NHS England National Commissiong Group Chronic Pulmonary Aspergillosis national service

The National Aspergillosis Centre

Annual Report 2013-2014

Aspergillus in a well-loved pillow

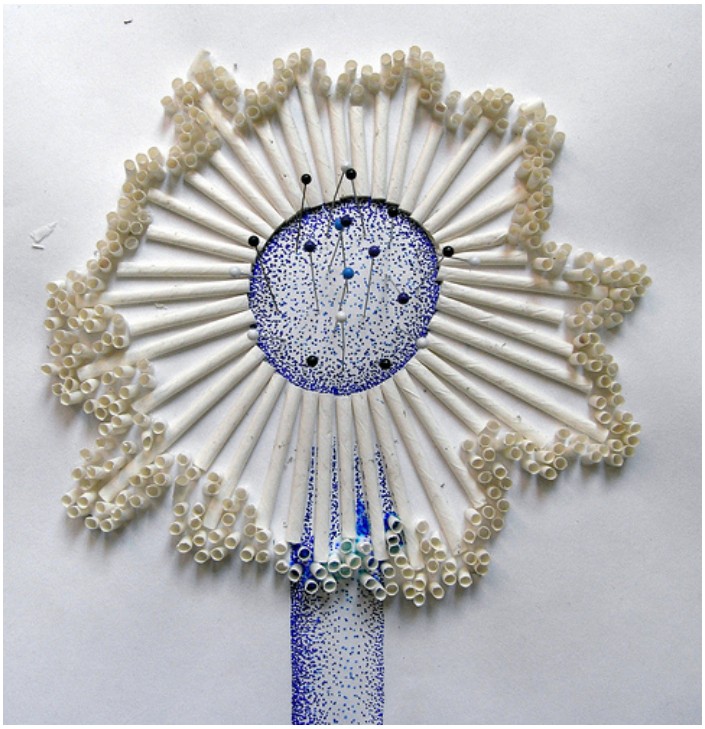
All night
you breathe
my hyphae.

Your white blood cells seek,
then eat me; snip, stop
my stitch-up.

You won't face months
of coughing up buttons, dark
mucous plugs.

No x-rays for balls of my silks.
No drugs trying to heal where I left
all my needles.

Caroline Hawkridge,
Writer-in-Residence,
National Aspergillosis Centre



Sarah Woodward, Stockport College

Contents

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 and a big jump to 125 in 2013/14. The number of deaths (n= 51) was higher than the 32 in the previous year. 16 patients were discharged from service. This left a total caseload in March 2014 of 312 and increase from 264 patients at the end of the prior year. These figures do not include 11 from Wales and 1 from Northern Ireland.

Consistent antibody testing for protection against Pneumococcal and *Haemophilus* antibodies and immunisation until protection complete, may be responsible for the marked reduction in admissions to hospitals. Vitamin D replacement has also been more consistently applied. A high quality database for drug interactions has improved prescribing, and has been released online through The Aspergillus Website and made into an app.

In 2013/14 there was no growth in consultant sessions until March when a fourth consultant joined the team so a major continuing challenge to the service remains the volume of new patients referred requiring expert input, combined with both substantial patient complexity and large numbers of follow up patients. Individual funding requests for third or fourth line therapy have been 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. Antifungal resistant rates remain above 10%. Drug toxicities (notably photosensitivity with voriconazole and neuropathy with itraconazole and voriconazole) prevent continued therapy in many patients who are improving on therapy. Access to gamma interferon replacement therapy for deficient patients has been almost impossible, because of changes to the approval process within the NHS.

The NAC is augmented by several othr developments including the appointment of 3 new senior academics doing basic and translational science in Aspergillus, the continued growth of the encylopaedic Aspergillus Website, education programs in fungal diseases, notably a 12 month Masters course in Medical Mycology and the online LIFE program (Leading International Fungal Education) in english and Spanish and an extensive series of external postgraduate talks on aspergillosis, across the world. Three honorary professors were appointed in 2013 to support the service and especially its education programs; Dr David Warnock, lately of the US Centers for Disease Control, Dr Juan Luis Rodrigues Tudela, lately of the Sapnish Mycology Reference Laborarory, now at the Global Action Fund for Fungal Infections (GAFFI) in Geneva and Dr Peter Donnelly from University Hospital in Nijmegen and Chairman of the EORTC Infectious Diseases Group. International activity to improve patient outcomes across the world is being co-ordinated by GAFFI, including a focus on chronic pulmonary aspergillosis after TB, and it was launched in London, New York, Sao Paolo and Delhi in late 2013.

2 Activity

The total referrals, inpatient stays, procedures, death and caseload in 2013/14 were as follows:

Activity Measure / Currency	Month Activity												YTD Actual*
	M01 Apr	M02 May	M03 Jun	M04 Jul	M05 Aug	M06 Sep	M07 Oct	M08 Nov	M09 Dec	M10 Jan	M11 Feb	M12 Mar	
Referrals	25	30	27	19	35	21	37	34	23	22	24	25	317
New Patients Testing	5	7	10	5	13	8	19	10	9	9	9	2	125
Outpatient - Follow-Up Attendances	139	122	85	104	125	86	126	119	87	142	106	126	1,367
Caseload - Band 1	95	97	98	104	103	102	110	117	118	122	122	127	127
Caseload - Band 2	147	148	150	142	149	155	155	157	161	162	163	159	159
Caseload - Band 3	18	17	16	20	21	21	24	24	23	24	23	24	24
Occupied Bed Days	102	51	96	185	57	173	87	156	88	35	60	8	1,098
Inpatient Discharges	4	4	4	6	3	6	3	7	5	4	3	2	51
Surgical Resection	0	2	0	1	0	0	0	0	0	0	0	1	4
Embolisations	1	1	0	1	0	2	0	2	0	1	0	0	8
Discharge from Service	3	0	1	3	0	0	1	2	1	0	4	1	16
Deaths	3	7	1	3	5	3	1	3	6	7	3	3	51

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

Of the 317 new 'aspergillosis' referrals from England and Scotland during the year 2011/12, 125 (39.4%) had CPA. There were eight inpatient admission diagnoses/transfers, of whom seven died. Among the outpatient referrals, the mean time from referral to being seen was 7 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 6 weeks, less than the previous year. In addition the service cares for 11 patients from Wales and 1 from Northern Ireland and 1 from the Republic of Ireland.

There has been a growth in Band 1 from 95 to 127 patients, Band 2 patients have grown from 138 to 159, and Band 3 from 19 to 24 patients. These shifts include 51 deaths and 16 discharges from service. Four patients were presumptively cured with surgery.

Admission days were substantially lower than the previous year at 1,098 compared with 1,613, almost in line with the forecast of 1000. 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 Mycology Reference Centre, Manchester

The Mycology Reference Centre Manchester (MRCM) has completed its fifth year of operations. There have been many developments in its portfolio of tests and activities as well as continued growth in testing.

1) Primary activities and developments:

1. Ongoing validation and familiarisation of new tests in portfolio
2. Expansion of training and educational activities, including short training courses, and hosting university work placement students who have successfully completed their IBMS Registration portfolios.
3. Highly successful completion of the first year of a Masters degree in Medical Mycology, in collaboration with the University of Manchester. This Masters is accredited by the Institute of Biomedical Sciences, and individual units are accredited by the Royal College of Pathologists
4. Band 5 Healthcare Scientist post made permanent
5. Clerical Officer appointed and in post
6. Successful business case made and appointment of a Band 2 MLA
7. Income: internal and external: increase of 6.3% compared to 2012-2013
8. Income: environmental monitoring business unit: increase of 68% compared to 2012-2013
9. Environmental surveillance services: projects commissioned by UHSM Estates Department/UHSM Infection Control unit: complying with the UHSM policy: "Prevention of Nosocomial Invasive Aspergillosis During Demolition/Construction and Renovation Activities"
    - Heart Biopsy Suite
    - Transplant Out Patients Department
    - ENT Theatres: ventilation system upgrade
    - Catheter Laboratories
    - Completion of Neonatal Unit extension project
    - Paediatric OPD Courtyard Project
10. Highly successful organisation and running of 50th Anniversary Meeting of the British Society for Medical Mycology, April 2014: 143 attendees
11. Publications 2013: 21 (Appendix 3)

2. Developments and research activities:

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

- Evaluation of a lateral flow device (ISCA Diagnostics/OLM Medical) for the detection of an Aspergillus exoantigen
- 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

- Ongoing evaluation of improved methods for detection of anti-*Aspergillus* antibodies
- Methods development and validation of pyrosequencing for detection of azole antifungal resistance mutations in *Aspergillus fumigatus* in respiratory samples
- Monitoring of NAC/CPA patients houses, workplaces for *Aspergillus*

Other services for non-CPA patients:

- Real-time PCR for Pneumocystis DNA
- Successful launch and sustained demand for the ß-1,3-D-glucan ELISA test (Fungitell): a pan fungal assay for fungal cell wall glucan, including *Aspergillus* and *Candida*, offered nationwide
- Environmental monitoring (air sampling and dust analysis) of patients's houses, schools and workplaces for indoor moulds, including Aspergillus.

3. Training:

- Ongoing 4 year training programme for two trainee clinical scientists funded by NHS NW SLA. One has been employed as a Band 7 Clinical Scientist in Edinburgh Royal Infirmary. One appointed as a five-year Higher Specialist Scientific Training post at Manchester Royal Infirmary
- Ongoing three-year Healthcare Scientist training post under the Department of Health's Modernisation of Scientific Careers scheme.
- UCL/BSMM distance learning Masters in Medical Mycology: one staff member enrolled
- Individual modules of University of Manchester Masters in Medical Mycology, in collaboration with MRCM approved by Royal College of Pathologists and awarded 75 credits
- All three Clinical Scientist trainee students gained distinction in their Masters courses (two University of Manchester, one University of Nottingham
- Contributions to the development of an on-line histopathology of fungal infections training course, in collaboration with LIFE and GAFFI.

