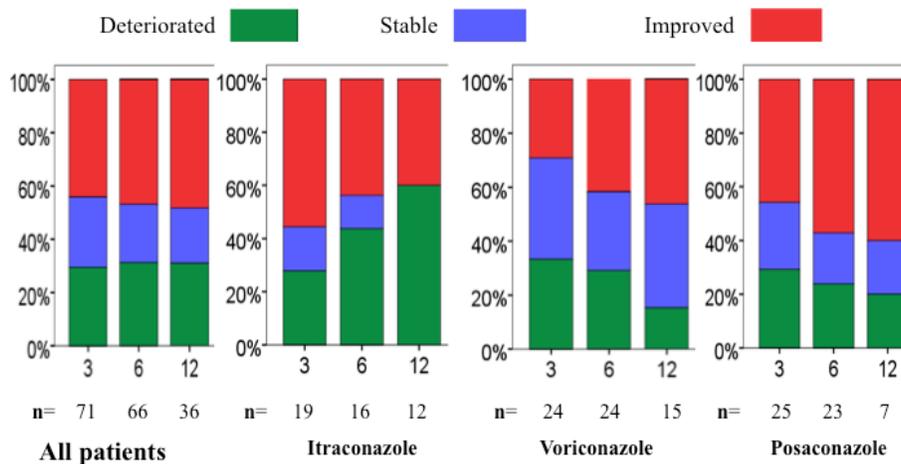
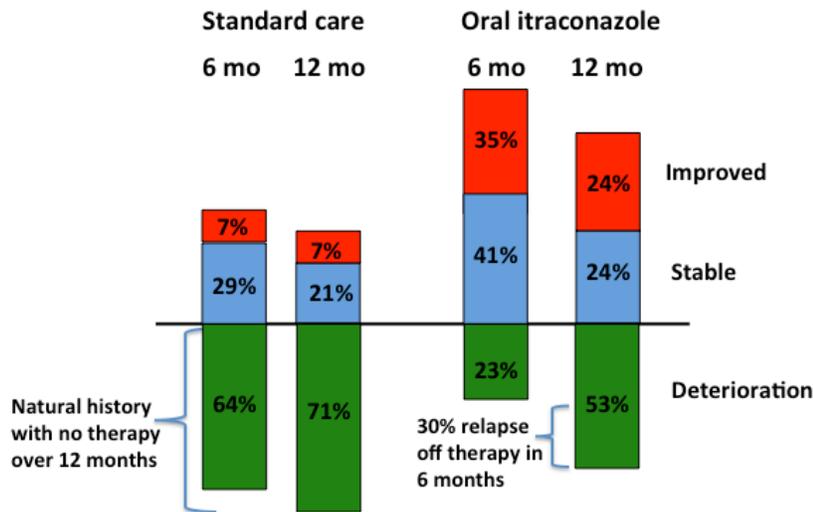




NCG Chronic Pulmonary Aspergillosis national service

The National Aspergillosis Centre

Annual Report 2012-2013



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Appendix 1 Categorisation of complexity (Banding)

Appendix 2 Referral to appointment time audit - April 2012 – March 2013

Appendix 3 Patient user survey January - February 2013.

Appendix 4 Publications from the Manchester Fungal Diseases Group (2011)

[Cover figure:

Top. Chronic pulmonary aspergillosis - response to itraconazole after 6 months therapy, compared to standard therapy (no antifungal), then all followed up for 6 months. (Agarwal R, Vishwanath G, Aggarwal AN, Garg M, Gupta D, Chakrabarti A.

Itraconazole in chronic cavitary pulmonary aspergillosis: a randomised controlled trial and systematic review of literature. *Mycoses*. 2013;56(5):559-70.

Bottom: Quality of Life change over time ($\pm \geq 4$ total SGRQ score, range 1-100) for patients starting itraconazole, voriconazole and posaconazole for chronic pulmonary aspergillosis. (Al-shair K, Atherton GTW, Harris C, Ratcliffe L, Newton P, Denning DW. Long-term antifungal treatment improves health status in patients with chronic pulmonary aspergillosis; a longitudinal analysis. *Clin Infect Dis* 2013 In press.)]

1 General Overview and highlights

This report covers the fourth full year of this nationally commissioned service. The number of new patients testing has increased over the last year; 66 in 2009/10, 58 in 2010/11, 74 in 2011/12 and 89 in 2012/13. The number of deaths (n= 32) was similar to the previous year which included three from Scotland. 18 patients were discharged from service which included one surgical resection. This left a total caseload in March 2013 of 264 patients (not including 12 from Wales and 1 from Northern Ireland).

Significant improvements in the service have included the addition the detection of beta-1,3-D-glucan in blood as a generic marker for fungal infection, provision of additional written information on admission to hospital and embolization, maintaining the high quality of care with a year on year increasing number of patients and regular monitoring and replacement of vitamin D deficiency, especially those on voriconazole. Gamma IFN production deficiency was recognised as being particularly common in CPA patients.

Challenges to the service remain the volume of new patients referred requiring expert input, combined with both substantial patient complexity and large numbers of follow up patients. Both inpatients and outpatients require high level consultant input and often urgent admission. Individual patient requests for third or fourth line therapy are extraordinarily time consuming of consultant time. Travelling distances and cost for some patients and relatives continues to be a problem, often delaying first appointments. The volume of samples being processed by the Mycology Reference Centre continues to rise, and there have many maternity leaves to accommodate. There is a continuing problem with antifungal resistance and drug toxicities (notably photosensitivity with voriconazole and neuropathy with itraconazole and voriconazole). Access to gamma interferon replacement therapy for deficient patients has been very difficult.

