR 1.07, 95% CI 1.01 – 1.2, p= 0.02 & OR 0.89, 95% CI 0.89 – 0.98, p= 0.02 respectively). The impact domain showed a trend but it did not reach a statistical significance (p= 0.07).
Conclusion: The SGRQ showed better discriminating validity among different levels of CPA severity than generic health instrument. This suggests that SGRQ may provide CPA studies with better statistical power than SF-36 summary scores to identify meaningful differences in daily clinical practice.
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36: Aspergillus bronchitis in non-immunocompromised patients – case series, response to treatment and criteria for diagnosis
A Chrdle, S Mustakim, R Bright-Thomas, T Felton, CG Baxter, DW Denning

Purpose: Few patients have been described previously with Aspergillus (Aspergillary) bronchitis, unless immunocompromised. We reviewed records of patients referred who fulfil proposed criteria for Aspergillus bronchitis.

Method: From >400 patients referred to the National Aspergillosis Centre we conducted a retrospective chart review of possible Aspergillus bronchitis. Patients with persistent chest symptoms or bronchial obstruction who did not fulfill criteria for allergic, chronic or invasive pulmonary aspergillosis were analysed. Patients with an elevated Aspergillus IgG or precipitins and a positive culture or Aspergillus real-time PCR, were reviewed.
Results: 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). 4 were overtly immunocompromised, 2 were not immunocompromised at at all, and 11 had subtle immunocompromising factors. 16 had a productive cough and 8 high volume tenacious sputum. 8 had MRC dyspnoea scores of 4-5 (1 = normal, 5 is breathless getting dressed or talking). 7 had recurrent chest infections, and 4 significant fatigue. 3 had lost weight and 2 prior haemoptysis. 12 of 14 (86%) 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. 7/15 (47%) had a major response to oral antifungal therapy the first course given for 1-52 weeks (median 20 weeks) and 5/8 (63%) who disconinued therapy relapsed. 8 of 15 (53%) had adverse reactions to itraconazole, 3 of 4 (75%) with voriconazole.
Conclusion: Patients with underlying structural lung disease usually with immunological compromise of varying severity may present with Aspergillus (aspergillary) bronchitis. We suggest that the combination of relapsing chronic bronchitis symptoms with microbiological (culture or PCR) and immunological (Aspergillus IgG) evidence of Aspergillus infection are characteristic of Aspergillus bronchitis. This entity needs to be distinguished from asymptomatic fungal colonisation as well as invasive, allergic and chronic pulmonary aspergillosis. Aspergillus bronchitis responds to antifungal therapy.
1National Aspergillosis Centre, University Hospital of South Manchester, Manchester, UK 2Pathology Department, Hospital Sungai Buloh, Selangor Darul Ehsan, Malaysia 3Manchester Cystic Fibrosis Unit, University Hospital of South Manchester, Manchester

134: The Systems Biology of Azole resistance in *Aspergillus fumigatus*
M Bromley, MF Fraczek, M Kapushesky, I Gut, N Fedorova, W Nierman, DW Denning, P Bowyer

Purpose: Treatment for fungal disease is limited to a small number of drug classes including azoles candins and polyenes. Long term azole therapy for invasive, allergic and chronic pulmonary aspergillosis is the norm, and increasingly used. Antifungal drug resistance complicates therapy with worse outcomes. The mortality of patients with multi-azole resistance aspergillosis was 88% compared with 30-50% who were infected with azole sensitive strains. *Aspergillus fumigatus* zole resistance in several centres has recently increased in frequency, in Manchester 10% to 50% of resistant isolates carry non-CYP51A mutations, which remain unidentified. These isolates represent both a diagnostic challenge and an opportunity to study the underlying non-target basis of azole resistance in *A. fumigatus.*
Methods: To identify the biological systems that play a role in acquired drug resistance, we used a multi-omics approach involving Illumina GAII genome sequencing of resistant

clinical isolates, RNAseq of strains in the presence and absence of azoles, saturation transposon mutagenesis to discover genes involved in azole resistance and sensitivity and high throughput gene knockout to identify genes and pathways involved in azole resistance and sensitivity.
Results: Currently >25 strains resistant to Itraconazole, Voriconazole, Posaconazole or to multiple azoles, some from the same patient, others from diverse sources, have been sequenced. RNAseq of sensitive strains in the presence or absence of azole reveals 156 up – regulated and 201 down – regulated transcripts including efflux transporters, transcription factors, gliotoxin biosynthetic genes and lipid biosynthetic genes. Insertional mutagenesis reveals a number of transcriptional networks involved in azole resistance including 4 key transcription factors. Finally analysis of drug resistant strains coupled with RT-PCR analysis of transporter gene expression has allowed us to identify two efflux transporters involved in azole resistance as well as evidence that up-regulation of CYP51B may play a role in resistance.
ConclusionThe combination of different -omics techniques has allowed us to analyse drug resistance systems in A. fumigatus with identification of 9 novel genes or pathways involved in resistance. Azole resistance is a complex phenomenon in A. fumigatus, as might be expected from its remarkable versatility.
1School of Translational Medicine, University of Manchester, Manchester, UK 2EMBL outstation, Hinxton Hall, European Bioinformatics Institute, Cambridge, UK 3Infectious Disease, JCVI, Rockville, USA

131: Aspergillosis Patient Support Meeting - Actual and Virtual
MB Kirwan, GL Powell, DL Kennedy, CV Harris, GT Atherton

Purpose: The UK National Aspergillosis Centre (NAC) was commissioned in 2009 to provide highly-specialised quality care for Chronic Pulmonary Aspergillosis patients. The official launch incorporated the first Aspergillosis Patient Meeting, positively evaluated by those patients and carers in attendance. Monthly meetings have continued with developments, offering a combination of interactive educational talks and peer group support. Subjects are patient requested and focussed and include nutrition, anti-fungal drugs, physiotherapy, environmental exposure risks and a virtual clinic "visit" role-play. The aims of the meetings are to provide ongoing support to Aspergillosis patients and carers; to empower them to improve their quality of life; promote self-management skills; encourage concordance with anti-fungal treatment; develop strategies to improve physical functioning; reduce risk of environmental exposure; feedback on patient engagement in research and a platform for the patients' voices to be heard. These meetings are a valuable tool for empowering patients.
Methods: A suitable meeting room to seat people comfortably with nearby toilet access is required. Disabled access is a pre-requisite for debilitated oxygen-dependant, wheelchair-assisted patients and any in-patients transferred directly from the ward.
The meeting room requires audio-visual projection and flip-chart for interactive discussions and explanations. Expert speakers are from the NAC team, the wider hospital Trust and external experts.
The virtual aspect of the meeting is achieved by streaming live onto the Internet and is recorded for future presentation and reference. Internet chat software enables remote,