4. Challenges:

- Ongoing leave entitlements of staff, and part-time returns to work

4 Clinical service developments and personnel

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

1) <u>Clinical and administrative personnel</u>

The following staff were appointed or redeployed to contribute to the NAC:
Professor David Denning, Professor of Medicine and Medical Mycology (5 PAs)
Dr Pippa Newton, Consultant in Infectious Diseases (6 PAs)
Dr Eavan Muldoon (5 PAs)
Dr Chris Kosmidis (5 PAs)
Dr Ibrahim Hassan, Consultant in Microbiology (1 PA)

Dr Riina Richardson, Consultant in Oral Microbiology & Infectious Diseases (4 PAs)
Ioanna Lazana physician in Infectious Diseases (50%)
Ms Deborah Kennedy, Specialist Nurse (40%)
Mrs Georgina Powell, Specialist Nurse (80%)
Ms Deborah Hawker (50%)
Mr Philip Langridge, Senior Specialist Physiotherapist (50%)
Miss Reyenna Sheehan, Specialist Physiotherapist (20%)
Dr Iain Page, Clinical Fellow (100%)
Dr Gemma Hayes, Clinical Research Fellow 100%
Mrs Christine Harris, NAC manager (100%)
Dr Graham Atherton, Senior Clinical Information Architect (Patient engagement) 25%
Ms Marian Webster (50%)
Ms Debbie Kirby, Medical Secretary (50%)
Mrs Megan Hildrop Clerical Assistant cover (25%)

2) 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/fortnightly clinic – This clinic is held fortnightly to deal with backlog of referrals and immunology referrals. If the immunology referrals are complex they are referred to Dr Hana Alachkar at Salford. This clinic was discontinued in January 2014, because Dr Alachkar could not continue.

DFS (discharge from service) –Patients are discharged from service when appropriate and can also be referred back to service if deterioration of disease occurs.

Infectious Diseases 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 CTs, embolisation etc.

4) Home delivery of antifungal agents
Healthcare at Home continue 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 CCG funded patients with other forms of aspergillosis. There was a problem in delivery

during the year, and no new patients were registered to receive antifungal delivery. By March 2014 142 CPA patients and 32 non-CPA patients were receiving home delivery with considerable savings rendered to the NHS and extremely few problems. About 40 patients are waiting to be registered for home delivery of antifungals.

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 specimen containers, and some complaints from laboratory staff. As Aspergillus PCR on sputum is not available elsewhere in the country, some of these samples are also transported in the post. PCR much more sensitive than 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

Home nursing follow up service for CPA patients at home has been discontinued. The quality of service delivered by Healthcare at Home was too variable to be useful.

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

The St. George's Respiratory Questionnaire (SGRQ) is routinely and frequently used as a proxy measure of patients' well-being or quality of life as it is widely used for several chronic respiratory diseases.

8) ICP applications to NHS England for third or fourth line antifungal therapy

Forty nine Individual Case Panel (ICP) applications were made in 2013-2014. Of these, 26 were for posaconazole (20 approved, 6 declined), 11 for micafungin intravenously (all approved) and 6 for AmBisome (all approved). The applications were assessed by a highly experienced part clinical panel on the basis of a detailed summary of each patient's 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.

5 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 when urgent cases are booked in, this pushes back routine appointments. Adhoc clinics were added in where appropriate. There have been another increase in transport difficulties over the last year, compared with the prior 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 2013/14. Most of these have been completed:

- Aspergillus PCR (completed, being written up)
- CF genotype in ABPA (ongoing)
- Vitamin D (comleted and presented)
- Multi-azole resistant cases (in analysis)
- Induced sputum yield of Aspergillus PCR and culture (completed, being written)
- Aspergillus nodules and masses (presented, being written up)
- Smoking history recorded (completed, feedback provided)
- Single and multiple dose AmBisome efficacy and side effects for CPA (completed, and being written up)
- Frequency of HIV testing (completed, feedback provided)
- SQRQ sensitivity to antifungal response (completd and published in Clin Infect Dis)
- Survival in CPA patients (Completed, presented and submitted for publication)
- Gamma interferon production deficiency (Completed, presented, being written up)
- Nebulised amphotericin B for patients with ABPA and SAFS (Completed, presented and in press in J Asthma)

6 Patient and public engagement

1. Aspergillus Website @ *www.asperweb.co.uk*

The most used resource for patients & carers to access information about aspergillosis in its many forms, though NAC patient surveys in the past have suggested that it is only accessed by approximately 51% (2012) then 54% (2013) of our patients and this is largely because they have no access to the World Wide Web (i.e. no computer to browse or internet connection). Over the last 12 months significant effort has been made to overcome some of these barriers by remodelling the website dedicated to patients so that it can be more effectively read using the new smaller and cheaper browsing devices available on smartphones and tablets. It is gratifying to note that the most recent patient's survey (Appendix 2) shows use of The Aspergillus Website by patients has risen to 57% - a marked improvement and our highest ever figures.Satisfaction with the website stayed at 99%.

2. Patients & carers support meeting

This monthly meeting aims to give support to all who attend the NAC clinics. This allows people who do not have computer access to find informal support from NAC staff and is intended to encourage face to face social support between patients & carers. The meeting was attended by 7% of all patients who responded to the patient's survey in 2014 whereas 6% attended in 2013. This increase may have something to do with the change in venue to be closer to NAC clinic and it being held on a Friday to coincide with the main clinic day. We have recorded many (30%) more new people attending the meeting since the move. Around 160 people have attended this meeting since inception which is attended by 8 – 12 people each month. The meetings are lead and organised by Dr Graham Atherton and Chris Harris. The subjects covered and their on-line links are listed below. As of July 2014 they had been accessed over 31,000 times.

April 2013	Mike Bromley	New antifungal drugs
April 2013	Iain Page	TB & Aspergillosis in Gulu, Africa
April 2013	Led by Graham Atherton	Entire meeting
May 2013	Phil Langridge	Managing Breathlessness
May 2013	Alison Wearden	Psychology: Stress and aspergillosis
May 2013	Led by Graham Atherton	Entire meeting
June 2013	Steve Webster	Caring for Carers
June 2013	Graham Atherton	Damp Homes & Health
June 2013	Led by Graham Atherton	Entire meeting
July 2013	Julia Hamer	NHS New Structure and NAC
July 2013	Graham Atherton	Heat waves
July 2013	Graham Atherton	Side effects of medications
July 2013	Led by Graham Atherton	Entire meeting
August 2013	David Denning	Management of Chronic Pulmonary Aspergillosis
August 2013	Graham Atherton	IgE summary for the layperson
August 2013	Led by Graham Atherton	Entire meeting
September 2013	Eavan Muldoon	Comparing parts of UK & US Healthcare systems
September 2013	Graham Atherton	IgG - summary for the layperson
September 2013	Led by Graham Atherton	Entire meeting
October 2013	Danielle Yuill	Giving patients a VOICE project (Patients helping in research

		at NAC)
October 2013	Graham Atherton	Interpreting chest X-rays
October 2013	Led by Graham Atherton	Entire meeting
November 2013	Caroline Hawkridge	Using Creative Projects to enhance awareness
November 2013	Graham Atherton	How antifungal drugs work
November 2013	Led by Graham Atherton	Entire meeting
December 2013	Led by Graham Atherton	Christmas Quiz 2013
January 2014	Graham Atherton	New antifungal drug class reported
January 2014	Pippa Newton	What is Pseudomonas?
January 2014	Led by Graham Atherton	Entire meeting
February 2014	Graham Atherton	Building offline community (Entire meeting)
March 2014	Graham Atherton	Offline community building

One comment from participants is the inability of nurses to attend the meeting since the move to Fridays was a drawback.

3. Regional support groups

Most of those people who do not attend the support meeting at NAC (70%) cite the reason as 'not held at a convenient time or place'. This means that we are still missing a reasonable fraction of our patients & carers need for support, though of course some of those will find support online in our online support groups. One solution to this was to encourage the setting up of regional support groups run by volunteer patients and we now have six active groups throughout the UK that meet at least a few times a year. Most are used by quite small numbers of people (2 – 5) and meetings act as simple social events for people to meet others with the same illness but one in particular (Wigan) has a highly active leader and hosts 10 – 15 people every month with invited speakers.

Each group advertises its presence with the local medical organisations, performing two services: offering a service to medical professionals as well as patients and increasing awareness of aspergillosis nationally. Each group is dependent upon its leader to be well enough and have the time & energy to give to run the group so meetings are often only held sporadically.

Useful as these local meetings are in themselves it is hoped that such meetings could become a focal point that provides computer access so that a member of NAC staff could 'attend' the meeting remotely online and the Wigan &West Midlands groups are about to begin that practice regularly. One such online meeting has been held for the London

group too with some success (overall 6 attended though these where not restricted to the south east of the UK). A national (international) meeting was trialled successfully too at a meeting of a group in San Francisco with 12 attending.

The 2014 patient's survey showed that 49% of people were aware of our regional support groups, which is encouraging as is the 11% who want more information about setting one up. 5% have gone so far as to make contact with a group.

4. Patients communities

The new Patient's Website [www.nacpatients.org.uk] received 15,000 unique visitors in June 2014 though transfer from the old website was very incomplete at that time. There are long standing online communities on Yahoo! (1106 members and an average of 250 messages per month) and Facebook (370 members and very active), as well as 400 LinkedIn members (Aspergillus and Aspergillosis Group).

The group of patients & carers that attend the monthly support meeting at NAC have played an integral role in developing and publishing the NAC community booklet that is being published quarterly and distributed to all patients via the clinics at NAC. This booklet is intended to bring some of the information and support available online to those who cannot get access to a computer. Given that slightly more than 40% of our fall into this category that should mean that in the average week when we see 60 patients around 25 will not be able to access the internet. It is therefore gratifying that we are seeing 20 booklets a week being taken away from the clinic as it looks like we are fulfilling a need in a way that most of those patients find useful and accessible.

5. Poetry

The work of Caroline Hawkridge the NAC poet in residence has resulted in several major outputs. These include:

1. Contributions to a themed issue of the journal Philosophy, Activism and Nature (http://www.panjournal.net/issues/10):

Aspergillus in a well-loved pillow by Caroline Hawkridge,
Filamentous fungi by Caroline Hawkridge

2. Poetry readings at the international launch of the Global Action Fund for Fungal Infections at the House of Commons by the actor Rupert Everett.

3. *Aspergillosis Support Group Poem* written with Caroline Hawkridge, Writer-in-Residence, National Aspergillosis Centre

Hope is…'

Hope is when someone listens to me,
when they hear what I say.
Hope is when tomorrow is another day
and not just yesterday again.