2 Activity

The total referrals, inpatient stays, procedures, death and caseload in 2012/13 were as follows:

Activity Measure / Currency	Month Activity												Contract Currency Y/N	Annual Plan †	Year	
	M01 Apr	M02 May	M03 Jun	M04 Jul	M05 Aug	M06 Sep	M07 Oct	M08 Nov	M09 Dec	M10 Jan	M11 Feb	M12 Mar			YTD Actual	YTD Plan
	Referrals	16	27	27	19	27	17	23	19	20	25	24		18	N	0
New Patients Testing	4	6	6	11	9	5	6	6	9	10	5	12	Y	75	89	75
Outpatient - Follow-Up Attendances	65	79	98	95	111	97	97	120	101	102	123	116	N	0	1,204	0
Caseload - Band 1	79	83	84	85	87	97	93	96	95	95	93	95	Y	93	95	93
Caseload - Band 2	123	123	123	123	126	133	133	128	131	134	137	138	Y	155	138	155
Caseload - Band 3	18	18	17	17	16	16	17	18	19	19	19	19	Y	18	19	18
Occupied Bed Days	148	143	145	77	125	20	132	233	70	181	164	175	Y	1,000	1,613	1,000
Inpatient Discharges	7	9	6	7	7	1	6	11	4	8	8	9	N	0	83	0
Surgical Resection	0	1	0	0	0	1	0	0	0	0	0	0	Y	7	2	7
Embolisations	1	1	0	1	0	0	1	2	0	1	2	7	Y	25	16	25
Discharge from Service	3	0	1	1	1	0	2	2	1	2	3	2	N	0	18	0
Deaths	2	1	2	2	3	1	4	5	3	5	4	0	N	0	32	0

* The NCG fund patients from England and Scotland only

Appendix 1 shows the Banding criteria used

Of the 262 new 'aspergillosis' referrals from England and Scotland during the year 2011/12, 89 (34%) had CPA. There were eight inpatient admission diagnoses/transfers. Among the outpatient referrals, the mean time from referral to being seen was 9 weeks, 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 patients are removed, the mean delay between referral and first visit is 7.6 weeks, less than the previous year. Appendix 2 shows the area of residence, date of referral and date of appointment. In addition the service sees 12 patients from Wales and 1 from Northern Ireland and 1 from the Republic of Ireland.

There has been a growth in Band 1 from 79 to 95 patients, Band 2 patients have grown from 124 patients to 138, and Band 3 from 15 to 19 patients. These shifts include 32 deaths and 18 discharges from service. Only 2 patients were presumptively cured with surgery.

Admission days were 1,613, substantially more than forecast at 1000 (61% 'over-performance'), similar to the previous year's 'over performance of 56%. This excludes 213 days spent in the hospital by CPA patients but not on active antifungal therapy, for other reasons, usually IV antibiotics but including one surgical case and one Welsh patient for AmBisome.

3 Service developments and personnel

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

1) Mycology Reference Centre Manchester (MRCM):

1. Expansion of test portfolio
2. Expansion of training and educational activities, including training courses and preceptorships. and hosting university work placement students
3. Development of a Masters degree in Medical Mycology, in collaboration with the University of Manchester
4. Successful business case for a part-time Consultant Medical Mycologist
5. Appointment of a molecular mycology technician
6. Successful business case for a clerical Officer
7. Host for one year a Consultant Clinical Microbiologist from Sri Lanka under the Department of Health's Medical Training Initiative
8. In April 2012 the MRCM, as part of the Manchester Medical Microbiology Partnership, successfully passed a CPA interim accreditation inspection with no non-compliances

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

- A comparison of agar gel double diffusion with counterimmunoelectrophoresis for the detection of *Aspergillus* precipitins
- *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.
- Ongoing evaluation of automated DNA extraction robots in order to respond to the dramatic increase in PCR assay requests

Other assays and services:

- Real-time PCR for *Pneumocystis* DNA
- β -1,3-D-glucan ELISA (Fungitell): a pan fungal assay for fungal cell wall glucan, including *Aspergillus* and *Candida*
- Environmental monitoring (air sampling and dust analysis) of patients's houses, schools and workplaces for indoor moulds, including *Aspergillus*.
- Environmental monitoring of hospital environments for pathogenic fungi: major projects: completed and ongoing commissions from UHSM Estates Department, including dealing with pigeon droppings (*Cryptococcus neoformans* and allergy and high counts of *Aspergillus* in numerous old building areas).
- UHSM neonatal unit: construction and refurbishment: 24 months
- Authoring and adoption of UHSM Aspergillosis Policy

Visitors:

Dr Maithili Kavathekar (Consultant Medical Microbiologist, India)

Staff training for the benefit of CPA patients: environmental mycology course (1 week), Fungal Diversity Centre, Utrecht, Holland

Training:

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

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

Two jointly-organised three-day preceptorships for infectious diseases and haematology specialists from the Middle East and Africa.

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 (6 PAs)

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 (4PAs)

Ioanna Lazana physician in Infectious Diseases (50%)

Ms Deborah Kennedy, Specialist Nurse (75%)
Mrs Georgina Powell, Specialist Nurse (40%)
Miss Deborah Hawker, Specialist nurse (50%) (from October 2012)
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%)
Mrs Christine Harris, NAC manager (100%)
Dr Graham Atherton, Senior Clinical Information Architect (Patient engagement) 25%
Ms Anne Ryan, Medical Secretary (50%)
Ms Debbie Kirby, Medical Secretary (50%)
Mrs Megan Hildrop Clerical Assistant cover (25%)

3) National Aspergillosis multidisciplinary 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 on alternate months (as most cases have now been reviewed) to assess 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, Healthcare 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 heavy to carry. The delivery service has been extended to PCT funded patients with other forms of aspergillosis. By March 2013 157 CPA patients and 25 non-CPA patients were receiving

home delivery with considerable savings rendered to the NHS 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. It has also proved helpful to assess patient status and advise accordingly if they are too ill to attend.