virtually attending patients the facility to post real-time questions. A two-way conversation is maintained throughout the duration of the live meeting.
Publicity is through the Aspergillosis Patient Website, email circulars and newsletter distribution during out-patient clinics. Talks and typed meeting-notes are uploaded onto the patient's website for future reference. Refreshments are provided by the Fungal Research Trust. For health and safety purposes, an Aspergillosis Nurse Specialist is present to intervene should any patient develop a clinical need.
Results: The benefits of the meetings are the promotion and encouragement of patients to become experts in their own health, through empowerment, by empathetically tailored education, based on their own patient stories and experiences, delivered by their own expert clinical, scientific and research focused staff. The meetings are continually positively evaluated by the patients and carers as helping them understand more about their diagnosis and treatment plans.
A testament to the meetings success is the continued high attendance and increasing number of on-line attendees. The meeting gives an opportunity to meet and speak, often for the first time, to fellow Aspergillosis sufferers. It gives them a chance to share their stories in a friendly, supportive arena. A direct response to the meetings is the patients' initiatives to raise funds for the Fungal Research Trust.
Conclusion: The Aspergillosis Patient Meeting is an innovative and creative approach to providing patient education and support. An integral component of the meeting delivery is the role of the Clinical Information Architect. Simultaneous actual and virtual meetings reach a much wider vulnerable audience, immediately and later. Importantly, those who are too ill or debilitated to travel still benefit from virtual attendance. Healthcare professionals can improve the quality of life of their patients with long-term condition by effectively providing patient education and support; in-reach in the hospital setting and more importantly, out-reach into the patients' homes.
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132: Comparison of Aspergillus diagnostic yields from bronchial aspirate, Bronchoalveolar lavage and sputa by Real-Time Polymerase Chain Reaction compared to standard fungal culture.
MB Kirwan, M Fraczek, J Martin, PV Barber, MD Richardson, CB Moore, DW Denning

Purpose: The primary objective of this small study was to compare Aspergillus species diagnostic yield from Bronchoalveolar lavage (BAL), bronchial aspirate and post bronchoscopy sputum samples by quantitative detection using Real Time - Polymerase Chain Reaction (RT-PCR) compared to standard fungal culture. Aspergillus is a major contributor to the morbidity and mortality of immunocompromised patients and those with primary diagnoses of asthma, bronchiectasis, cystic fibrosis and chronic pulmonary Aspergillosis. Despite impacting significantly on the disease burden of these patients, positive culture remain problematic from standard bronchoscopic and sputum sampling methods. Often presumptive clinical diagnosis is required in the absence of standard culturable results.

Methods: We prospectively recruited five patients from the National Aspergillosis Centre, Manchester UK who were scheduled for diagnostic bronchoscopy for suspected Aspergillus bronchitis. Patients were recruited under the auspices of the large Fungal Exposure and Colonisation in Respiratory Disease; Research Ethics Committee (REC) reference: 07/Q1403/70. Four patients had a primary diagnosis of bronchiectasis and all five a presumed clinical diagnosis of Aspergillus bronchitis. A sputum sample was obtained pre-bronchoscopy (n=4:5). During bronchoscopy after initial entry in to the main bronchi trap specimens were taken (n=4:5) and an initial wash of 5-20ml 0.9% Normal-Saline performed in n=4:5 patients. Based on chest radiograph, the bronchi with a consolidation or shadowing was wedged and between 10-120ml 0.9% Normal Saline instilled for the BAL. Volume instilled was discretionary by Bronchoscopist based on clinical condition and oxygen-saturations. A second sputum was obtained post-bronchoscopy (n=5:5). All specimens were transferred to the Mycology Reference Centre Manchester (MRCM) (http://www.mycologymanchester.org) for processing. Each sample was split into 3; one sent to the Clinical Sciences Laboratory University Hospital South Manchester for standard microscopy and fungal culture; one processed for DNA extraction and RT-PCR; one sample underwent microscopy, fungal culture and sensitivities within the MRCM.
Results: Pre-bronchoscopy sputa samples were obtained in 4 of 5 patients (n=4:5). 75% (n=3:4) positive standard culture rate compared to 100% (4:4) by RT-PCR. Bronchoscopic trap specimens were obtained in 4 of 5 patients (n=4:5). 50% (n= 2:4) positive standard fungal culture rate compared to 100% (4:4) by RT-PCR. Initial wash samples were obtained in 4 of 5 patients (n=4:5). 25% (n= 1:4) positive standard fungal culture rate compared to 100% (4:4) by RT-PCR. In standard practice this initial wash is usually discarded. BAL samples obtained on 5 of 5 patients (n=5:5) yielding a 20% (n= 1:5) positive standard fungal culture rate compared to 100% (n= 5:5) by RT-PCR. Post - bronchoscopy sputa samples were obtained in 5 of 5 patients (n=5:5) yielding 40% (n=2:5) by standard culture compared to 100% (4:4) by RT-PCR. One patient underwent bilateral BAL and 4 separate specimens obtained. Only 1 specimen proved positive on standard culture compared to 100% by RT-PCR.
Conclusion: These results demonstrate an important comparison between the diagnostic yields rates between standard fungal culture testing and RT-PCR using a commercial real-time assay for Aspergillus. This small single centre study suggests that improved respiratory Aspergillosis diagnostics can be achieved through RT-PCR.
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142: RT-PCR is significantly more sensitive in detecting Aspergillus in respiratory samples than culture

N Duddy, CB Moore, P Kent, M Richardson, D Denning, R Rautemaa-Richardson

Purpose: The National Aspergillosis Centre (NAC) is a specialist referral centre that has been providing long-term care for patients with chronic pulmonary aspergillosis in the UK since 2009. The Mycology Reference Centre, Manchester is the referral laboratory and provides a specialist mycology service for the NAC including detection,