Hope is daffodils and a bright shining light

at the end of a VERY dark tunnel.
Hope is feeling happy or at least normalised
when pain goes intolerable.

Hope is the spring that will come soon
and bring along the flowers that bloom.

Hope is that a solution may be found
to release me from the pain,
that there's better times to come.
Hope is having another day to spend
with my children and grandchildren.

Hope is friends out there we can turn to
for 'been there done that' advice
& 'this is how I coped with it'.
Hope is successful treatment
and seeing tomorrow's dawn and sunset.
Hope is breath for many years to come.

Hope is not for today. For today, to get out of bed, is all I can do
and its hours and hours before I can lay down my head.
But hope is for tomorrow, when all will be well
and this is the story I myself will tell.

Hope is like the sea that touches every part
of our planet no matter where patients live.
Together we can build "A SEA OF HOPE"
that anyone & Everyone can either dive
into or just "Dip their own toe".

Hope is to do some, to *do it yourself,*
that tomorrow is as good as today.

Hope is when someone listens to me,
when they hear what I say,

when they hear what I say.

7 Research outputs, other published research summary

1. Publications 2013
The Fungus@Manchester group published 49 peer-reviewed publications in calendar year 2013 (Appendix 3).

a) Findings affecting clinical practice

1. Agarwal R, Chakrabarti, A, Shah A, Gupta D, Meis J, Guleria R, Moss R & Denning DW. (2013). Allergic bronchopulmonary aspergillosis: review of

literature and proposal of new diagnostic and classification criteria. *Clin Exp Allergy*, **43**(8):850-73.

2. Baxter C, Dunn G, Jones A, Webb K, Gore R, Richardson M & Denning DW. (2013). Novel immunologic classification of aspergillosis in adult cystic fibrosis. *J Allergy Clin Immunol,* **132**(3):560-566.

3. Haylett A, Felton S, Denning DW & Rhodes L. (2013). Voriconazole-induced photosensitivity: photobiological assessment of a case series of 12 patients. *Br J Dermatol,* **168**(1):179-85.

b) CPA related publications

1. Al-Shair K, Atherton G, Harris C, Ratcliffe L, Newton P & Denning DW. (2013). Long-term Antifungal Treatment Improves Health Status in Patients With Chronic Pulmonary Aspergillosis: A Longitudinal Analysis. *Clin Infect Dis*, **57**(6):828-35.

2. Al-shair K, Atherton GT, Kennedy D, Powell G, Denning DW & Caress A. (2013). Validity and reliability of the St. George's Respiratory Questionnaire in assessing health status in patients with chronic pulmonary aspergillosis. *Chest*, **144**(2):623-31.

3. Baxter C, Denning DW, Jones A, Todd A, Moore C & Richardson MD. (2013). Performance of two *Aspergillus* IgG EIA assays compared with the precipitin test in chronic and allergic aspergillosis. *Clin Microbiol Infect*, **19**(4):E197-204.

4. Denning DW, Pleuvry A & Cole D. (2013). Global burden of allergic bronchopulmonary aspergillosis with asthma and its complication chronic pulmonary aspergillosis in adults. *Med Mycol*, **51**(4):361-70.

5. Denning DW, Pleuvry A & Cole D. (2013). Global burden of chronic pulmonary aspergillosis complicating sarcoidosis. *Eur Respir J*, **41**(3):621-6.

6. Farid S, Mohamed S, Devbhandari M, Kneale M, Richardson M, Soon SY, Jones MT, Krysiak P, Shah R, Denning DW & Rammohan K. (2013). Results of surgery for chronic pulmonary aspergillosis, optimal antifungal therapy and proposed high risk factors for recurrence - a National Centre's experience. *J Cardiothoracic Surgery*, **8**(1):180.

7. Hayes G & Denning DW. (2013). Frequency, diagnosis and management of fungal respiratory infections. *Curr Opin Pulm Med*, **19**(3):259-65.

8. Howard S, Pasqualotto A, Anderson M, Leatherbarrow H, Albarrag A, Harrison E, Gregson L, Bowyer P & Denning DW. (2013). Major variations in *Aspergillus fumigatus* arising within aspergillomas in chronic pulmonary aspergillosis. *Mycoses*, **56**(4):434-41

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, Rautemaa R. Aspergillus and Aspergillosis. In book Molecular Biology of Food and Water Borne Mycotoxigenic and Mycotic Fungi of Humans. Ed. R. Russell M. Paterson. CRC Press, Boca Raton, FL, USA, 2013.

2. Said Khayyata, Caroline B Moore, Malcolm D Richardsobn, Philip Hasleton, Carol Farver. (2013). Pulmonary mycotic infections. In Philip Hasleton, Douglas B Flieder (Ed.), Spencer's Pathology of the Lung. (1, pp. 226-287). Cambridge: Cambridge University Press.

2) CPA and aspergillosis abstracts presented

Chartered Society of Physiotherapy Annual Congress, Birmingham June 2013

Nebulised/ Bronchoscopically-instilled N-acetylcysteine for mucoid impaction
Langridge PJ, Denning DW

Introduction: Patients with acute or chronic bronchopulmonary disease may develop mucoid impaction. First line therapies include chest physiotherapy, normal/hypertonic saline, DNase, or oral mucolytics. N-acetylcysteine (NAC) is a mucolytic agent. Administration of nebulised NAC has the potential to reduce the need for bronchoscopy. NAC is available in the UK as a 20% (200mg/ml) sterile solution for injection.
Method: A literature search was conducted and other centres were contacted to investigate their use of NAC.
Results: There are few trials but several case reports in the literature relating to nebulised NAC. This literature was critically evaluated with comments on the historical constraints and how this is relevant to current practice. Safety and efficacy provided the focus for evaluation.

Key points about N-acetylcysteine	
Pros	**Cons**
Mucolytic	Sulphurous smell
Generally well tolerated	Acetylcysteine is not compatible with rubber, iron, copper and nickel
Readily available in hospitals	May provoke bronchospasm
Inexpensive	In vitro, NAC may antagonize aminoglycoside and ß-lactam antibiotics. In vitro NAC at concentrations less than 10% inhibits the growth of Pseudomonas strains, potentially causing false-negative sputum cultures
	Oxygen inactivates NAC
	Liquefies secretions that may need clearing

Subsequently, nebulised 20% NAC has been delivered by the Aspergillosis service respiratory physiotherapists using a PariSprint® nebuliser. A challenge test was conducted to ensure patient safety, and no adverse events were reported/observed
Conclusion: Instillation of NAC at bronchoscopy could resolve severe cases of mucoid impaction, and this is supported by cases in the literature. Nebulised NAC appears well tolerated but challenge testing is recommended to ensure safety. Centres routinely using NAC are encouraged to document and publish their experiences. Previous literature evaluating nebulised/ instilled NAC frequently does not relate to current practises (e.g. nebuliser outputs and treatment outcome evaluation). For a tertiary lung centre, NAC provides an alternative to existing therapies to treat mucoid impaction in a range of respiratory conditions. Future rigorous study investigating efficacy in treating mucoid impaction is warranted.

The Role of Physiotherapy in the National Aspergillosis Centre
Langridge PJ and Sheehan R

Introduction: The National Aspergillosis Centre (NAC) treats patients with a variety of complex problems associated with an Aspergillosis diagnosis. Antifungal treatment is costly and evidence for cost-effectiveness is essential. Sputum samples obtained at patients' clinic visits aid diagnosis/management. Respiratory physiotherapists were initially recruited to the NAC team to procure these sputum samples during clinic visits. This role has broadened over time. To date no publications describe the physiotherapy role in Aspergillosis disease management. Worldwide there are only two known physiotherapists specialising in Aspergillosis or Aspergillus-related diseases.
Results: Service users are surveyed annually about their experiences of NAC physiotherapy input. 99% of those struggling to provide sputum samples managed to do so after physiotherapeutic interventions. Annual survey of service users showed 87% were very satisfied with the service and the remaining 13% were satisfied.
Physiotherapist interventions include: nebulised medication challenge testing, exercise advice/testing; pulmonary rehabilitation referral; instruction in airway clearance techniques; dysfunctional breathing assessment/treatment; sputum induction.
Conclusion: Physiotherapy contributes significantly to the management of those attending the National Aspergillosis Centre. Future work could include further improving accessibility to physiotherapists for service users, as well as more stringent evaluation of physiotherapeutic interventions e.g. longitudinal studies.

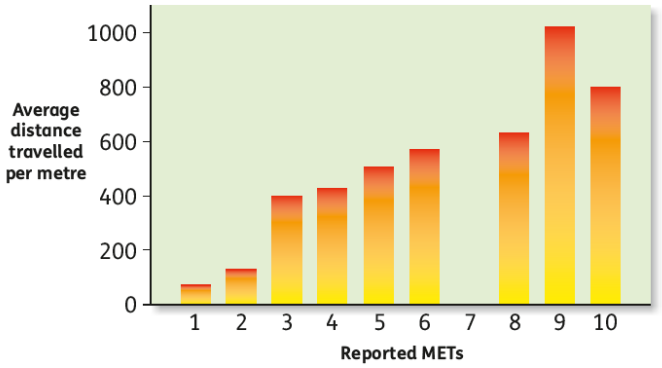
Reported Metabolic Equivalent of Task (MET) as a predictor of performance in incremental shuttle and six minute walk tests
Langridge PJ

Introduction: It may be desirable for the clinician to assess exercise capacity. Historically this takes the form of a subjective report and/or an observed exercise tolerance test. Two such tests used are the 6 minute walk test (6MWT) and the incremental shuttle test (ISWT). However, neither of these is readily applied to large numbers of patients ad hoc in the outpatient clinic setting. An alternative was sought. There is little published work comparing patient self-report of MET values and measured performance in field walking tests. The Veterans Specific Activity Questionnaire (VSAQ) uses MET values and has been validated to estimate exercise tolerance in patients referred for laboratory exercise testing. What relationship it has to distance travelled in field walking tests had not previously been determined.
Method: Patients attending routine pulmonary function testing or ambulatory oxygen assessment completed the VSAQ before undertaking their ISWT (n=80) or 6MWT (n=30) tests, a sample of

convenience with cardiac/respiratory diagnoses. Participants undertook their planned field walking tests but additionally were asked to complete the VSAQ. Data was collected by respiratory physiologists.