6) Home nursing

Procurement and contract exchange was achieved for home nursing CPA visits, and the first patients selected for this service. However the quality of service delivered by Healthcare at Home has been very variable, and a new tender was in preparation in March 2013 for retendering.

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. In the previous annual report we described its reliability and validity compared with the general health survey (SF-36) and MRC dyspnoea score in 88 patients. It performed well, and was better than the SF36.

We have now examined the sensitivity to clinical response and failure of the SQRQ 122 CPA patients was assessed at baseline and quarterly over 12 months, compared with lung function, BMI, MRC dyspnoea scale and disease severity (Banding). The mean age was 59 years and 45% were female. Overall, patients with CPA had substantial health status impairment at baseline. After treatment, 47-50% gained substantial health improvement with a reduction of score of 14 at both 6 and 12 months, while 32% deteriorated with a rise of 11 and 14 scores after 6 and 12 months of treatment and observation respectively, and 21% were not much different (stable). Patients gained therapeutic benefit irrespective of their illness severity where >50% of those who had "poor" and "very poor" at baseline improved with reduction of ≥ 4 scores after 6 months of treatment. Replicating this analysis using much wider scale, we found that at least 50% of "poor/very poor" health status category at baseline improved significantly to "fair" or "good/very good" categories. Side effects burdened considerably health status. In multivariate analysis, dyspnoea and disease severity defined significantly health status impairment. A higher deterioration rate was seen at 12 months with itraconazole, compared with voriconazole and posaconazole. Using a more stringent change in score of +/-10, at 3, 6 and 12 months, 21 (20%), 25 (26%) and 11 (25%) had marked improvement. Conversely, 15 (14%), 20 (21%) and 6 (14%) had deteriorated significantly, at the same time intervals. There were no striking differences between the different azoles, using this more challenging quality of life shift.

8) ICP applications to the NCG for third or fourth line antifungal therapy

Thirty eight Individual Case Panel (ICP) applications were made in 2012-2013. Of these, 18 were for posaconazole (15 approved, 3 declined), 7 for micafungin intravenously (all approved) and 13 for AmBisome (all 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. There has been an increase in transport difficulties over the last year. Many patients have complained that the journey is not only costly but difficult to make when they are so unwell. While they do not meet the criteria for local transport making a long journey is exhausting, particularly as most are very breathless and often require several modes of transport to get to Wythenshawe. Some local CCG's are helpful but the criteria for assessment is often too rigid and does not allow for the complexity of the patients' symptoms and long difficult journey.

2. Clinical audits

Several clinical audits have been undertaken in 2012/13. Most of these have been completed:

- Vitamin D status
- Smoking history recorded
- Single dose AmBisome efficacy and side effects (extended)
- Frequency of HIV testing
- SQRQ sensitivity to antifungal response
- Survival in CPA patients
- CF genotype in ABPA and bronchiectasis patients
- Gamma interferon production deficiency
- Pneumococcal serotype vaccine responses in CPA, ABPA, SAFS
- Nebulised amphotericin B for patients with ABPA and SAFS

3. Long term posaconazole usage and effectiveness

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

5 Patient engagement

1. Access and availability of meetings to patients and carers

The last 12 months of activity for our Patients & Carers support initiatives has been busy. Our monthly Patient & Carers support groups have been moved to Friday to try to make it more convenient to accommodate more people following a Patient's survey. This reported that 30% of our patients might attend a support group meeting if it was at a more convenient time & place. The meetings now take place on the same day of the week as the main CPA clinic in order to allow people attending the clinic to walk a short distance after their consultation to attend the meeting. This has been successful and has attracted 32% more people to each meeting overall.

Continuing efforts are being made to enable those who cannot attend but would like to listen despite having no computer. We have enabled them to use their phone to listen in. Trials have been successful and this facility will be regularly used in future.

Recordings of each meeting (52 meetings) are available online and have now been watched over 22,000 times. Overall we are having some success in providing support to new groups of people throughout the UK. More people are now able to attend (and are attending) the regular monthly meetings at NAC, some are able to attend local support groups in their area, others have been able to listen in to meetings remotely without the use of a computer. In addition, there are now 1050 patients and carers supported online via Aspergillosis Support Yahoo group, 240 via our Facebook Group and 90 writing their stories on our Wiki page.

2. Topics covered

Some of the subjects covered are listed below:

March 2013	Caroline Hawkrigde	Creative writing projects
March 2013	Riina Richardson	How to avoid exposure to moulds
March 2013	Phil Langridge	Staying strong in hospital
Feb 2013	Dr. Khaled Al-shair	Maintaining or Improving your health status in CPA
January 2013	Debbie Kennedy	Oral Antifungals and TDM
January 2013	Khaled Al-shair	Measuring health status in Chronic Pulmonary Aspergillosis: Lessons we have learnt
January 2013	Reyenna Sheehan	How to use your inhaler
Dec 2012	Graham Atherton	Christmas Quiz
Nov 2012	Libby Radcliffe	Aches and pains
Nov 2012	Malcolm Richardson	Everyday moulds
October 2012	Paul Bowyer	Aspergillus research - What's new
October 2012	Phil Langridge	Nebulisers - What we use and why
October 2012	Chris Harris	Healthcare at Home
Sept 2012	Graham Atherton	Latest Advances - Aspergillosis

August 2012	Jacky Smith	Tackling cough
July 2012	Cheryl Pearse	How to give up smoking at UHSM
June 2012	Caroline Hawkridge	Creative Writing

3. Supporting carers

Carers have only been nominally supported in the past as they accompany patients to our support meetings but their support is vital to aid the effective treatment of a patient. We have started to suggest patients & their carers separate during the meeting in order to facilitate conversations with staff and the carers about issues they feel are important and to give out information relevant to their needs. Two meetings have been attended by a volunteer worker from Manchester Carers Centre (Steve Webster) who has engaged our carers in several conversations and gave the whole group a talk on why support for carers is important to both patient and carer, what support is available and so on. Steve is actively seeking to set up a regular support group with ourselves for our patients and we will supplement those meetings with online support via a dedicated group.