identification and susceptibility testing of yeasts and moulds. Since January 2010, culture, PCR and serology have been employed to detect *Aspergillus* in respiratory samples. MycXtra DNA extraction and MycAssay Aspergillus RT-PCR kits (Myconostica, Cambridge, UK) are used according to the manufacturer's instructions. This system detects DNA from *Penicillium* spp. in addition to that of *Aspergillus*. The BSOP57 method, 'Investigation of Bronchoalveolar lavage, Sputum and Associated Specimens' is used for culture. The correlation between the performance of PCR and culture in the detection of *Aspergillus* in respiratory samples from chronic and allergic pulmonary aspergillosis patients has not been analysed before.
This retrospective audit aims to analyse the concordance between two methods (culture and PCR) for the detection of *Aspergillus* of the first 100 NAC patient respiratory samples.
Methods:A database search of the laboratory reporting system was used to collect the data. The first 100 consecutive respiratory samples of NAC patients where PCR and fungal culture had been performed were included.
Results: The 100 samples included in the study had been collected between January and April 2010 (80 days) from 83 patients that attended the NAC. A total of 42 samples were found positive for *Aspergillus* with either method. Of the patient samples, 40% were positive by PCR and 18% by culture. Four cases were negative in PCR but positive in culture. There was a 66% concordance between the two methods. In two cases the positive PCR was due to *Penicillium* sp. as detected by culture. In addition, two cases of *Penicillium* was detected by culture but the PCR remained negative. Of the 40 cases positive in PCR, 50% gave a strong signal ($CT \leq 36$) including the two false positive cases, and 50% gave a weak signal ($36 < CT \leq 38$). In this patient group and sample type the sensitivity of the PCR was 90% and that of the culture was 33% (P=0.0156). The specificity of the PCR system was 98%.
Conclusion:PCR was found to be significantly more sensitive in detecting *Aspergillus* in respiratory samples than culture.

120: Repeated courses of intravenous amphotericin B therapy including intermittent long-term treatment in patients with chronic pulmonary aspergillosis
P Newton, C Harris, DW Denning

Purpose: Intravenous (IV) amphotericin B therapy is a recognised treatment for patients with chronic pulmonary aspergillosis (CPA). There are limited data available on the use of IV amphotericin B therapy in this patient group and none on repeated courses. This audit was therefore undertaken to ascertain whether CPA patients derive clinical benefit from IV amphotericin B therapy.
Methods: CPA patients who received two or more courses of IV liposomal amphotericin B therapy (Gilead Sciences), either as repeated short courses or a short course(s) followed by intermittent long-term therapy, at our clinical centre were identified. A retrospective review of patient case-notes was performed using a standardised proforma. Data collected included patient demographics, the indication for treatment, the dose and duration of treatment and the subsequent clinical response.
Results: 9 CPA patients (5 females, 4 males) aged between 47 and 74 years (median 61 years) at the time of their first dose of IV amphotericin B were identified. 4 patients had

repeated short courses of treatment (2 courses, n=3; 3 courses, n=1) whilst 5 patients had at least 1 short course of treatment prior to commencing long-term intermittent IV amphotericin B therapy. The dose of IV amphotericin B given for short courses and intermittent long-term treatment ranged between 2.53 - 4.62 (mean 3.03) mg/Kg daily and 2.53 - 6.7 (mean 4) mg/Kg/dose three times a week respectively. The duration of treatment ranged between 3 - 36 days (mean 20.3) and 4 - 12 (mean 11.2) months respectively for short versus intermittent long-term courses of treatment. Indications for repeated short courses of IV amphotericin B were primarily deterioration in respiratory symptoms (62%) and / or constitutional symptoms (56%). Intermittent long-term therapy was generally given to patients who had no other oral options available either due to drug intolerance and / or the development of azole drug resistance. Intermittent long-term therapy was delivered via a Portacath IV line.
Improvements in respiratory and constitutional symptoms were observed in 5 out of 9 (56%) and 4 out of 9 (44%) patients receiving repeated short courses of IV amphotericin B respectively. All patients (n=5) on intermittent long-term therapy noticed an improvement in their symptoms (respiratory, n=1; constitutional, n=4). An improvement in the immunological markers of Aspergillus infection were noted in 3 out of 6 (50%) and 1 out of 3 (33%) patients with adequate immunological data available in the short course versus intermittent long-term IV amphotericin B groups respectively. Of the 5 patients who had long-term intermittent IV amphotericin B therapy, 1 patient stopped treatment following a pneumonectomy and the other 4 patients subsequently failed this treatment.
Conclusion: Around 44 - 56% of CPA patients receiving repeated short courses of IV amphotericin B therapy noted an improvement in their respiratory and / or constitutional symptoms. Intermittent long-term therapy was reserved for patients with limited treatment options and all patients in this treatment group gained clinical benefit from this treatment.

97: Microevolution of *Aspergillus fumigatus* in aspergillomas

SJ Howard, A Pasqualotto, M Anderson, H Leatherbarrow, A Al-Barrag, E Harrison, L Gregson, P Bowyer, DW Denning

Purpose: Aspergillomas (fungal balls) form over weeks or months when spores germinate on the bronchial or cavity wall, where mycelia and debris attach to form an amorphous mass. Aspergillomas are most commonly seen in chronic pulmonary aspergillosis (CPA). Most patients with simple pulmonary aspergillomas are asymptomatic initially, although symptoms are often severe when aspergillomas are associated with multi-cavity CPA. A characteristic feature is haemoptysis, which varies from trivial to fatal in severity. Furthermore aspergillomas are a risk factor associated with the development of azole resistance.
Methods: Aspergillomas were removed from 3 patients; Patients 1 and 2 during surgery, and Patient 3 at autopsy. Overall 92 *Aspergillus fumigatus* were isolated from throughout the dissected fungal balls, with individual colony picking. Microsatellite typing was conducted to determine the genetic type, and a phylogenetic tree was constructed using this data. Minimum inhibitory concentrations (MICs) were performed by modified European Committee for Antibiotic Susceptibility Testing (mEUCAST) method, against

itraconazole, voriconazole and posaconazole. The entire coding region of the *cyp51A* gene was amplified in 22 isolates.
Results: Isolates from Patient 1 revealed azole susceptible and resistant *A. fumigatus*, although *cyp51A* sequences were all wild-type, so the mechanism of resistance remains ill-defined. In these isolates significant genetic differences were observed in 5 of 6 microsatellite loci, splitting the isolates into at least 2 distinct clades. In Patient 2, isolates were less variable; all were azole susceptible, and microvariation was only seen in 2 microsatellite loci. Finally only azole resistant strains were isolated from Patient 3, although the pattern of cross-resistance was notably different for posaconazole, ranging from 0.125->8mg/L. Interestingly two different amino acid alterations were found in this aspergilloma, both at codon 220 (M220K and M220T). The phylogenetic tree, constructed using microsatellite data, revealed isolates from different aspergilloma patients did not cluster.
Conclusions: Diverse microevolutionary alterations were observed in this set of aspergilloma isolates; revealing differences in azole susceptibility, mechanisms of resistance and genetic type (sometimes even within the same aspergilloma).