Results:

VSAQ correlated more closely with ISWT (n=26) than 6MWT(n=30) (0.73 vs 0.46, significance $p<0.01$ and <0.001 respectively**).** Subsequent paired t-test analysis of ISWT (n=80) and VSAQ showed significance <0.001 with a Pearson correlation of 0.67.



Conclusion: The reported MET values using the VSAQ correlated more closely with the ISWT than the 6MWT. Consideration of VSAQ as a measurement of exercise capacity appears justified. Comparisons with other outcome measures e.g. MRC score / quality of life scores are merited, as well as longitudinal studies evaluating VSAQ score changes with disease progression. The VSAQ offers a quick to administer tool to evaluate exercise tolerance.

European Respiratory Society, September 2013

Prevalence of possible severe asthma with fungal sensitisation (SAFS) and allergic bronchopulmonary aspergillosis (ABPA) in a UK secondary care hospital.

Jonny E. Seher, Roger Howels, Rob Niven, David W. Denning, Stephen Scott.

Background: Severe asthma with significant symptoms is often difficult to treat. Investigating and treating possible *Aspergillus* involvement such as SAFS or ABPA with antifungal medication may improve symptoms. Aspergillus sensitisation is also associated with bronchiectasis is in asthma. We wished to explore the prevalence of these conditions in secondary care. ABPA rates on hospital referral in other countries vary from 0.7 to 3.5% (typically 2.5%) and no estimate of the rate of SAFS has been made.

Method: All total and *Aspergillus* specific IgE results for a 1 year period were reviewed along with Aspergillus (ASP) IgG from the hospital pathology database. CXR reports for those with any positive ASP were also reviewed.

Results: 406 results were identified, 76 were invalid and 330 remained. 138 (42%) had IgE >100; 27(8%) met the criteria for *Aspergillus* sensitisation in asthma (raised *Aspergillus* IgE) and 17 (5%) had raised ASP IgE although only 5 (2%) had all the criteria for ABPA (raised ASP precipitins, eosinophils & CXR change). Overall 44 (13%) patients had raised IgE and ASP IgE.

Conclusion: Over a 1 year period in a UK secondary care hospital, 13% of patients could potentially benefit from antifungal treatment of allergic aspergillosis of the lungs.

Union against TB and Lung Diseases, Paris, October 2013

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

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The University of Manchester, UK, Manchester Academy Health Science Centre (MAHSC), UK, National Aspergillosis Centre, University Hospital of South Manchester, UK, National Aspergillosis Centre UK; Gulu Regional Referral Hospital, Uganda; Gulu District Health Office, Uganda; St. Mary's Hospital, Lacor, Gulu region, Uganda; Gulu University, Uganda;

Introduction: 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 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.

Methods: 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

Results: 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.

Conclusion: 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.

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/µL	-
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 Single Multiple	97 (24%) 22 (6%) 75 (19%)	61 (31%) 11 (5%) 50 (25%)	36 (18%) 11 (6%) 25 (13%)	0.004 0.990 0.001
Aspergilloma on CXR Possible Probable	12 (3%) 9 (2%) 3 (1%)	5 (3%) 5 (3%) 0	7 (4%) 4 (2%) 3 (2%)	0.507 1.000* 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.

Trends in Medical Mycology, Copenhagen, October 2013

The clinical response to a short-term course of intravenous liposomal amphotericin B therapy in patients with chronic pulmonary aspergillosis
P. Newton, C. Harris, D.W. Denning

Objective: This audit was performed to assess whether patients with chronic pulmonary aspergillosis (CPA) experience a sustained clinical benefit from a short course (< 6 weeks) of intravenous liposomal amphotericin B therapy (LAmB).
Methods: CPA patients who had received their first short-course of intravenous LAmB therapy (Gilead) at the National Aspergillosis Centre in Manchester were identified. A retrospective patient case-note review was performed using a standardised proforma. Data collected included patient demographics, indication for LAmB treatment, the dose and duration of therapy and the clinical response to treatment. Patients who received <3 doses of LAmB were not evaluated for response (n=2).
Results: 48 CPA patients (23 females, 25 males) were identified aged 28-86 years (median 64) when treated. The median duration of prior azole therapy was 11.5 months (range 0 – 51 months). The dose and duration of intravenous LAmB given ranged between 2.47 - 5 (mean 3.03) mg/Kg daily and 1-36 (mean 16.9) days respectively. 1 patient was unable to tolerate the test dose of LAmB and received no further treatment. The primary reason for therapy was either respiratory

(48%) or both respiratory and constitutional symptoms (52%). The average number of respiratory and constitutional symptoms per patient was 4.5 (range 1-7) symptoms.
15 of 47 (32%) patients developed an acute kidney injury whilst on LAmB therapy resulting in the need for IV rehydration; 3 with other contributing factors to their renal impairment. 5 patients needed to stop their LAmB treatment early, two of whom had received a LAmB dose reduction. 4 other patients successfully completed their LAmB course following dose reduction.
30 of 46 (65%) patients experienced a clinical response to LAmB therapy. Improvements in respiratory and constitutional symptoms were seen in 27 (58.6%) and 19 patients (41.3%) respectively. 27 (90%) out of 30 patients who completed the St George's Respiratory Questionnaire (SGRQ) Quality of Life Score pre and post treatment noticed an improvement in a least one modality with 18 (60%), 16 (53.3%), 12 (40%) and 15 (50%) patients experiencing an improvement in their symptom, impact, activity and total scores respectively. Response was usually delayed and only apparent at follow up post-discharge.
Improvement in the immunological markers of *Aspergillus* infection were observed in 9 (26.4%) out of the 34 patients who had adequate immunological data available. 13 patients had *Aspergillus* PCR performed on their sputum prior to LAmB treatment and 10 had a positive PCR result. Following treatment the *Aspergillus* PCR in sputum became negative in 7 patients.
Conclusion: 65% of CPA patients receiving their first course of LAmB treatment experienced a clinical response. Improvements in respiratory and constitutional symptoms were seen in 58.6% and 41.3% of patients respectively. An acute kidney injury was observed in 32.6% of patients receiving LAmB therapy with 5 (10.9%) patients needed to stop their treatment course early. Routine intravenous rehydration at initiation of LAmB therapy and avoidance of other factors that may contribute to an acute kidney injury should be considered in all patients receiving LAmB therapy.

Nebulised Amphotericin in Allergic bronchopulmonary Aspergillosis (ABPA) and severe asthma with fungal sensitization (SAFS).
Livingstone Chishimba Robert M. Niven, Georgina Powell, Philip Langridge, David W. Denning

Background and rationale: Allergic bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal sensitization (SAFS) are debilitating lung diseases whose treatment is not yet fully established. Some published case reports/series suggest that nebulised amphotericin (liposomal) may have a role in the treatment of cystic fibrosis (CF) ABPA but little is known regarding its appropriateness in asthmatic ABPA and SAFS patients. We assessed the efficacy and safety of nebulised Amphotericin as second and third line therapy.
Methods: 20 adult asthmatics with SAFS (n=11) and ABPA (n=9) were treated with nebulised amphotericin between January 2011 and May 2013. All patients had either failed itraconazole (n=8), voriconazole preceded by itraconazole (n=5) or developed adverse events (AEs) to either agent (n=7). 10mg of Nebulised amphotericin B (Fungisone) was administered using a Pari LC plus nebulizer twice/day, preceded by salbutamol, under direct physiotherapist observation. We audited clinical, radiological and immunological response, including change in the Asthma Quality of Life Questionnaire (AQLQ-J) scores .We also examined Asthma Control Questionnaire (ACQ) scores, change in lung function (FEV1) , change in IgE (total and specific) and healthcare utilization. Patients were followed up for 12 months during which they were evaluated at months 2, 4, 6, 9 and 12 months.
Results: There were 20 patients analysed (SAFS, n=11) and (ABPA n=9), M: F= 8:12, median age 65.5 yrs (range=24-78). The median duration of therapy was 30 days (IQR, 0.0-142). Clinical benefit was observed in 2 (10 %) in which mean ACQ score improved from 6 to 2, overall mean AQLQ score improved by 0.95 and mean FEV1 improved by 1.2 L(63.1%). Seven (35%) failed the challenge due to adverse events (bronchospasm). 11 (55%) discontinued within 12 months of therapy due to delayed bronchospasm (n=3, within 4 weeks), equipment

problems/patient inconvenience (n=4) and lack of clinical benefit (n=4) (fig 1). There were no significant changes in immunological and radiological outcomes.
Conclusion: Our data suggests that the overall efficacy of nebulised amphotericin in this group of patients may be poor and is associated with high frequency of adverse events. However, the responses were excellent in 2 (10%) patients. It is not clear which patients are likely to respond. Further studies need to be conducted to establish the optimal dose range (dose, frequency), nebulizer type , pressures and identification of patients who may respond.

Advances Against Aspergillosis, Madrid, January 2014

Rapid discrimination of *Aspergillus fumigatus* cyp51A resistance mutations in patient samples by pyrosequencing
L Novak Frazer, R Masania, DW Denning & MD Richardson,

Purpose: A significant proportion of patients who attend the National Aspergillosis Centre suffer from azole resistance in *Aspergillus fumigatus* attributable to mutations in the target site (*cyp51A*). Our challenge is to elucidate whether the resistance observed clinically in patients who do not respond to long-term azole therapy and who have been confirmed to be positive for *Aspergillus* by PCR is due to mutations in the *cyp51A* target.
Methods: Primers were designed using Qiagen Assay Design software. DNA extracted from wild-type *A. fumigatus* and isolates confirmed by Sanger sequencing to be carrying *cyp51A* mutations were processed with Qiagen QIAamp DNA Mini Kits. Patient sputum samples were processed with Myconostica MycXtra to recover DNA and then confirmed to be positive for *Aspergillus spp*. by Myconostica MycAssay Aspergillus PCR. Amplification of *cyp51A* from *A. fumigatus* isolates and patient samples for pyrosequencing was carried out on an Applied Biosystems Veriti PCR. Pyrosequencing was carried out on a Qiagen PyroMark Q24 platform. All pyrosequencing results were confirmed by Sanger sequencing.
Results: We have developed a pyrosequencing assay which can detect all the TR, G54, L98 and M220 mutations that have been described to date. We have processed isolates with confirmed mutations to confirm the validity and reliability of our assay. We will also process *Aspergillus*-positive patient sputum and BAL samples for the presence of these mutations. Our intention is to validate this assay and provide it as a routine service for future patients undergoing azole therapy.
Conclusion: We have shown that *cyp51A* mutations can be monitored with this new pyrosequencing assay. The aim will be to have the results available to clinicians within 24h of a positive *Aspergillus* PCR. The assay is amenable to processing many patient samples simultaneously and may be useful in quickly determining the genetic cause of azole therapy failure. In addition, the presence of mutant and WT sequences can be detected simultaneously and the ratio quantified. The advantage of using pyrosequencing is that this technique can be adapted easily for new *cyp51A* gene mutations as they arise. In addition, it can be adapted for detecting mutations in other genes involved in azole resistance in *A. fumigatus* and in *cyp51A* and other genes involved in drug resistance in other fungal species. It is envisaged that the results of this assay will have a positive impact on patient treatment and antifungal stewardship.