4. Regional support groups

Last year we initiated local support groups that are run by volunteers around the UK and we now have groups in London, Liverpool, Bristol, East Midlands, West Midlands, West Yorkshire and most recently Wigan. Each group holds meetings two to four times a year and actively promotes support for aspergillosis patients via the media, press and specialist hospital departments & GP surgeries. These meetings provide access to NAC support without the need for a computer, and promote active face to face meetings throughout the UK. One or two groups have held online meetings alongside 'physical' face to face meetings to cover their area. All have been successful in identifying and supporting new people suffering from aspergillosis.

5. Damp homes

Part of the support we are asked to provide involves advising people who live in damp, mouldy homes. Our patients are often sensitive to inhaling moulds in the air of their home and can be or become allergic to Aspergillus or other mould spores. It is in their interest to minimise their exposure to allergens and potential infections, so it is also in their interests to minimise the damp in their homes.

We have begun collaborating with the Institute for Specialist Surveyors and Engineers (ISSE: www.isse.org.uk – an educational organisation for the construction trade) with the aim of better understanding how we can help the construction & remediation trades & regulatory bodies prevent damp in new and existing homes and to try to help promote the prevention of health problems caused by damp. This is a complex, multidisciplinary area, as is the understanding of the effects that damp may have on human health so the construction of a 'Damp buildings and Health' organisation should have great benefit in getting academics together with doctors, those in charge of standard construction practices, those who oversee what construction materials are used, those who oversee building construction quality and more. As a first step we have a professional group in LinkedIn entitled 'Damp buildings and human health' which currently has 75 members from a wide variety of backgrounds and is growing fast. There are multiple active

discussions that are on-going in that group and we have identified a number of areas where better information is needed. These include:

Better information is needed in several professions on:

- what the health effects of damp are likely to be
- the impact & severity of likely health effects
- causes & prevention of condensation
- dispute resolution between landlords & tenants based on who is responsible for damp
- how to build/retrofit energy efficient homes that resist damp
- the urgent need for adequate ventilation alongside improved insulation

6 Research outputs, other published research summary

1. Publications 2012

The group published 49 peer-reviewed publications in calendar year 2012 (Appendix 4).

a) Findings affecting clinical practice

1. Chrldle A, Mustakim S, Bright-Thomas RJ, Baxter CG, Felton T, Denning DW. *Aspergillus* bronchitis without significant immunocompromise. *Ann New York Acad Sci* 2012; 1272: 73-85.
2. Chishimba L, Niven RM, Cooley J, Denning DW. Voriconazole and posaconazole improves asthma severity in allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitization. *J Asthma* 2012;49:423-33.

b) CPA related publications

1. Harrison E, Singh A, Smith N, Fraczek M, Moore CB, Denning DW. Mannose binding lectin genotype and serum levels in patients with chronic or allergic pulmonary aspergillosis. *Int J Immunogenetics* 2012;39:224-32.
2. Pendleton M, Denning DW. Multifocal pulmonary aspergillomas – a management challenge. *Ann NY Acad Sci* 2012;1272: 58-67.
3. Brown GD, Denning DW, Gow NA, Levitz SM, Netea MG, White TC. Hidden killers: human fungal infections. *Sci Transl Med* 2012; 4(165):165rv13.

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>

c) Book chapters

1. Richardson MD, Warnock DW. *Fungal Infection: Diagnosis and Management*, 4th Edition. Wiley-Blackwell, Chichester, 2012, pp. 445.

2. Said Khayyata, Moore CB, Richardson MD, Hasleton P, Farver C. Pulmonary Mycotic Infections. In: Spencer's Pathology of the Lung, 6th Edition (Eds. P Hasleton and DB Flieder, Cambridge University Press, Cambridge, pp. 226-287.

2) CPA abstracts presented

Fatigue and poor lung function are significantly associated with impaired health-related quality of life (HRQoL) in a large cohort of patients with chronic pulmonary aspergillosis.

Khaled Al-shair; Graham T. W. Atherton; Deborah Kennedy; Georgina Powell; David W. Denning.

The National Aspergillosis Centre, University Hospital of South Manchester, Manchester University, Manchester UK

Introduction: Fatigue is a prominent disabling symptom in several chronic pulmonary diseases; however, its impact on HRQoL in patients with chronic pulmonary aspergillosis (CPA) has not been investigated.