137: Aspergillus-related respiratory diseases can impact pneumococcal antibody levels and response to both pneumococcal polysaccharide vaccines and pneumococcal conjugate vaccines.
GL Powell, J Morris, R Borrow, DW Denning

Purpose: Streptococcus pneumoniae is a leading cause of infection worldwide. The 23 valent polysaccharide vaccine (PPV-23) was introduced in 2003 in the UK for all people aged 65yrs and over, the 7-valent pneumococcal conjugate vaccine (PCV-7) was introduced into the infant immunisation programme in 2006, replaced by PCV-13 in April 2010. Our objective was to establish if patients with chronic respiratory disease who have not achieved adequate pneumococcal antibody response following PPV-23, can achieve adequate response to the PCV-7 or PCV-13.
Methods:Patients attending specialist respiratory clinics routinely had pneumococcal antibody levels tested. Antibody levels to 12 serotypes were reported for patients with chronic pulmonary aspergillosis (CPA), allergic bronchopulmonary aspergillosis (ABPA), bronchiectasis and asthma/severe asthma with fungal sensitisation (SAFS). A level of >0.35µg/ml signified adequate response and patients with low levels to >6/12 serotypes were given PPV-23. Those who continued to have low levels went on to receive 1 or 2 PCV doses, either PCV-7 or PCV-13 (only 1 patient received PCV-7 followed by PCV-13).
Results: All patients had received PPV-23 within the previous 5 years and had not achieved adequate antibody levels. They were, therefore, eligible for repeat vaccine with PCV rather than PPV. Pre and post-vaccination serotype-specific IgG levels were available for 20 patients – CPA n=13 (3 of whom received PCV 13), ABPA n=3, bronchiectasis n=1 and asthma/SAFS n=3. 17 patients received PCV-7 and 3 received PCV-13. For those who received 1st dose of PCV-7 the best responses were achieved for serotypes 4 (41% increase); 6B (36% increase); 18C (47% increase); 19F (24% increase); 23F (59% increase) and 7F (29%). The poorest serotype levels were for serotypes 1 & 5 (not contained in PCV-7). Following a single dose of PCV-13, 2 out of 3 patients (all

CPA) had an overall adequate response. 12/20 patients required a 2nd dose of PCV 7 or 13, due to poor response. To date only 3/12 had antibody levels measured post 2nd vaccine dose. 2 CPA patients had a 2nd dose of PCV-7 with neither responding. The other patient received PCV-13 following PCV-7 with adequate response.
Conclusion: Although the numbers of patients are small and comparison between the disease groups was not possible we were able to show that PCV is an effective 2nd line vaccine (post PPV-23) for certain serotypes, however most patients (60%) do need to have a 2nd PCV dose. The efficacy of PCV-13 in adults over 65yrs is being evaluated via a randomised controlled trial. Efficacy of PCV-13 following PPV-23 in our aspergillosis patients, also needs further investigation, as the numbers reported here are small.

139: Impaired switching of the normal IL1 response to *A. fumigatus* in chronic cavitary pulmonary aspergillosis (CCPA)
NL Smith, A Simpson, DW Denning, P Bowyer

Purpose: *Aspergillus fumigatus* causes invasive aspergillosis (IA) in immunocompromised subjects, but can also cause CCPA in immunocompetent subjects. Little is known about the genetic factors influencing susceptibility to CCPA. Studies have demonstrated that the IL1 pathway is involved in the response to A. fumigatus, with alveolar macrophages co-cultured with this fungus shown to produce the proinflammatory cytokines IL1α, IL1β and IL6, and to induce NFκB activation. IL1RN is a negative regulator of the IL1 pathway.
Method: For the expression work, monocyte-derived macrophages were generated from blood from 10 healthy volunteers and 10 CCPA patients attending our clinic. These were co-cultured with live *A. fumigatus* conidia (Af293 strain) and RNA was extracted at various timepoints (0hr-9hr). RNA from the patients and the healthy subjects was pooled. cDNA was generated and RT-PCR was completed on 84 test genes using the Human Innate and Adaptive Immune Responses RT^2 Profiler PCR Array (SABiosciences). Expression was normalised to HPRT1, RPL13A and GAPDH and fold changes were generated compared to the Healthy 0hr (baseline) expression level. For the genotyping work, the Sequenom® MassArray® iPLEX™ Gold system was used to genotype HapMap tagging SNPs in the IL1B and the IL1RN genes. Six SNPs in IL1B and 10 SNPs in IL1RN were analysed, in 112 CCPA (±aspergilloma) patients and 279 healthy controls. Genotype and allele frequencies were compared using $\chi 2$ and Fisher's exact tests.
Results: In the CCPA group, expression of IL1A and IL1B increased after exposure to *A. fumigatus* until 9hr, while in the healthy group expression initially increased until 3hr and then decreased at 6hr and 9hr. Expression of IL1F8 did not alter much in either group until 9hr, when it increased dramatically in the healthy group but remained low in the CCPA group. Expression of IL1RN increased in both groups after exposure to *A. fumigatus*. SNPs in IL1B (rs3136558, A/G, intronic) and IL1RN (rs4252041, C/T, 3' UTR) were significantly associated with CCPA. The AA genotype of rs3136558 (OR 1.75, 95% CI 1.08, 2.84) and CC genotype of rs4252041 (OR 4.38, 95% CI 1.31, 14.65) were more common in the CCPA group compared to the healthy group.
Discussion: The expression profiles observed in the macrophages from healthy subjects for IL1A and IL1B suggest an initial pro-inflammatory response to the presence of

conidia, and then a reducing inflammatory response at 6hr-9hr as germtubes and hyphae become the predominant fungal morphology. As expression did not reduce in the CCPA cells, it may be that these cells do not respond to the change in fungal morphology, or, alternatively, show a delayed response. As IL1F8 expression increased in the healthy group as IL1A and IL1B expression decreased, it appears that in the healthy macrophages a switching of the proinflammatory response from an IL1A and IL1B driven response to an IL1F8 driven response occurs. These differential gene expression profiles, and the SNPs identified support a role for the IL1 pathway in the response to *A. fumigatus* and in susceptibility to aspergillosis.