Aspergillus pulmonary nodules; presentation, radiology, and histology features
Muldoon EG, Page I, Bishop P, Denning DW.

Purpose: Pulmonary aspergillosis has a number of different manifestations. Classically pulmonary aspergillosis in immunocompetent patients presents as a saprophytic infection in a pre-existing cavity. However, pulmonary *Aspergillus* disease can present as a nodule(s), without cavitation, which may be mistaken for malignancy. The introduction of lung cancer screening by low dose CT imaging will yield many non-malignant nodules in non-immunocompromised

patients. The purpose of this study is to review the presentation, radiology and histological features of nodules caused by *Aspergillus spp*.
Methods: Sixty-eight patients who had histological features of aspergillosis on lung biopsy, from 2003-2013 were identified. These patients radiology was then reviewed. Patients with cavitating lung lesions, aspergillomas, or those without parenchymal lung abnormalities were excluded. Patients with a diagnosis of invasive aspergillosis were also excluded. Demographic data and laboratory data was recorded on each patient, in addition to their clinical presentation.
Results: Seven patients with pulmonary nodules and histology features diagnostic of aspergillosis were identified. The mean age of the patients was 58 years (range 46-67). Five (71%) were men. The mean Charleston co-morbidity score was 3.7 (2-6). Five patients (71%) were former smokers. None of the patients was in receipt of immunosuppressive drugs, the mean lymphocyte count pre-operatively was 1.5 x 10^9/L (Laboratory normal range 1.5-4, range 1.1-1.9), two patients (29%) were mannose binding lectin deficient. Three patients (43%) did not have an elevated *Aspergillus* IgG. Three patients had a single nodule identified on computerised tomography (CT), two had two nodules and two had three nodules present. The mean size of the nodules was 2cm (range 1.3-3.2cm), none had cavitation radiographically. Five patients had lesions in the upper lobes on CT (four in the right upper lobe), while one patient had nodules in the right lower lobe and one in the left lower lobe. Only one patient had significant lymphadenopathy on CT. On presentation, all the patients complained of cough, five complained of dyspnoea, two complained of weight loss, and one complained of haemoptysis. Five patients underwent lung biopsy and histological examination. All five had evidence of fibrosis, granulation tissue and fungal hyphae were visualised. The remaining two patients had bronchoscopy and bronchoalveolar lavage; inflammatory cells and branching hyphae were identified.
Conclusion: Pulmonary nodules are a less common manifestation of aspergillosis in immunocompetent patients. Their natural history is not yet defined, although in this series all of the patients presented with cough. These nodules may be difficult to distinguish from other lung pathology on CT findings alone.

Antifungal drug interactions database and apps for iPhone and Android
Graham Atherton, Susan Banfield, Jennifer Bartholomew and David W. Denning

Introduction
Drug:drug interactions (DDIs) account for 3-5% of serious adverse reactions, which themselves are common causes of hospital admission and sometimes death. In 433 patients >60 years old taking at least 2 agents, the incidence of DDI-related ADRs was 6.5%. Systemic azole antifungal medications have a high potential to cause DDIs with many drugs. Some interactions reduce the efficacy of azoles (ie rifamycins), others the efficacy of the interacting drug (ie low dose ritonavir), or lead to excess concentrations of the interacting drug (ie ciclosporin, warfarin, digoxin, benzodiazepines etc). Some interactions occur with amphotericin B and echinocandins. Both medical professionals and patients (& carers) need support in this area because of the range and complexity of possible interactions. We have created a quick reference for guidance.
Methods
Information on interactions with itraconazole, voriconazole, posaconazole, fluconazole, amphotericin B, micafungin and caspofugun has been collated from a number of sources: manufacturers' Summary of Product Characteristics, Stockley's Drug Interactions, consideration of the effects of each drug on CYP P450 isoenzymes & p-glycoprotein, clinical considerations and primary literature. For each interacting pair of drugs the interaction is classified as of 'major' (red), 'moderate' (amber) or 'minor' (green) significance. 'Major' interactions are those that could cause significant harm, even if rare & which require avoidance, with 'minor' interactions generally increasing the risk of one or more adverse effects. Where no interaction is expected

there is no entry. For each interacting pair of drugs, patients are informed of the action their doctor should be taking & effects to look out for. Doctors are provided with the mechanism of the interaction, evidence of an existing interaction and action to take.

Results

We have constructed a searchable database of interactions between systemic antifungal drugs and every other prescribed drug currently available to provide a reference for both doctors and patients. The information is provided free of charge at The Aspergillus Website (www.antifungalinteractions.org) and for convenience and maximum accessibility is also available as an APP for smartphones both for iPhones and Android devices ('Antifungal Interactions'). There are 739 drugs listed and 8 antifungals. 398 interactions are rated as minor, 1375 moderate and 443 severe, a total of 2216 recorded interactions. The user simply chooses the drug they wish to investigate from a list and with one button click they will be taken to a 'traffic light' system of warnings - green for minor, orange for moderate and red for severe interaction. If there is no interaction noted or known this is also indicated. The online database is updated regularly with additional publications and constant review. The app database is updated every 6 months. It will shortly be available in a new form that will be more useful to doctors and other medical professionals, written out in a far more detailed format for professional use.

Conclusion

A DDI resource is available for antifungal drug interactions, to reduce adverse drug reactions and loss of antifungal efficacy.

Impaired Th1 and Th17 immunity in chronic pulmonary aspergillosis

Doffinger R, Harris C, Ceron-Gutierrez L, Newton P, Alachkar H, Kumararatne DS, Barcenas-Morales G, Denning DW.

Background: Chronic pulmonary aspergillosis (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). TH1 responses have been found to be crucial for effective defence against Aspergillus spp. TH17 immunity has been recently as well associated to the defence of fungal infections. Methods: We performed active cytokine-profiling by inducing whole blood cultures collected from 150 CPA patients in parallel with healthy controls. Bloods were taken at the NAC in Manchester and then sent by courier to the Cambridge Cytokine Laboratory for experimental activation on the same day and subsequent analysis. Production of various cytokines including IFN-g, IL17a, TNF-a, IL-6, IL-12 and IL-10 after in vitro whole blood stimulation of by a variety of stimuli including PHA, LPS, Beta-Glucan, Zymosan, BCG, IFN gamma, IL-12, and IL-18. Cytokines were measured by ELISA or multiplexed particle based flow cytometry. Results: We have extended our analysis of a previously presented small cohort to more than 150 CPA patients applying an array of stimulations targeting T-, Nk-, and Monocyte subsets. Results show a highly significant impairment of IL17 production after polyclonal T-cell stimulation with PHA (means: 394pg/ml vs 87 pg/ml; $p < 0.0001$) across the cohort. Impaired IFN gamma was evident after all stimulations but was most pronounced after induction with LPS (means 131 pg/ml vs 37 pg/ml; $p < 0.0001$), after correction on lymphocyte numbers. Distinct response pattern could be identified showing (1) overall low IFN gamma production (2) Selectively low production after T-cell stimulation (3) Normal T-cell induced IFN gamma but impaired (innate) induced NK-cell derived IFN gamma production. We noted as well increased production of the inflammatory cytokines TNF and IL-6. Patients had also significantly increased numbers of monocytes (means 0.37 vs 0.55; $p<0.0001$), which are a major source of these inflammatory cytokines. Stratifying on monocyte counts normalised the production after most stimuli in vitro. Conclusion: Results suggest significant impairment of IFN gamma and IL17 mediated immunity with a major involvement of TH17 and NK-cell subsets.

Baseline parameters of survival in chronic pulmonary aspergillosis
Lowes D, Al-Shair K, Harris C, Rautemaa-Richardson R, Denning DW.

Background: Chronic pulmonary aspergillosis (CPA) is a chronic, usually progressive infection in nonimmucompromised patients. Many underlying pulmonary diseases are associated with CPA. Contemporary series suggest a 75-85% 5 year mortality.
Methods: Data from 392 patients treated for CPA at the UK's National Aspergillosis Centre (NAC) prior to June 2012 were retrospectively analysed. The impact of age, sex, previous pulmonary conditions, dyspnea score, quality of life score and radiological appearances was assessed using Kaplan-Meier curves, Log-Rank tests and the Cox proportional hazards modelling. A sample of patient notes were used to examine the medical history and estimate the onset of CPA and the time taken from onset to referral to the NAC. Cause of death was recorded were possible. Statistical analysis was performed using IBM SPSS statistics package version 20. The project was registered with the hospital trust's clinical audit department.
Results: The mean age at referral was 59.4 years (range 18 to 86 years), 59.4% were males. Survival of patients with CPA at the NAC was 86% at one year from referral, and 57% at five years. Subgroups with worse prognosis included those with a history of non-tuberculous Mycobacterium infection (p=<0.000). Age at referral was a strong predictor of mortality (Hazard ratio 1.058 per year, p=<0.000). The median time from estimated onset of CPA to referral to the NAC was 8 months (range 0 to 21 years).
Discussion: A number of factors associated with increased risk of mortality from CPA were identified. The survival of CPA patients treated at NAC was better than reported previously by others. The longterm antifungal therapy approach undertaken at the NAC may contribute to this. Survival of patients may be under-estimated due to some patients presenting many years after the probable onset of disease.

The Temporal Sequence of the Transition from Asthma through Allergic Bronchopulmonary Aspergillosis to Chronic Pulmonary Aspergillosis
Lowes D, Chishimba L, Denning DW.