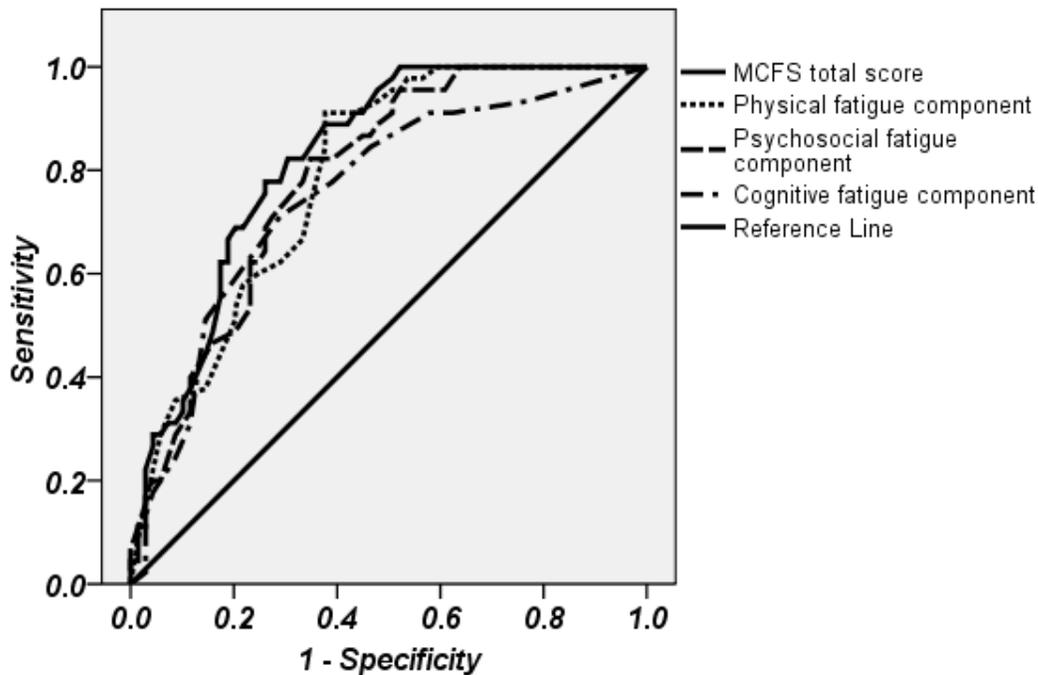
Method: Our 154 patients with CPA completed the Manchester COPD Fatigue Scale (MCFS, Thorax 2009) and the SGRQ in our specialist referral centre. MCFS measures total fatigue and sub-components comprehensively. Lung function and body mass index were measured. Univariate and multivariate linear and binary analysis, and the principal component analysis (PCA) were used.

Results: The mean (SD) age (61.1 (10.8)) years and 44% were female; FEV₁% (63.3 (24.9)), BMI (23.7 (5.2)), SGRQ total score (55.6 (23.5) and MCFS total score (30 (14.9)).

PCA showed that 27 items of MCFS loaded clearly on three components: physical and psychosocial and cognitive fatigue.

Univariate analysis showed a strong association between total SGRQ score and MCFS score ($r=0.81$, $p<0.001$). Using total SGRQ as a dependent variable, linear multi-variate analysis showed that fatigue was the strongest factor ($\beta = 0.83$ $p<0.0001$) associated with impaired health status followed by FEV₁% ($\beta = -0.22$, $p=0.009$), but no statistically significant association with age, BMI and pack/years. This model explained 70% of the variance of SGRQ total score.

Using patients' self-assessment grades of SGRQ (Very poor, poor, fair, good and very good), one-way ANOVA showed that patients with "very poor" health status had the highest fatigue scores (45 (6.4)), following by poor (35 (10.1)), fair (30 (10.4)), good (14 (10.9)) and very good (0) ($p<0.001$). Splitting the group to (very poor and poor) versus (fair, good and very good), the ROC curve analysis indicated significant ability of MCFS and its components to detect change in HS (AUC = 0.82; range 0.75 – 0.9, $p<0.0001$) as demonstrated in figure 1.



Furthermore, binary regression analysis showed that only fatigue score (OR=0.92, 95% CI 0.87-0.97; $p=0.002$) and FEV₁% (OR=1.04, 95% CI 1.01 – 1.07, $p=0.02$) are significantly associated with impaired health status after correcting to age, gender and DLCO%.

Conclusion: This is the first study directly implicating fatigue as a major factor affecting health-related-quality of life in patients with CPA.

The IL1 pathway in defence against *A. fumigatus* and in development on CCPA

Nicola L Smith, Paul Bowyer, Angela Simpson, David W Denning

The University of Manchester, Manchester Academic Health Science Centre, NIHR Respiratory and Allergy Clinical Research Facility, University Hospital of South Manchester NHS Foundation Trust, Manchester, UK

The fungus *Aspergillus fumigatus* can cause chronic cavitary pulmonary aspergillosis (CCPA) in overtly immunocompetent individuals. This is a serious and debilitating condition involving the formation and expansion of cavities within the lung, some containing an aspergilloma. Although overtly immunocompetent, some immunogenetic defect is likely, and a few genetic associations with CCPA are described in small groups of patients.

We analysed SNPs in genes involved in the IL1 pathway in relation to CCPA in a much larger group of subjects ($n=112$ CCPA, $n=279$ healthy). Tagging SNPs were selected to encompass the whole gene, plus up- and down-stream regions. SNPs were identified as associated with CCPA using χ^2 tests. We also analysed the expression of many of these genes and others in co-culture experiments involving macrophages from CCPA patients

stimulated with *A. fumigatus* over 9 hours and compared expression with healthy controls.

SNPs associated with CCPA were found in both IL1B and IL1RN. Macrophages from CCPA patients showed unrestrained rises in the proinflammatory genes IL1A, IL1B and IL6 at 9 hours, with a similar expression pattern in the downstream signalling genes IRAK2, TRAF6 and TREM1. This continued proinflammatory response was in contrast to the reduced expression observed in these genes in the healthy group. This may be linked to a lack of production of the regulatory cytokine TGFB1 at 9 hours.

Association of these SNPs suggests a role for the IL1 pathway in both susceptibility to CCPA and in continuing inflammation and disease progression. Further analysis of these pathways may be useful as a therapeutic option.

27380-Case Report: Pulmonary Arteriovenous Malformation With Proximal Artery Aneurysm: A Newly Described Vascular Pathology With Successful Radiological Intervention

Heather Green, Viveka Biswas, Samantha Decalmer, Pippa Newton, Richard Sawyer, Ray Ashleigh.

Pulmonary arteriovenous malformations (PAVM) are rare but clinically significant findings. They are usually congenital but may be acquired. In the cerebrovascular tree, AVM can be associated with an afferent artery aneurysm. This has never been reported in PAVMs. We describe such a case, and discuss etiology and therapeutic intervention.