138: Genetic associations with plasminogen and related genes with chronic cavitary (CCPA) and allergic bronchopulmonary aspergillosis (ABPA) compared with healthy and asthmatic controls

NL Smith, P Bowyer, DW Denning, A Simpson

Purpose: Various genes and SNPs have been identified as associated with invasive aspergillosis (IA), but much less is known about the genetic factors influencing susceptibility to CCPA, ABPA and severe asthma and fungal sensitisation (SAFS). Plasminogen (PLG) binds to *A. fumigatus*, and can be converted to plasmin while bound. Expression of genes encoding proteins that are involved in this conversion (PLAU and PLAUR) is upregulated in monocytes exposed to *A. fumigatus*. Plasmin can act as a chemoattractant for monocytes and induces expression of inflammatory cytokines and chemokines by these cells. Plasminogen activator tissue (PLAT) also acts to promote the conversion of plasminogen to plasmin.
Method: The Sequenom® MassArray® iPLEX™ Gold system was used to genotype HapMap tagging SNPs in the PLG and PLAT genes. 23 SNPs in PLG and 11 SNPs in PLAT were analysed in 95 ABPA patients, 47 SAFS patients and 112 CCPA patients (±aspergilloma), and in 152 atopic asthmatics and 279 healthy controls. Genotype and allele frequencies were compared using $\chi 2$ and Fisher's exact tests. Frequencies in the CCPA group was compared to the healthy group, and frequencies in the ABPA and SAFS groups were compared to both the healthy group and the atopic asthmatic group.
Results: Four SNPs in PLAT were significantly associated with CCPA compared to the healthy group. The GG genotype of rs879293 (G/A) was significantly less common in the CCPA subjects (OR 1.65). The AA and GG genotypes of rs8178880 (A/G; OR 3.26) and rs8178890 (G/A; OR 2.66) respectively, were more common in the CCPA subjects. The G allele of rs2070712 (A/G; OR 1.52) was more common in CCPA. It is interesting that some of these associations are with the common allele. The AA genotype of rs8178880 (A/G; OR 2.73-3.82) was also significantly associated with ABPA, and the G allele of rs2070712 (A/G) showed a trend towards association with ABPA, but did not reach significance. All of these are novel associations not been described previously. The SNPs are intronic and their function is currently unknown. One SNP in PLG was associated with SAFS; the AA genotype of rs4252200 (A/G; OR 6.20-6.23) is significantly more common in the SAFS group compared to the healthy and atopic asthma groups. This SNP in 3' of PLG and this is again a novel association. No significant association was found with any of the diseases tested and rs4252125, which has previously been associated with IA.

Conclusion: The SNPs identified in PLAT and PLG may influence susceptibility to aspergillosis by affecting the conversion of plasminogen to plasmin in response to *A. fumigatus*, or may affect the binding of plasminogen to this fungus. Remarkably SNPs in PLG and PLAT have been found associated with each of the disease phenotypes tested raising fundamental questions of pathogenesis and susceptibility to non-invasive forms of aspergillosis.

96: Reduced gamma interferon (gIFN) production in chronic pulmonary aspergillosis (CPA)

R Doffinger, C Harris, S Lear, P Newton, H Alachkar, DS Kumararatne, DW Denning

Purpose: TH1 responses are crucial for effective defence against Aspergillus spp. Two patients with poor lymphocyte proliferation and gIFN production and CPA have been described. CPA is a slowly progressive destructive disease, usually of the upper lobes, which is characterised by chronic inflammation and a failure to halt the intra-cavitary growth of A. fumigatus (usually)

Methods: We analysed gIFN, TNFalpha, IL-6, IL-12 and IL-10 production after in vitro stimulation of Whole Blood culture to a variety of defined stimuli including LPS, beta-glucan, PHA, IFN gamma, IL-12 and IL-18 to interrogate the IL-12 and gIFN dependant pathways. Blood was collected from CPA patients and a healthy control in Manchester attending the NAC and sent by courier to Cambridge for analysis. Cells were processed the same day in Cambridge. Cytokines were measured by ELISA or multiplexed particle based flow cytometry.

Results: Results from 30 CPA patients were available. Only 7 (23%) of the patients showed normal in vitro gIFN production. 9 (30%) had a reduced (2-5 fold) and 14 (47%) a very low (> 5 fold) gIFN production when compared to healthy controls.

Different patterns can be observed among the gIFN deficient responses with more than half of them (54%) being deficient in their response to all stimuli. Approx one third (35%) did have a normal response to PHA. A smaller group (11%) showed a weak response to PHA only. In comparison, there was a normal response to gIFN and a normal production of and response to IL-12, a major physiological inducer of gIFN. IL-12 had a normal capacity to synergistically up-regulate the production of gIFN.

More than two thirds of the patients showed an increased production of TNF-alpha and IL-6.Three patients were treated with gIFN with clinical improvement (2 with community acquired acute Aspergillus pneumonia which became CPA). This was paralled by improved gIFN secretion in vitro, suggestive of the positive feedback loop being inducible with treatment.

Conclusion: The majority of patients with CPA appear to have low gIFN production, but a normal response pathway. As treatment with gIFN is usually reasonably well-tolerated, supplementation should be considered. Additional work is required to ascertain if the low gIFN production remains permanent or is remediable with treatment. Increased TNF and IL6 production is of interest.

7 Statutory reports

MRSA

No cases of MRSA and the hospital has had a great reduction in MRSA bacteraemia with >365 days without a case to July 2012.

C. difficile infection

Two community acquired cases, one on treatment for non-tuberculous mycobacterial (severe pseudomonas colitis) and another on oral antifungals and antibiotics.

HIRS

1 HIRS report only. Incident detail: Wrong result of Aspergillus galactomannan test reported through to Alexandra Hospital Pathology Dept.

SUI

None

8 Financial position

Expenditure 2011/12

The original plan for 2011/12 was set at £5.1m and included £2.6m of drug costs. During 11/12 the NCG contract operated via a block base supplemented by activity related marginal rate variable payments. Drugs expenditure was included within the contract and treated as a direct pass through.

Overall the total cost of the service in 2011-12 was £5.11m against a plan of £5.12m. The £11k underperformance included worse than planned performance against the drugs pass through which was £130k worse than plan and was matched by below plan expenditure. This was offset by overperformance of £119k on the variable element of the contract which included occupied bed days which were 502 above plan.

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

Activity Type	**Plan**		**Actual Outturn**	
	Activity	**Cost £'s**	**Activity**	**Cost £'s**
Referrals	**65**	**£96,655**	**74**	**£110,038**
Band 1	104	£216,736	79	£164,636
Band 2	112	£413,280	124	£457,560
Band 3	21	£97,230	15	£69,450
Total Banded	**237**	**£727,246**	**218**	**£691,646**
Occupied Bed Days	894	£238,698	1396	£372,732
Surgical Resections	6	£66,216	7	£77,252
Embolisation	20	£23,300	17	£19,805
Fixed service element		£1,378,564		£1,378,564
Total		**£2,530,679**		**£2,650,037**

Drugs (ICP)	246,250	
Posaconazole	206,850	588,093
Other antifungal drugs	2,140,543	1,875,635
Drugs Total	**£2,593,643**	**£2,463,728**
Total	**£5,124,322**	**£5,113,765**

ICP = Individual Case Panel

Financial Forecast 2012/13

The 12/13 the NCG contract will no longer include a plan for drugs expenditure as funding has been retained by NSCT and will be paid on an actual basis subject to the submission of supporting information.