Introduction: Allergic bronchopulmonary aspergillosis (ABPA) is an uncommon complication of asthma, occurring in 0.7-4.1% of cases in secondary care. There are an estimated 4,800,000 cases of ABPA worldwide. Development of chronic pulmonary aspergillosis (CPA) in patients with ABPA is a well-recognised but poorly understood phenomena. Whilst oral itraconzole is frequently used in the management of patients with ABPA, voriconazole and posaconazole is often used in those who develop CPA. The temporal sequence of the transition from asthma through ABPA to CPA is not well described.
Method: Patients with problematic CPA in the UK are cared for at one national centre, the National Aspergillosis Centre (NAC), based at the University Hospital of South Manchester. These patients are screened for a dual diagnosis of ABPA and CPA. In cases referred to the NAC prior to 1st of June 2012 in whom a dual diagnosis was suspected, the full medical records were reviewed and discussed by a multi-disciplinary team to make judgements on the likely onset of asthma, ABPA and CPA. ABPA was defined as the highest serum total IgE of greater than 1000 IU/L, or raised serum anti-Aspergillus IgE (or positive Aspergillus skin prick test), a history of asthma, with compatible symptoms of ABPA. CPA was defined as positive Aspergillus precipitins, or highest serum anti- Aspergillus IgG of >40 mg/L with radiological findings consistent with CPA (Nodule disease, lobar shrinkage and fibrosis, pleural capping, and cavity formation with or without fungal balls).
Results: Of all patients referred to the NAC prior to 1st of June 2012 (392 patients), 42 were recorded as having a co-existing diagnosis of asthma, ABPA and CPA. On review of the medical

records, 20 were considered to have a clear progression from asthma, through ABPA to CPA. Seven patients did not have CPA, five patients did not to have ABPA but a Th-2 response to chronic pulmonary aspergillosis, with a high total IgE. Six patients were considered to have developed CPA due to causes other than ABPA. The remaining four patients had too much missing data in the medical records to allow timing and diagnostic judgements to be made. Of the 20 patients included, twelve were female and 8 were male. Figure 1 shows the ages at which the 20 patients developed asthma, ABPA and CPA, including long-term asthma remissions. Patients one to 15 developed chronic cavitary pulmonary aspergillosis, patients 16 and 17 developed Aspergillus nodule disease, and patients 18, 19 and 20 all developed the radiological appearance of CPA but remained anti-Aspergillus IgG negative. The patient documented on line 2 is case 44 in the case histories from www.aspergillus.org.uk.
Discussion: The overlapping criteria for the diagnosis of CPA and ABPA make the diagnosis of CPA in patients with ABPA challenging. There is considerable range in the length of time the patients in this series had asthma and ABPA prior to the onset of CPA. A clearer definition of CPA in ABPA is needed to guide diagnosis and criteria for escalation in antifungal therapy.
Figure 1: The age at which patients developed asthma (and long-term asthma remissions), allergic bronchopulmonary aspergillosis and chronic pulmonary aspergillosis.

Detection of Aspergillus antibodies by a new indirect haemagglutination assay
Richardson MD, Page ID, Rautemaa-Richardson RMK, Denning DW

Purpose: Measuring Aspergillus antibodies is an important part of the diagnostic pathway for allergic bronchopulmonary aspergillosis (ABPA) and chronic pulmonary aspergillosis (CPA). It may represent a major public health issue on a global scale as 20-35% of patients develop Aspergillus antibodies following tuberculosis treatment and 63% of these develop pulmonary aspergillosis within 3 years. The worldwide 5 year period prevalence of (CPA) secondary to tuberculosis in, for example, the Congo and Nigeria has been estimated at between 0.8 and 1.37 million cases, with 43 cases per 100,000 population. Detection of specific antibodies provides key diagnostic evidence in chronic aspergillosis. There are numerous EIA formats for quantifying antibodies but these are not suitable for use in developing countries with limited laboratory resources. Haemagglutination tests involve coating erythrocytes with antigens. Erythrocytes clump together when antibodies cross-react with antigens on more than one cell and become visible to the human eye. The method also detects all Aspergillus antibody types. Its simplicity and speed (~2 hours) and commercial production make it highly suited for epidemiological and prevalence studies in low and middle resource countries. The goal was to compare the efficacy of an indirect haemagglutination assay designed to detect Aspergillus agglutinating antibodies with an agar double diffusion system used for the detection of Aspergillus precipitins.
Methods: Serum samples from patients with a diagnosis of chronic pulmonary aspergillosis were tested by ELI.H.A. Aspergillus indirect haemagglutination (ELITech MICROBIO, Signes, France), and by an Aspergillus immunodiffusion system (Microgen Bioproducts Ltd, Camberley, UK). For the indirect haemagglutination assay sera were serially diluted to 1:2560. For the immunodiffusion assay patient sera were diluted to 1:16. The antigens used in these assays were a combination of cytoplasmic (somatic) and culture filtration extracts.
Results: In the indirect haemagglutination assay sera with a titre 1:2560 in the agglutination assay. Precipitin titres of 1:4 were all in the positive range of the agglutination assay. Sera recorded as weak precipitin positive (titre of 1:2) were all positive in the agglutination test but with a range of agglutinin titres (1:320 â€“ >1:2560). The immunodiffusion test takes 5 days to perform. The total performance time of the indirect haemagglutination test is 3 hours.
Conclusion: The EliTech indirect haemagglutination assay for the detection of Aspergillus antibody in patients with chronic manifestations of pulmonary demonstrated has many advantages compared with precipitin tests: it was rapid, very user friendly and easy to read. This is an ideal

near point-of-care test for field studies and for community clinics. Furthermore, this test can be used for screening patients and support our efforts to understand the global epidemiology of chronic pulmonary aspergillosis.

8 Education and professional outreach

The NAC and MRCM are now acting as a major focus for both undergraduate and postdgraduate education. Undergraduate education has been focussed on special study modules and Personal Excellence Path (PEP) blocks. The success of the undergraduate teaching in infection has lead to a compulsory but short new component in year 4 on infection teaching, which is welcome and will involve teaching ~240 students over 9 months.

A Masters course in Medical Mycology has grown out the NAC, and enrolled its first 3 students in 2013, from Ukraine, Libya and Uganda. The second year has enrolled 9 students, from many countries.

The development of an online education resource called Leading International Fungal Education (LIFE) has now completed 24 months (www.LIFE-Worldwide.org). It is funded by the Fungal Infection Trust and includes regular new items on public health mycology. It has been translated into Spanish. A quarterly newsletter is mailed to about 5,000 health professionals worldwide.

The Global Action Fund for Fungal Infections (GAFFI) was set up in 2013 with the mission of improving access to diagnostics and antifungal treatments for fungal diseases worldwide (www.GAFFI.org). As part of the program, working with health professionals in each country, the burden of fungal infection has been estimated in 33 countries, including CPA and ABPA.

The senior staff attached to NAC have delivered over 100 external lectures across the UK and internationally, building on their experience and expertise acquired at the NAC. Guidelines for the management of CPA are being developed in Europe and the USA, based primarily on the NAC experience.

9 Statutory reports

MRSA
No cases of MRSA were reported.

C. difficile infection
No cases of *C. difficile* infection were reported.
One case of CPE (carbapenamase producer)

2HIRS reported
SUI's
One SUI reported

Complaints
There were three complaints made.

10 Future developments

Progress on developments planned for 2012/13 were:

- Procurement and implementation of an IV antifungal at home service to minimise hospital stay. Not achieved. Reorganisation of procurement and too many competing activities at UHSM.
- Evaluation of non-*fumigatus* IgG antibody tests for patients with negative *fumigatus* IgG antibody. In analysis
- Comparison of different Aspergillus antibody tests in a comprehensive standardised way with UK and Ugandan samples, comparing 6 different tests. Completed, in analysis; marked differences in performance which will impact on diagnostic service
- Reporting of the histological findings of *Aspergillus* nodules, a newly discovered sub-type of CPA. Partially completed
- Reporting and analysing the parameters associated with prolonged survival in CPA. Completed
- Completion of the audit on repeated courses of amphotericin B on CPA status. Completed
- Audit of the utility of induced sputum to capture Aspergillus by culture or PCR, as opposed to expectorated sputum. Held up by data transfer errors, and then PHE IT support, so repeated and in analysis.
- An Education Fellow (pre-SPR) to join the service, to assist with providing continuity of care for inpatients and assist in multiple teaching activities. Completed and highly beneficial to service and educational programs.
- A teaching academic consultant to be appointed to contribute primarily to non-CPA patients and provide high level MSc teaching in the University. Completed
- An additional band 5 (newly qualified) nurse to join the nursing team to reduce the routine tasks of our most experienced specialised nurses. Not completed. Recruitment failed.

Developments planned for 2014/15 include:

- Recruitment of an additional nurse to support the growing number of patients.
- Implementation of an antibiotic at home service (OPAT), to include antifungal therapy.
- Merging of the infection specialities at UHSM into one administrative group.
- Implementation of the Aspergillus IgG antibody comparision indings in the MRCM.
- Development of a routine azole resistance service using pyrosequencing in the MRCM, and then clinical validation (2 year process).

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

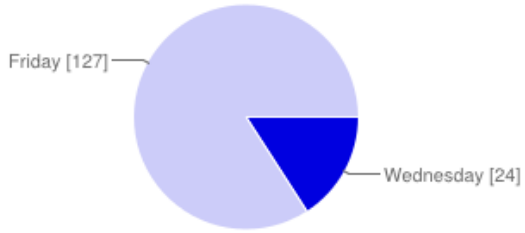
- Significant impairment of respiratory function, sufficient to impair activities of daily living, but ambulant
  and/or
- Concurrent anti-mycobacaterial treatment
  and/or
- Failed or developed toxicity to itraconazole capsules
  and
- No evidence of azole antifungal resistance

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 or renal disease

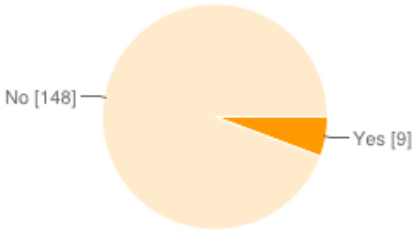
Appendix 2
National Aspergillosis Centre patients' survey

Which day did you attend the clinic?