Case report: A 75 year old man presented to hospital with 2 weeks of breathlessness, productive cough, and hemoptysis. He was tachypneic (24/minute) and arterial blood gases showed compensated type two respiratory failure. His medical history included pulmonary tuberculosis (TB) aged 10, 15, and 19 years. A contrast-enhanced CT was performed to investigate the hemoptysis and respiratory failure. Prior radiology was limited to chest radiographs. The CT showed 2 vascular nodules thought to be either aneurysms or AVMs (fig 1). Angiography was performed to confirm diagnosis, and to provide treatment. On angiography, Nodule A showed early venous filling in the exiting vein, characteristic of a shunt, indicating PAVM. Nodule B had no features of a shunt nor any associated vessels other than the vessel entering and leaving. This was therefore a saccular aneurysm proximal to the PAVM (figure 2).

The PAVM feeder artery was coiled, then an Amplatz plug deployed within the aneurysm, prior to a Nestor and coils positioned proximal to the plug. The procedure was uncomplicated with complete resolution of hemoptysis. Follow up CT at 6 weeks showed occlusion of both the AVM and aneurysm.

To our knowledge, this is the first description of a PAVM with an associated aneurysm. The case was treated successfully with radiological intervention without complication. Causality is unclear. It is likely that the PAVM was congenital. Although TB is associated with acquired PAVMs, this AVM was in the middle lobe, which had no features of previous TB. Given the presence of a pulmonary artery aneurysm in a patient with an extensive history of TB, a Rasmussen's aneurysm was considered. However, Rasmussen's aneurysms result from weakening of vessel wall due to adjacent cavitary TB: this was not present. It is possible that this aneurysm was due to abnormal, turbulent flow in the afferent vessel of the PAVM as is the postulated cause of aneurysms

associated with cerebrovascular AVM. Regardless of etiology, we have described successful management in a previously unreported pulmonary vascular pathology.

Vitamin D deficiency in asthma patients with Allergic Bronchopulmonary Aspergillosis (ABPA).

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Background: Vitamin D deficiency is being increasingly recognized in chronic lung disease. Recent studies suggest that ABPA correlated with vitamin D deficiency among Cystic Fibrosis (CF) patients, and that heightened Th2 reactivity in ABPA correlated with lower mean serum vitamin D levels. However, this correlation remains unknown in asthma patients with ABPA.

Methods: 144 asthma patients (with ABPA, n=80), (without ABPA, n=64) who attended our hospital between January 2011 and May 2012 were prospectively evaluated for 25-hydroxyvitamin D (25-OHD3), lung function and IgE levels. Patients were retrospectively reviewed for clinical characteristics and prognosis compared with patients with normal VitD levels.

Results: VitD deficiency (<25 nmol/L) occurred in 61(42.4%) of 144 asthma patients of whom 18 (12.5%) were severely deficient (< 25 nmol/L). Patients with ABPA had higher mean serum VitD levels compared with non-ABPA controls, though the difference was not statistically significant (68.8 ± 38.3 nmol/L vs 57.6 ± 35.7 nmol/L ($p=0.59$)). Moreover, the FEV1 was significantly lower in the deficient group compared with the group with normal levels ($P=0.030$). Further, patients with low VitD levels had a poorer prognosis compared to those with normal levels.

CONCLUSION: Our data suggests that asthmatic ABPA patients may have higher vitamin D status than non-ABPA patients and that there may be an association between lung function and Vitamin D status. However, the causal effect relationship needs to be established.

Long term antifungal treatment (LTAFT) is effectively associated with improvement in health status (HS) in patients with chronic pulmonary aspergillosis (CPA)

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Introduction:

CPA is a chronic progressive respiratory infectious disease results in significant lung tissue destruction with a 50%+ 5 year mortality. Response to antifungal therapy is slow, with ~80% of patients who respond doing so by 6 months. We recently demonstrated the reliability and validity of SGRQ in examining HS in CPA (Chest, in press), and now present longitudinal data on the efficacy of LTAFT in improving HS in CPA patients.

Method:

HS of 98 CPA patients were assessed 3 times over 6 months using the well-established standardized SGRQ. CPA severity was assessed using our published CPA banding system. FEV₁, BMI, dyspnoea (using MRC dyspnoea scale) were measured.

Results:

Mean age was 58 years and 48% were female; and 25, 58 and 15 had band 1, 2 and 3 CPA respectively. At visit 2 and 3 (V2 and V3), we found that overall total and domain SGRQ scores were either lower (improved health status) or similar compared to V1 (table 1).

Categorizing the cohort by those who reported improvement or deterioration by a total SGRQ score of ≥ 4 at V3 comparing to V1, we found that 43% improved, 22% remained stable and 35% deteriorated. The median (IQR) of total SGRQ score of the improved group at V3 was 58 (42 – 66) compared to 71 (60 – 79) at V1; and for the deteriorated group was 67.5 (57-76) at V3 compared to 62 (41 – 67) at V1. The deteriorated were older (62 (9.8) years versus 56.1 (9.3) (p=0.008); and trended to have lower BMI, more dyspnoea and worse lung function. Moreover, binary regression multivariate analysis showed that age maintained its association with deterioration in HS (OR 1.13, 95% CI 1.01 – 1.26, p=0.03) after correcting for gender, BMI and FEV₁%.

Of the 37 patients started on an antifungal agent at V1 who took it for 3+ months (including a 3 week IV course of amphotericin B), 22 (59%) improved, 11 (30%) were stable and 4 (11%) deteriorated at V3.

Conclusion,

LTAFT prevented/reduced the progression of CPA and patients preserved overall good HS. More therapeutic approaches for this progressive disease are urgently needed.