The contract is set at £2.66m and includes a fixed element of £1.35m with 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. See below
- 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. No progress, due to surgical reluctance.
- 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. SGRQ now validated and implemented as the base score for QoL. Evaluation of change with antifungal therapy ongoing (needs enough cases started on therapy for evaluation)
- 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. Vaccines routinely given, with use of both Prevar 13 and Pneumovax used, alongside Menitorix (HIB), if indicated.
- 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. Improved process in 2011/12 with better collective understanding of patient needs and likely responses.

- 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. Unlikely to be fundable. Conceptual agreement and funding agreed for a placebo-controlled delayed start itraconazole study in Kenya, following an epidemiology study to determine frequency of the problem, in HIV and non-HIV infected patients.

Developments planned for 2010/11

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. Procured and implemented
- 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. Completed and now frequently done.
- Detailed audit of the utility of PCR testing in respiratory specimens in CPA patients as a marker of antifungal failure. Done and routine part of care.
- Implementation of direct detection of resistance to antifungals from PCR positive, culture negative specimens. Worked up, but some technical challenges, so not yet implemented.
- Implementation of METS[1] as a measure of respiratory distress, alongside walking distance and MRC dyspnoea scores. Evaluated, but not yet completed.
- Trial of posaconazole for patients who have exhausted other treatment options and stand to benefit substantially from antifungal therapy (pending NCSG approval). Not done do to NCSG not approving the concept of a trial period for each patient.
- 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. Implemented.
- Proposal for a prospective study of posaconazole for CPA to Merck Done verbally, with no real interest.
- 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]. Analyses nearly complete, not relayed back yet.

[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.

Developments planned for 2011/12

- Implementation of a distance home nursing service to minimise patients visits, for infirm and very distant patients
- Procurement and implementation of an IV antifungal at home service to minimise hospital stay.
- Increased patient engagement activities and support of regional support groups.
- Full evaluation of fatigue as component of ill health and a fatigue score as a measure of patients' well being, compared with SGRQ QoL score.
- Evaluation of change of SGRQ with therapy as a proxy marker of patient response
- Evaluation of non-*fumigatus* IgG antibody tests for patients with negative *fumigatus* IgG antibody.
- Implementation of METS[2] as a measure of respiratory distress, alongside walking distance and MRC dyspnoea scores.

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

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 2011 – March 2012

* The month seen is not always the month they are determined to have CPA, because of missing diagnostic data. Red highlight refers to direct inpatient transfers or diagnosed in hospital.

MONTH	INITIALS	IDENTIFIER	DATE REFERRED	APPOINTMENT DATE	WAITING TIME	POSTCODE	AREA	COMMENTS	Band	Antifungal at 1st visit	Antifungal at 3 months
APRIL	TS	4205689	01/03/2011	04/04/2011	4 weeks	BL4	Bolton		B1	Itra	
	EMcI	4207091	04/03/2011	15/04/2011	5 weeks	EH19	Scotland		B2	Vori	Vori
	LT	4200163	Feb (in-pt)	13/04/2011		BL1	Bolton	Transition from IA to CPA	B2	Vori	Vori
	JQ	4209569	14/03/2011	Urgent admission		SY3	Shrewsbury		B2	Vori	AmB
	SP	4183811	15/10/2010	01/04/2011	6 months	L35	Merseyside	Patient DNA x 2	B1	Itra	Itra
	GN	4205699	01/02/2011	08/04/2011	10 weeks	CV34	Warwickshire		B2	Vori	Vori
	WE	4210488	12/04/2011	29/04/2011	2 weeks	M38	Worsley	Admitted from clinic	B2	Vori	Vori
MAY	DS-M	4211220	11/04/2011	20/05/2011	5 weeks	TQ2	Torquay		B1	Itra	Vori
	FW	4214361	18/04/2011	27/05/2011	5 weeks	SN7	Oxon		B2	Vori*	Vori
	SA	4199274	07/01/2011	16/05/2011	4 months	WA9	St Helens	Patient DNA x 1	B1	Itra	Vori
	MN	4204405	30/03/2011	Ward transfer		M41	Manchester		B1	Itra	
JUNE	NS	765658	19/05/2011	24/06/2011	4 weeks	M21	Manchester		B1	Itra	Itra
	HA	214620	19/04/2011	03/06/2011	8 weeks	WA10	St Helens		B2	Vori*	Vori
	KP	4149468	29/03/2011	17/06/2011	12 weeks	DT12	Dorset	Transport issues	B2	Vori	Vori
	JR	4212964	09/05/2011	24/06/2011	6 weeks	L18	Liverpool		B1	Itra	Itra
	MH	4190521	13/09/2010	20/06/2011	9 months	ST6	Stoke on	cancelled 4 apts prior	B1	Itra	Itra

							Trent	to visit			
JULY	PP	4218482	20/05/2011	08/07/2011	7 weeks	FY4	Blackpool		B1	Itra	Itra
	JS	4212820	09/05/2011	01/07/2011	8 weeks	CA4	Cumbria		B1	Itra	Itra
	MF	4215584	09/05/2011	08/07/2011	9 weeks	SK3	Stockport		B1	Itra	Itra
	JH	4221665	05/07/2011	08/07/2011	3 days	CH64	Wirral	Urgent	B1	Itra	Vori
	MF	1079113	13/05/2011	15/07/2011	8 weeks	M22	Manchester		B1	Itra	Vori
	HD	4218870	31/03/2011	15/07/2011	15 weeks	NG10	Nottingham	Co-ordinating nerve conduction studies	B1	Itra	Vori
	BA	4218493	09/05/2011	22/07/2011	10 weeks	WN6	Wigan		B1	Itra	Itra
	MG	1108656	25/07/2011	29/07/2011	4 days	M23	Manchester	Urgent referral	B1	Itra	None
	JM	4223797	25/07/2011	Urgent admission		WN3	Wigan		B2	Vori	
AUG	TC	4227278	17/08/2011	Urgent admission		PA8	Scotland		B2	Vori	Vori
	DP	4227002	15/08/2011	Urgent admission		M29	Manchester		B2	AmB	
	JT	4222499	13/06/2011	12/08/2011	6 weeks	OL10	Oldham		B1	Itra	Itra
	AV	4226937	28/07/2011	19/08/2011	3 weeks	NN6	Northampton		B1	Itra	Itra
	DT	4211217	14/03/2011	19/08/2011	5 months	M5	Salford	reschedule x 2	B1	Itra	Vori
	CD	4222513	07/07/2011	26/08/2011	6 weeks	NG10	Nottingham		B1	Itra	Itra
	BG	4227793	15/07/2011	26/08/2011	4 weeks	WN1	Wigan		B1	None	None
	HW	4218855	03/06/2011	03/08/2011	8 weeks	BL3	Bolton		B1	Itra	Itra
SEPT	JB	4222516	08/07/2011	02/09/2011	8 weeks	M30	Manchester		B1	Itra	Itra
	JY	4223793	29/07/2011	16/09/2011	7 weeks	CM13	Essex		B1	Itra	Itra
	EM	4212395	14/03/2011	16/09/2011	6 months	IV2	Scotland	reschedule x 2 (in-pt stays)	B1	AmB	IV AmB