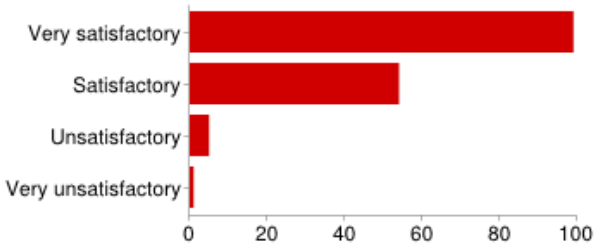
Wednesday	**24**	16%
Friday	**127**	84%

Is this your first visit to the National Aspergillosis Centre?



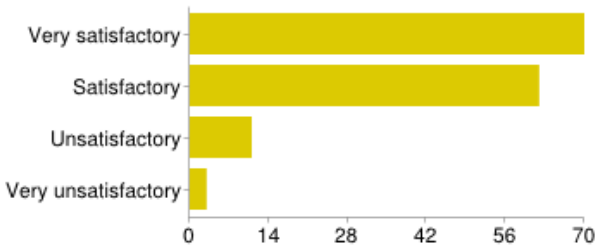
Yes	**9**	6%
No	**148**	94%

Reception [How did you feel about the time you had to wait for the following?]



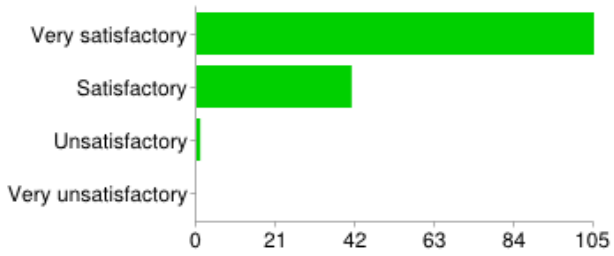
Very satisfactory	**99**	62%
Satisfactory	**54**	34%
Unsatisfactory	**5**	3%
Very unsatisfactory	**1**	1%

Doctor [How did you feel about the time you had to wait for the following?]



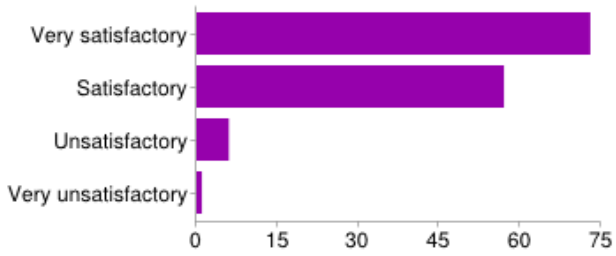
Very satisfactory	**70**	48%
Satisfactory	**62**	42%
Unsatisfactory	**11**	8%
Very unsatisfactory	**3**	2%

Aspergillosis nurses [How did you feel about the time you had to wait for the following?]



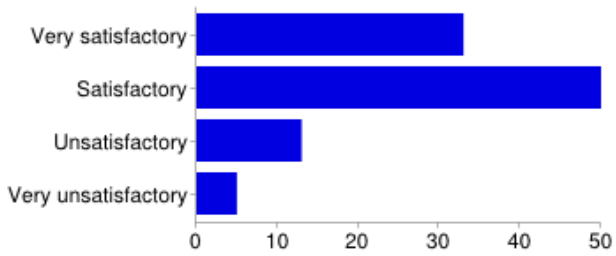
Very satisfactory	105	71%
Satisfactory	41	28%
Unsatisfactory	1	1%
Very unsatisfactory	0	0%

Blood tests [How did you feel about the time you had to wait for the following?]



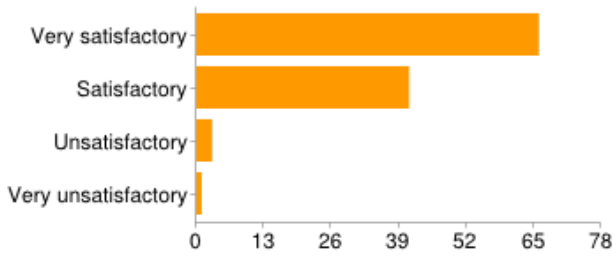
Very satisfactory	73	53%
Satisfactory	57	42%
Unsatisfactory	6	4%
Very unsatisfactory	1	1%

Pharmacy [How did you feel about the time you had to wait for the following?]



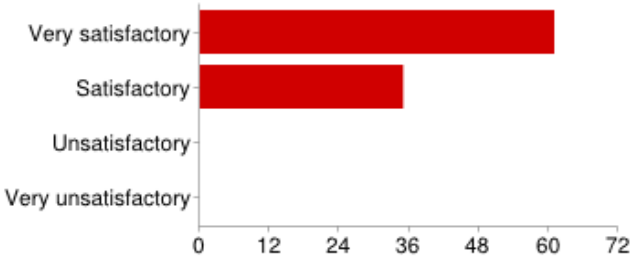
Very satisfactory	33	33%
Satisfactory	50	50%
Unsatisfactory	13	13%
Very unsatisfactory	5	5%

X-ray [How did you feel about the time you had to wait for the following?]



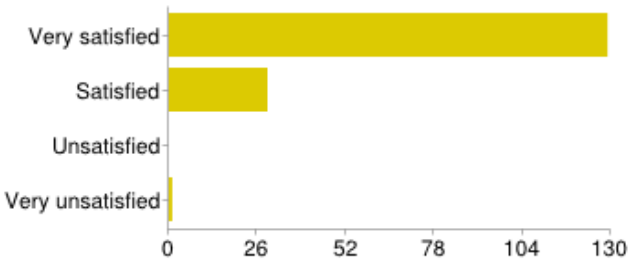
Very satisfactory	66	59%
Satisfactory	41	37%
Unsatisfactory	3	3%
Very unsatisfactory	1	1%

Lung function [How did you feel about the time you had to wait for the following?]



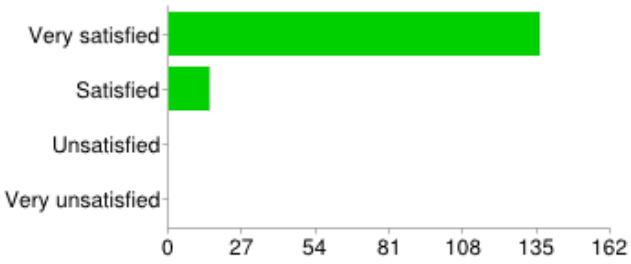
Very satisfactory	**61**	64%
Satisfactory	**35**	36%
Unsatisfactory	**0**	0%
Very unsatisfactory	**0**	0%

Receptionist [How satisfied are you with the courtesy shown to you by:]



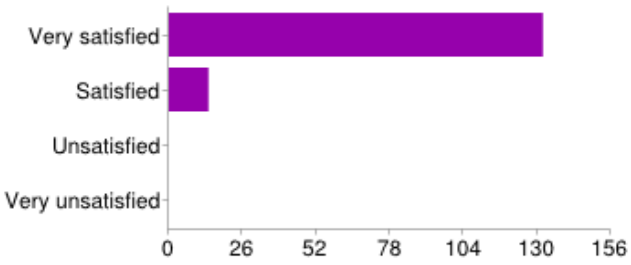
Very satisfied	**129**	81%
Satisfied	**29**	18%
Unsatisfied	**0**	0%
Very unsatisfied	**1**	1%

Nurses [How satisfied are you with the courtesy shown to you by:]



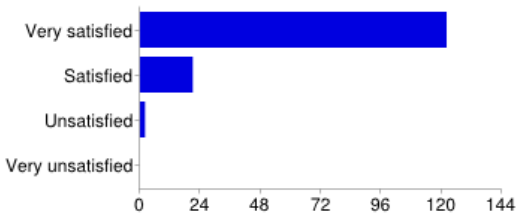
Very satisfied	**136**	90%
Satisfied	**15**	10%
Unsatisfied	**0**	0%
Very unsatisfied	**0**	0%

Doctor [How satisfied are you with the courtesy shown to you by:]



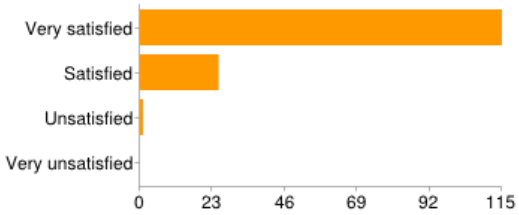
Very satisfied	**132**	90%
Satisfied	**14**	10%
Unsatisfied	**0**	0%
Very unsatisfied	**0**	0%

Doctor [How satisfied are you with the quality of care you received from:]



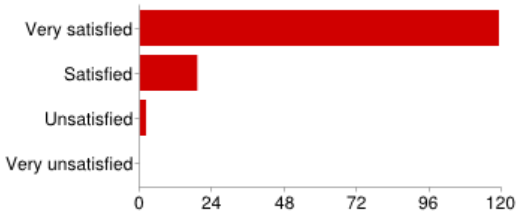
Very satisfied	122	84%
Satisfied	21	14%
Unsatisfied	2	1%
Very unsatisfied	0	0%

Clinic nurses [How satisfied are you with the quality of care you received from:]



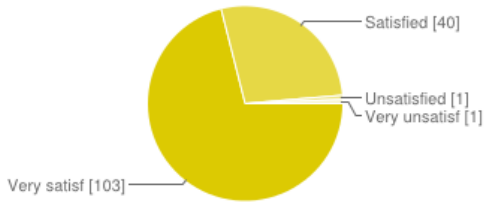
Very satisfied	115	82%
Satisfied	25	18%
Unsatisfied	1	1%
Very unsatisfied	0	0%

Specialist nurses (Aspergillosis nurses) [How satisfied are you with the quality of care you received from:]



Very satisfied	119	85%
Satisfied	19	14%
Unsatisfied	2	1%
Very unsatisfied	0	0%

How satisfied are you with communication with the NAC staff?

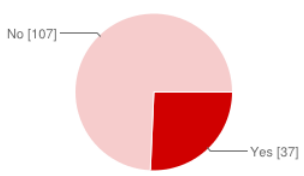


Very satisfied	103	71%
Satisfied	40	28%
Unsatisfied	1	1%
Very unsatisfied	1	1%

Any comments on your contact with one of our specialist nurses?