Table 1, SGRQ total and domains score in all visits; median (IQR) were presented

	Visit 1	Visit 2	P*	Visit 3	P#
SGRQ symptoms	69 (51-82)	69 (55-82)	0.78	69 (56-82)	0.55
SGRQ activity	54 (36-67)	50 (34-62)	0.045	48 (32-65)	0.02
SGRQ impact	80 (60-93)	79 (58-93)	0.94	79 (60-93)	0.77
SGRQ total score	64 (49-74)	64 (45-73)	0.22	61 (47-72)	0.19

(*)= Compared to visit 1; (#)= Compared to visit 1

Azole antifungal resistance in Aspergillus fumigatus complex: 2010 and 2011

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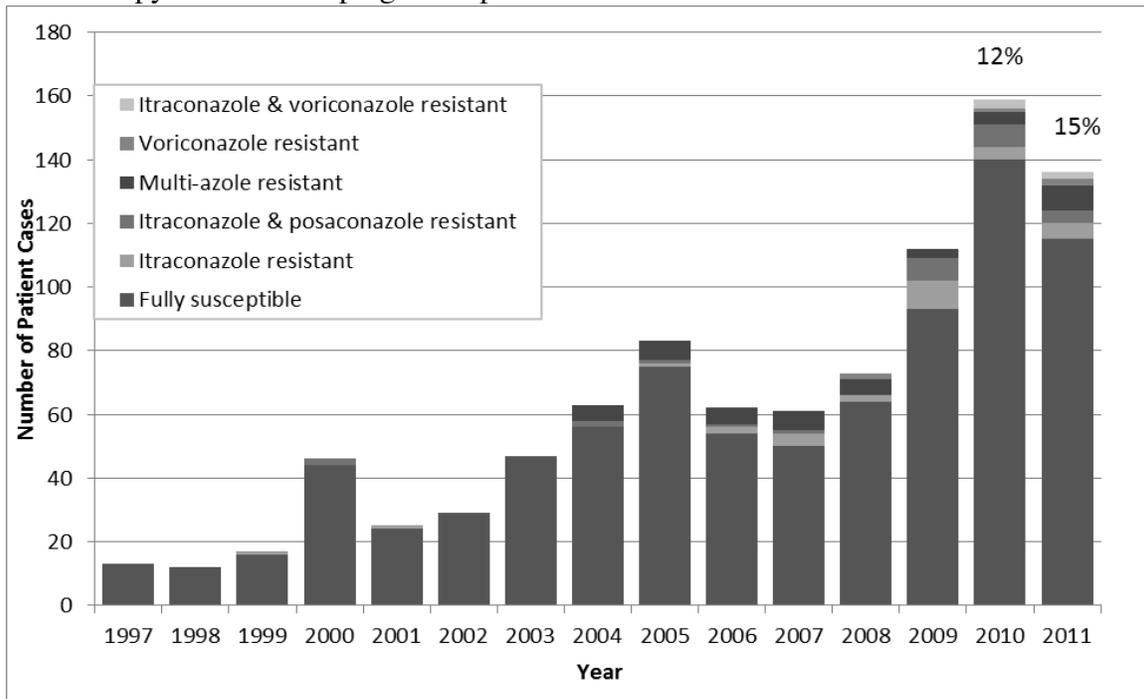
Objectives: Resistance to triazole antifungal agents in *Aspergillus fumigatus* has been increasing in frequency in recent years, primarily in patients with chronic forms of pulmonary aspergillosis. In the Mycology Reference Centre Manchester, 14% and 20%

of patients had resistant isolates in 2008 and 2009, respectively. During this period, 97% of isolates were itraconazole resistant, 3% were only voriconazole resistant and 78% of cases were multi-azole resistant. Here we update our previous experience with data from 2010-11.

Methods: We tested all *A. fumigatus* complex isolates submitted to our centre in 2010 and 2011 for susceptibility to itraconazole, voriconazole and posaconazole, using a modified EUCAST method (final inoculum of 0.5×10^5 CFU/mL). The breakpoint used for resistance was ≥ 4 mg/L for itraconazole and voriconazole, and ≥ 1.0 mg/L for posaconazole.

Results: Of 394 isolates (from 295 patients), 52 isolates (13%) were resistant to at least one azole. Chronic pulmonary aspergillosis was the most common underlying condition (80% of patients). Itraconazole, voriconazole and posaconazole resistance was seen in 87%, 52% and 57% of isolates, respectively. Multi-azole resistance was seen in 29% of isolates. In 2010 and 2011, 12% (n=19) and 15% (n=21) of patient cases had resistant isolates, resp. (graph). Of the 40 patients harbouring a resistant isolate, 93%, 50% and 58% were resistant to itraconazole, voriconazole and posaconazole, resp. Pan-azole resistance was reported in twelve cases (30%), of which 8 were new cases since 2010. Interestingly, cross-resistance between itraconazole and voriconazole, but not posaconazole was observed.

Conclusion: Azole resistance remains of major clinical concern, especially during long-term therapy of chronic aspergillosis patients.



Respiratory symptoms and chronic pulmonary aspergillosis after pulmonary tuberculosis in Gulu, Uganda

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15-25% of Africans treated appropriately for tuberculosis die within a few years of completing treatment. Chronic Pulmonary Aspergillosis (CPA) may be responsible for many of these deaths. CPA is a progressive condition leading to death prolonged fatigue and breathlessness over many years and ultimately death from respiratory failure or sudden massive haemoptysis. A recent controlled trial in India, however demonstrated treatment with generic fixed dose Itraconazole is well tolerated and leads to stabilization or improvement in 76% of patients.