	AO	4227795	04/08/2011	16/09/2011	6 weeks	WV16	Shropshire		B2	Itra	Itra
	JD	4227808		Urgent admission		WN6	Wigan		B3	Vori	Vori
	AC	4225227	03/08/2011	30/09/2011	8 weeks	NG5	Nottingham		B2	Vori	Vori
	DH	4205681		05/09/2011		PR3	Preston		B1	Itra	Itra
	AL	4227820	01/08/2011	12/09/2011	5 weeks	WN3	Wigan		B1	Itra	Itra
	AS	4229046	20/09/2011	ward transfer		WF2	Wakefield		B2	AmB	None
OCT	RW	4230026	17/08/2011	07/10/2011	7 weeks	NG3	Nottingham		B2	Itra	Awaiting vori after embolisation
	JF	4230039	19/08/2011	14/10/2011	8 weeks	SY22	Shropshire		B1	Itra	Itra
	PM	4224590	01/08/2011	14/10/2011	9 weeks	DE21	Derby	Pt rescheduled apt	B1	Itra	Itra
	RK	4230042	30/08/2011	21/10/2011	7 weeks	NG5	Nottingham		B1	Itra	Itra
	EM	4236149		26/10/2011		M28	Manchester		B1	Itra	
	TG	4231545	13/09/2011	24/10/2011	6 weeks	WN4	Wigan		B1	Itra	Itra
NOV	PT	4231078	23/09/2011	11/11/2011	7 weeks	LE7	Leicester		B2	Vori	Vori
	HMcK	4196209	18/10/2011	11/11/2011	7 weeks	CG49	Wirral		B1	Itra	Itra
	IN	701719	19/10/2011	25/11/2011	5 weeks	SK8	Stockport		B1	Itra	Itra
	GS	1121038	30/06/2011	15/08/2011	7 weeks	M6	Manchester	CPA diagnosis made October	B1	None	Itra

DEC	CG	4238786	12/11/2011	ward referral		WN5	Wigan		B2	Vori	Vori
	CS	4234714	17/10/2011	16/12/2011	8 weeks	DE55	Derby		B1	Itra	Itra
	MF	4239063	16/10/2011	16/12/2011	8 weeks	NG16	Nottingham		B1	Itra	Itra
	BB	1073757		ward transfer		M21	Manchester		B2	Vori	Vori

JAN	JD	534928	23/11/2012	13/01/2012	7 weeks	SK7	Stockport		B2	Vori	Vori

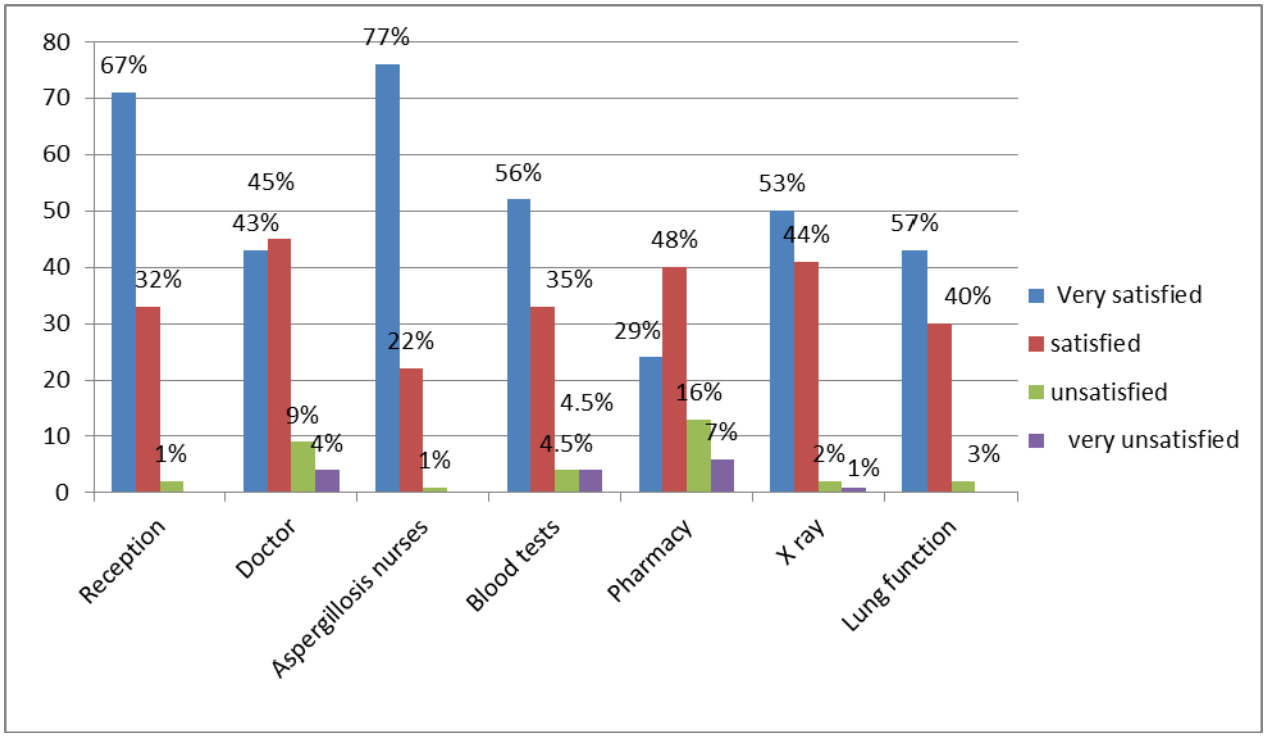
	DM	4243648	11/11/2011	13/01/2012	8 weeks	NG12	Notts		B2	Vori	Vori
	AR	4243651	18/11/2011	13/01/2012	7 weeks	OL11	Oldham		B1	Itra	Itra
	JR	4244660	28/11/2012	27/01/2012	8 weeks	TS19	Newcastle		B2	Itra	Vori
	JH	4241199	03/11/2012	23/12/2012	6 weeks	M29	Manchester		B2	Vori	Vori
	DH	143807	ward referral	16/12/2012		M22	Manchester		B2	Vori	Vori
	TR	4162193		06/01/2012		NG15	Notts	transition of disease	B1	Itra	Itra
FEB	EB	34312	02/12/2011	27/01/2012	6 weeks	SK8	Stockport		B1	Itra	Itra
	RH	4163793	29/11/2010	28/01/2011	8 weeks	PR1	Preston	complex disease	B1	Itra	Itra
	JB	4235244	03/10/2011	04/11/2012	4 weeks	TN39	East Sussex		B1	Itra	Itra
	JM	4247074	28/12/2011	24/02/2011	8 weeks	LS17	Leeds		B2	Vori	Vori
	AE	4244668	09/12/2011	10/02/2012	8 weeks	LL29	Wales		B1	Itra	Itra
	TL	4248003	11/01/2012	24/02/2012	6 weeks	WA8	Widnes		B1	Itra	Itra
	MJ	4244667	07/12/2011	03/02/2012	8 weeks	OX29	Oxford		B2	None	Vori
MARCH	JM	4250078	09/01/2012	02/03/2012	7 weeks	N28	Tyne&Wear		B1	Itra	Itra
	RS *	4211192	14/03/2011	09/03/2012	12 months	NG10	Notts		B2	Vori	Vori
	DH	4250114	30/01/2012	16/03/2012	6 weeks	NG5	Notts		B2	Vori	Vori
	AB	35849	05/03/2012	30/03/2012	2 weeks	SK6	Stockport		B2	Vori	Vori
	AB	4244649	23/11/2012	20/01/2012	7 weeks	BL1	Bolton		B1	None	Itra