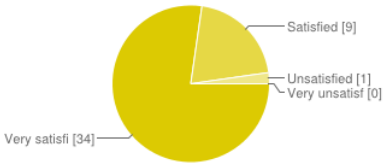
Very helpful and professional | Always friendly & helpful | Specialist aspergillosis nurse is a great support | Very satisfied helped me with all my questions | I received excellent support and advice | Very helpful with my meds | Lost appointment card advised of visit date | Very satisfied overall | Very helpful advice provided | Always try to help! | Not very helpful/dismissive | Very helpfukl

Have you received care from the specialist physiotherapists?



Yes	37	26%
No	107	74%

If yes, how satisfied were you with the service?



Very satisfied	34	77%
Satisfied	9	20%
Unsatisfied	1	2%
Very unsatisfied	0	0%

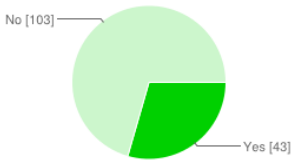
Any comments on the care provided to you by the specialist physiotherapists?

Very helpful | Phil is excellent

An immunologist attends the clinic twice a month. If you have seen the immunologist, have you any comments about this service?

Not aware of this service | Good | Seen at Salford Royal Hospital | No | Excellent service & efficient | The appointment was cancelled | Excellent

Have you been contacted by a member of the NAC team (other than the specialist nurses) after or in between clinic visits?

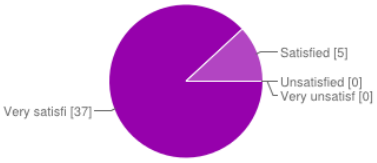


Yes	43	29%
No	103	71%

If yes, who was it?

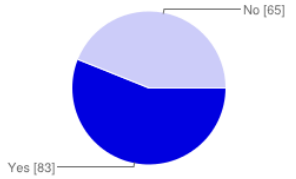
Graham Atherton | Georgina | Debbie | Kate or Kaz | Deborah | Ward nurse | Debbie/Georgina | Debbie & Georgina | Pippa | Georgina and Debbie | Georgina/Debbie | Not sure

And how satisfied were you with this support?



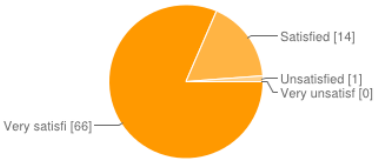
Very satisfied	37	88%
Satisfied	5	12%
Unsatisfied	0	0%
Very unsatisfied	0	0%

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



Yes	83	56%
No	65	44%

If yes, how satisifed were you with this support?



Very satisfied	66	81%
Satisfied	14	17%
Unsatisfied	1	1%
Very unsatisfied	0	0%

Appendix 3

Publications from the Fungus@Manchester Group (2013)

1. Agarwal R, Chakrabarti, A, Shah A, Gupta D, Meis J, Guleria R, Moss R & Denning DW. (2013). Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. *Clin Exp Allergy*, **43**(8):850-73

2. Almeida R, Loss O, Colabardini A, Brown N, Bignell E, Savoldi M, Pantano S, Goldman M, Arst H & Goldman G. (2013). Genetic bypass of *Aspergillus nidulans* crzA function in calcium homeostasis. *G3 (Bethesda),* **3**(7):1129-41.

3. Al-Shair K, Atherton G, Harris C, Ratcliffe L, Newton P & Denning DW. (2013). Long-term Antifungal Treatment Improves Health Status in Patients With Chronic Pulmonary Aspergillosis: A Longitudinal Analysis. *Clin Infect Dis*, **57**(6):828-35

4. Al-shair K, Atherton GT, Kennedy D, Powell G, Denning DW & Caress A. (2013). Validity and reliability of the St. George's Respiratory Questionnaire in assessing health status in patients with chronic pulmonary aspergillosis. *Chest*, **144**(2):623-31

5. Barrs VR, van Doorn TM, Houbraken J, Kidd SE, Martin P, Pinheiro MD, Richardson MD, Varga J & Samson RA. (2013). *Aspergillus felis* sp.nov., an emerging agent of invasive aspergillosis in humans, cats, and dogs. *PLoS ONE*, **8**(6):e64871

6. Baxter C, Denning DW, Jones A, Todd A, Moore C & Richardson MD. (2013). Performance of two *Aspergillus* IgG EIA assays compared with the precipitin test in chronic and allergic aspergillosis. *Clin Microbiol Infect*, **19**(4):E197-204

7. Baxter C, Moore C, Jones A, Webb A & Denning DW (2013). IgE-mediated immune responses and airway detection of *Aspergillus* and *Candida* in adult cystic fibrosis. *Chest*, **143**(5):1351-7

8. Baxter C, Rautemaa R, Jones A, Webb A, Bull M, Mahenthiralingam E & Denning DW. (2013). Intravenous antibiotics reduce the presence of *Aspergillus* in adult cystic fibrosis sputum. *Thorax*, **68**(7):652-7

9. Baxter C, Dunn G, Jones A, Webb K, Gore R, Richardson M & Denning DW. (2013). Novel immunologic classification of aspergillosis in adult cystic fibrosis. *J Allergy Clin Immunol,* **132**(3):560-566

10. Berepiki A & Read N. (2013). Septins are important for cell polarity, septation and asexual spore formation in *Neurospora crassa* and show different patterns of localisation at germ tube tips. *PLoS One*, **8**(5):e63843

11. Buied A, Moore C, Denning DW & Bowyer P. (2013). High-level expression of cyp51B in azole-resistant clinical *Aspergillus fumigatus* isolates. *J Antimicrob Chemother*, **68**(3):512-4.

12. Butler l, Brockley T, Denning DW, Richardson M, Chisholm R, Sinha S & O'Driscoll R. (2013). Acute *Aspergillus* pneumonia associated with mouldy tree bark-chippings, complicated by anti-glomerular basement disease causing permanent renal failure. *Medical Mycology Case Reports*, **2**:125-127

13. Denning DW & Bowyer P. (2013). Editorial Commentary: Voriconazole Resistance in *Aspergillus fumigatus*: Should We Be Concerned? *Clin Infect Dis*, **57**(4):521-3.

14. Denning DW, Pleuvry A & Cole D. (2013). Global burden of allergic bronchopulmonary aspergillosis with asthma and its complication chronic pulmonary aspergillosis in adults. *Med Mycol*, **51**(4):361-70

15. Denning DW, Pleuvry A & Cole D. (2013). Global burden of chronic pulmonary aspergillosis complicating sarcoidosis. *Eur Respir J*, **41**(3):621-6

16. Desbois AP, Sattar A, Graham S, Warn PA & Coote PJ. (2013). MRSA decolonization of cotton rat nares by a combination treatment comprising lysostaphin and the antimicrobial peptide ranalexin. *J Antimicrob Chemother,* **68**(11):2569-75

17. Espinel-Ingroff A, Arendrup MC, Pfaller MA, Bonfietti LX, Bustamante B, Canton E, Chryssanthou E, Cuenca-Estrella M, Dannaoui E, Fothergill A, Fuller J, Gaustad P, Gonzalez GM, Guarro J, Lass-Flörl C, Lockhart SR, Meis JF, Moore CB, Ostrosky-Zeichner L, Pelaez T, Pukinskas SRBS, St-Germain G, Szeszs MW & Turnidge J. (2013). Interlaboratory variability of caspofungin MICs for *Candida* spp. using CLSI and EUCAST methods: Should the clinical laboratory be testing this agent? *Antimicrob Ag Chemother*, **57**(12):5836-5842

18. Farid S, Mohamed S, Devbhandari M, Kneale M, Richardson M, Soon SY, Jones MT, Krysiak P, Shah R, Denning DW & Rammohan K. (2013). Results of surgery for chronic pulmonary aspergillosis, optimal antifungal therapy and proposed high risk factors for recurrence - a National Centre's experience. *J Cardiothoracic Surgery*, **8**(1):180.

19. Fraczek M, Bromley M, Buied A, Moore C, Rajendran R, Rautemaa R, Ramage G, Denning DW & Bowyer P. (2013). The cdr1B efflux transporter is associated with non-cyp51a-mediated itraconazole resistance in *Aspergillus fumigatus*. *J Antimicrob Chemother*, **68**(7):1486-96.

20. Gainza ML, Aguirre JM, Novak-Fraser L, Nieminen M, Moragues MD, Rautemaa R. (2013). Production of acetaldehyde by *Candida albicans* colonising patients with oral lichenoid disease. *J Oral Pathol Med*, **42**:243-9

21. Gregson L, Goodwin J, Johnson A, McEntee L, Moore CB, Richardson M, Hope WW & Howard SJ. (2013). In vitro susceptibility of *Aspergillus fumigatus* to isavuconazole: correlation with itraconazole, voriconazole, and posaconazole. *Antimicrob Agents Chemother*, **57**(11):5778-5780

22. Grice C, Bertuzzi M & Bignell E (2013). Receptor-mediated signaling in *Aspergillus fumigatus*. *Front Microbiol*, **4**:26.

23. Grönholm L, Lemberg KK, Tjäderhane L, Lauhio A, Lindqvist C & Rautemaa-Richardson R. (2013). The role of unfinished root canal treatment in odontogenic maxillofacial infections requiring hospital care. *Clin Oral Investig*, **17**:113-21.

24. Harries E, Carmona L, Muñoz A, Ibeas JI, Read ND, Gandía M & Marcos JF. (2013). Genes involved in protein glycosylation determine the activity and cell internalization of the antifungal peptide PAF26 in *Saccharomyces cerevisiae*. *Fungal Genet Biol*. **58-59**:105-15.

25. Hayes G & Denning DW. (2013). Frequency, diagnosis and management of fungal respiratory infections. *Curr Opin Pulm Med*, **19**(3):259-65

26. Haylett A, Felton S, Denning DW & Rhodes L. (2013). Voriconazole-induced photosensitivity: photobiological assessment of a case series of 12 patients. *Br J Dermatol,* **168**(1):179-85.

27. Herbst S, Shah A, Carby M, Chusney G, Kikkeri N, Dorling A, Bignell E, Shaunak S & Armstrong-James D. (2013). A new and clinically relevant murine model of solid-organ transplant aspergillosis. *Dis Model Mech*, **6**(3):643-51

28. Howard S, Pasqualotto A, Anderson M, Leatherbarrow H, Albarrag A, Harrison E, Gregson L, Bowyer P & Denning DW. (2013). Major variations in *Aspergillus fumigatus* arising within aspergillomas in chronic pulmonary aspergillosis. *Mycoses*, **56**(4):434-41

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