In 1970, 34% of 544 British patients with residual cavities after treated tuberculosis were found

Table 1 – Findings from survey of 400 patients previously treated for tuberculosis in Gulu, Uganda

Finding	All patients N = 400	HIV negative N = 200	HIV positive N = 200	p-value
Median CD4 count	-	-	415 cells/ μ L	-
CD4 below 200	-	-	30 (15% of all HIV positives)	-
Mean time since TB treatment	44 months	42 months	46 months	0.55**
Cough	77 (19%)	31 (15%)	46 (23%)	0.057
Haemoptysis	9 (2%)	4 (2%)	5 (2%)	1.000*
Fatigue	150 (37%)	75 (37%)	75 (37%)	1.000
Breathlessness	149 (37%)	75 (37%)	74 (37%)	0.918
Chest pains	166 (41%)	76 (37%)	90 (45%)	0.155
One or more chronic symptoms	238 (59%)	115 (57%)	123 (61%)	0.415
Pleural thickening on CXR	69 (17%)	45 (23%)	24 (12%)	0.006
Cavities on CXR	97 (24%)	61 (31%)	36 (18%)	0.004
Single	22 (6%)	11 (5%)	11 (6%)	0.990
Multiple	75 (19%)	50 (25%)	25 (13%)	0.001
Aspergilloma on CXR	12 (3%)	5 (3%)	7 (4%)	0.507
Possible	9 (2%)	5 (3%)	4 (2%)	1.000*
Probable	3 (1%)	0	3 (2%)	0.123*
Chronic symptoms and x-ray changes	60 (15%)	36 (18%)	24 (12%)	0.093

Note – p-value for difference between HIV positive and negative cases calculated by chi-squared except for rows marked * where Fishers exact test was used.

to have antibodies to *Aspergillus*. Half of these developed an aspergilloma within a 2 year follow up period. Our group has recently estimated the global 5 year period prevalence of CPA at 0.8 to 1.3 million cases with 43 cases per 100,000 in a representative sub-saharan country (DR Congo). This estimate was based on the results of the 1970 survey and current published data on the frequency of residual cavitation after completing tuberculosis treatment. It does not take account of the possibility of increased susceptibility due to HIV/AIDS.

We aim to measure the prevalence of CPA in Gulu, Uganda. Diagnosis requires a combination of a) chronic respiratory symptoms, b) radiological changes (either aspergilloma or progressive cavitation / pleural thickening on chest x-ray) and c) evidence of *Aspergillus* infection (culture growth from respiratory sample or specific antibodies). We recruited 400 patients who completed tuberculosis treatment within the last 7 years, plus 300 healthy controls, between October 2012 and January 2013. All. Chronic respiratory symptoms were present in 59%. Chest x-ray demonstrated cavitation in 24%, pleural thickening in 17% and aspergilloma in 3%. Overall x% of patients had both chronic symptoms and x-ray changes consistent with CPA.

These initial results suggest that CPA may well be a common complication of treated pulmonary tuberculosis. Serum has been taken from patients and will be screened for antibodies to *Aspergillus*. We plan to perform a re-survey of this cohort in 2014 with repeat chest x-ray. This will allow us to identify progression of cavitation. We will then be able to state the frequency of CPA as a complication of tuberculosis in this African population.

7 Statutory reports

MRSA

No cases of MRSA.

C. difficile infection

One case of *C. difficile* infection reported.

No HIRS reported and no complaints

SUI's

None

8 Financial position

Expenditure 2012/13

The original plan for 2012/13 was set at £2.7m excluding drug costs.

During 12/13 the NCG contract operated via a block base supplemented by activity related marginal rate variable payments. Drugs expenditure was managed s part of the contract as a direct pass through.

The activity based contract performance in 2012-13 was £2.73m against a plan of £2.66m

The £64k overperformance included better than planned performance against occupied bed days which were 613 above plan and despite better than expected referrals patient numbers were lower than expect, the particularly within band 2.

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	75	£109,500	89	£129,940
Band 1	93	£190,278	95	£194,370
Band 2	155	£561,720	138	£500,112
Band 3	18	£81,846	19	£86,393
Total Banded	266	£833,844	252	£780,875

Occupied Bed Days	1,000	£262,000	1,613	£422,606
Surgical Resections	7	£75,859	2	£21,674
Embolisation	25	£28,600	16	£18,304
Fixed Service Element		£1,353,750		£1,353,750
Total		£2,663,553		£2,727,149

Drug expenditure increased significantly (44%) compared to 2011/12 compared to 2011/12 rising from £2.5m to just over £3.5m.

Financial Forecast 2013/14

The 13/14 contract is set at £6.5 m and includes a fixed element of £1.35m with the balance attributable to achievement of agreed patient numbers, activity levels and in a change from 2012/13 again includes drugs.

9 Future developments

Developments planned for 2012/13 include:

- Procurement and implementation of an IV antifungal at home service to minimise hospital stay.
- Evaluation of non-*fumigatus* IgG antibody tests for patients with negative *fumigatus* IgG antibody.
- Comparison of different Aspergillus antibody tests in a comprehensive standardised way with UK and Ugandan samples, comparing 6 different tests.
- Reporting of the histological findings of *Aspergillus* nodules, a newly discovered sub-type of CPA.
- Reporting and analysing the parameters associated with prolonged survival in CPA.
- Completion of the audit on repeated courses of amphotericin B on CPA status.
- Audit of the utility of induced sputum to capture Aspergillus by culture or PCR, as opposed to expectorated sputum.
- An Education Fellow (pre-SPR) to join the service, to assist with providing continuity of care for inpatients and assist in multiple teaching activities.
- A teaching academic consultant to be appointed to contribute primarily to non-CPA patients and provide high level MSc teaching in the University.
- An additional band 5 (newly qualified) nurse to join the nursing team to reduce the routine tasks of our most experienced specialised nurses.

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-mycobacterial 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