* patient was given several apts but had moved house

Appendix 3
National Aspergillosis Centre patients survey

The survey was issued to all Friday clinics in February 2012 of which a total of 108 patients returned the survey. Over 80% of the patients have CPA in Friday clinic. Only 3 (3%) people completed the survey who were attending clinic for the first time. Of the xx attending Friday clinic, 86 have CPA.

Waiting times



48/652 (7%) of replies overall were not satisfied with waiting times, with particular problems while waiting for Pharmacy (23%), Doctor (13%) and Blood tests (8%). Reception, Nursing care and Lung function and X-ray had very low (1-2%) dissatisfaction.
Patients were 100% satisfied with the courtesy shown by Doctors, Specialist Nurses and Receptionists with Nurses in particular getting well over 90% very satisfied.

Quality of Care

319/321 (>99%) were satisfied (13%) or very satisfied (87%) with quality of care offered by Doctors, Clinic Nurses and Specialist Nurses.

Communication

99/100 (99%) satisfied (29%) or very satisfied (72%) with communication between themselves and NAC staff.

59/104 (57%) have received or made calls from/to NAC staff in-between clinic visits and all were satisfied (11%) or very satisfied (89%) with the support offered.

Physiotherapists

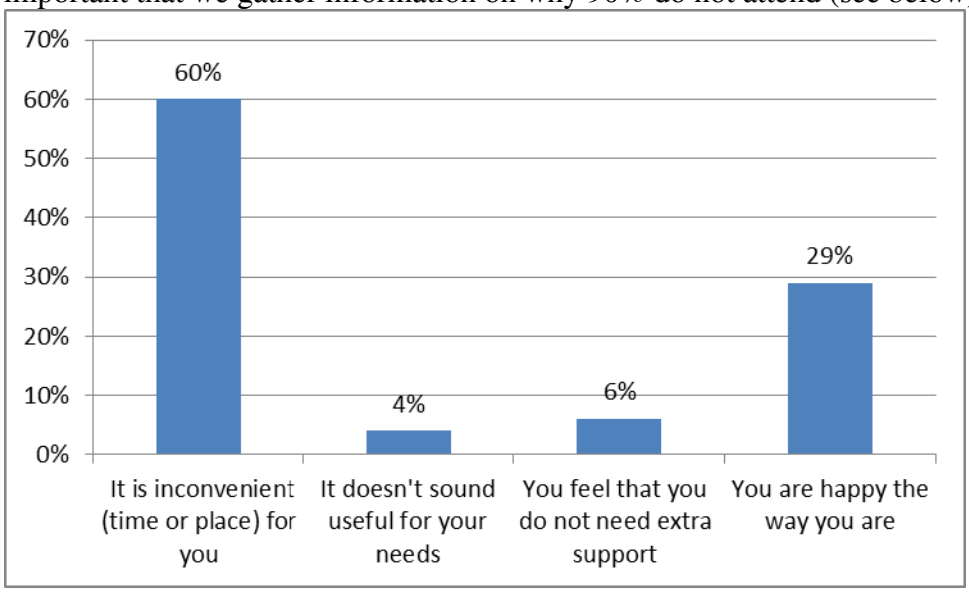
34/105 (32%) have received care from NAC specialist physiotherapists and of these all were satisfied (23%) or very satisfied (77%).

Aspergillus Website

53% use the Aspergillus Website and all are satisfied (51%) or very satisfied (49%).

Patients Support Meetings

10% of patients asked have attended a meeting, and 26% have viewed the recordings of the meetings that are available on the Aspergillus Website. In addition 9% have viewed meetings 'live' online – making a maximum possibility of 45% of our patients (neglecting overlaps where the same patients may have used more than one method of accessing a meeting) have accessed at least one meeting over the last year.
We know that 47% of our patients do not use the Aspergillus Website and most of those people will not have access to the internet, so it is important that we reach these patients with support. The main way we do this is using the face to face Monthly Meeting so it is important that we gather information on why 90% do not attend (see below).



39% are not interested in attending a Support Meeting though some of those may be persuadable (e.g. those who replied 'It doesn't sound useful for my needs'). However importantly 60% seem to be interested but cannot attend as it is held at an inconvenient time or place for them. Some of these may well be those attending online or watching recordings but our figures show that there must be some who do not attend a support meeting in any way but would like to do so.
To address this problem we have started supporting a series of local support groups (4 so far in the UK covering Liverpool, East Midland, West Midlands and London) with 2 more possibly on the way (Cheltenham & Scotland). These groups are locally run by

patients or carers and have met several times over the last 7 months providing access to social support and our advice & information. Roughly 15 - 20 more patients have been supported in this way.

Travel to the Clinic

8% travel to the clinic by public transport, of which all are satisfied (67%) or very satisfied (33%) with the service.

Participation in Clinical Research

89% are generally happy to participate in clinical research, of which all are satisfied (28%) or very satisfied (68%) with the procedures and consent performed by staff.

Appendix 4

Publications from the Manchester Fungal Diseases Group (2011)

1. Adamama-Moraitou KK, Pardali D, Day MJ, **Denning** DW, Papazoglou L, Papastefanou A, Rallis TS. Aspergillus fumigatus Bronchopneumonia in a Hellenic Shepherd Dog. J Am Anim Hosp Assoc. 2011; 47: e13-8.
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