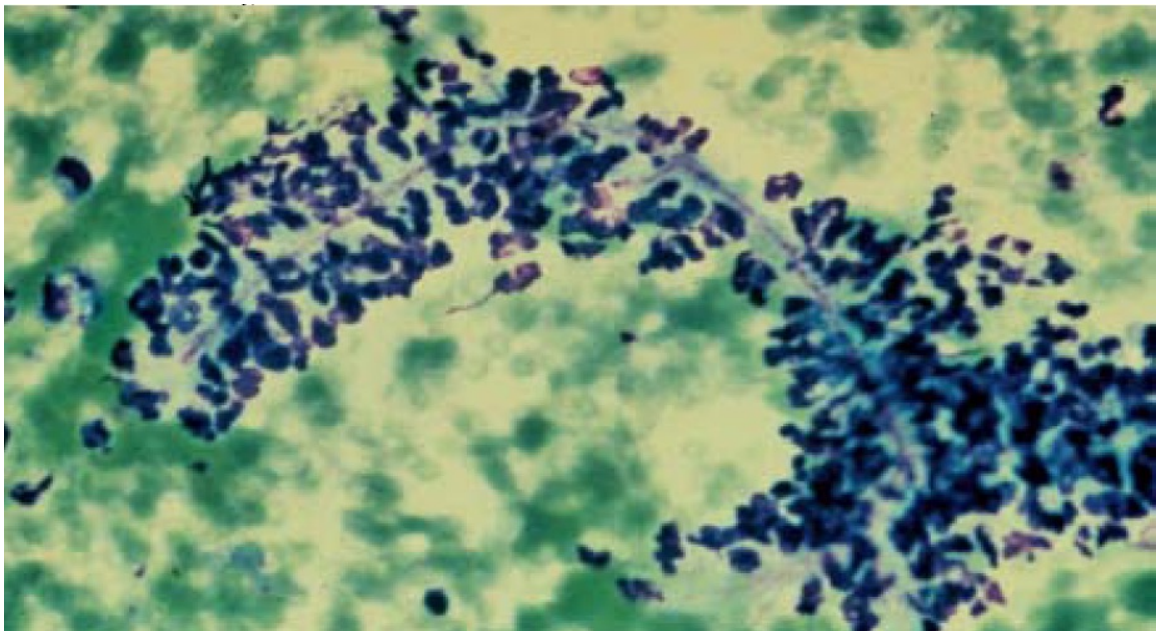
NHS National Commissiong Group Chronic Pulmonary Aspergillosis National service

The National Aspergillosis Centre

Annual Report 2014-2015



Contents

Cover photo shows many neutrophils crowded around and attacking hyphae of *Aspergillus fumigatus*, rather ineffectively in this case as the neutrophils are from a patients with chronic granuloatous disease. Courtesy of Drs Brahm Segal and Steven Holland, NIH.

1 General Overview and highlights

This report covers the fifth full year of this nationally commissioned service. The number of new patients with CPA has increased annually; 66 in 2009/10, 58 in 2010/11, 74 in 2011/12 and 89 in 2012/13, 125 in 2013/14 and 119 in 2014/15. Forty nine patients died and 21 were discharged from service, leaving a total of 363 on service from England and Scotland and an additional 13 patients from Wales on April 1st 2015. This represents a 9.4% growth in end of year patients in one year, and a 39% growth over 2 years. Non-CPA patients with aspergillosis are also being referred in larger numbers.

There have been additional innovations in our patient support work, with a quarterly Community Booklet being distributed in clinics and a 'buddy' phone system introduced. The website for patients and monthly meetings are well attended either in person or online – this outreach extends across the UK into the whole English speaking world, and supports patients with all forms of aspergillosis. Travelling distances and cost for some patients and relatives continues to be a problem, often delaying first appointments.

The implementation of a trial of therapy for posaconazole has greatly reduced administrative effort, allowing needy patients to go on the drug rapidly and been successful in only allowing those who truly benefit to stay on therapy. An audit of 55 patients who had commenced a trial of posaconazole identified 4 who successfully completed a trial and stayed on therapy, 4 who failed the criteria for success and stopped therapy, 12 had significant adverse reactions at 4 months and 3 at 6 months, 5 had died, and others were still under review. Longer term IV therapy had been implemented for 3 patients, following a national ICP process.

The volume of samples being processed by the Mycology Reference Centre continues to rise, notably for aspergillus PCR. Antifungal resistant rates in *A. fumigatus* remain above 10%.

International clinical guidelines for the diagnosis of management of aspergillosis generally and CPA specifically have been formulated by a joint committee of the European Society for Clnical Microbiology and Infectious Diseases and the European Respiratory Society. For CPA this work was lead by the NAC and will be published in the European Respiratory Journal. A separate guideline effort of the Infectious Diseases Society of America is in the final stages of drafting.

The whole research group published 38 papers and book chapters including some key observations including multiple genetic links with CPA, an estimate of the number of cystic fibrosis patients with aspergillosis globally and several key fundamental observations about *A. fumigatus*. The first of the country burden of fungal disease papers, from Nigeria, was published with an estimated 120,700 CPA patients in Nigeria, contrasing with 290,000 folllowing TB in India.

2 Activity

The total referrals, inpatient stays, procedures, death and caseload in 2014/15 were as follows:

Activity Measure / Currency	Month Activity												Contract Currency	
	M01 Apr	M02 May	M03 Jun	M04 Jul	M05 Aug	M06 Sep	M07 Oct	M08 Nov	M09 Dec	M10 Jan	M11 Feb	M12 Mar	Y/N	YTD Actual
Referrals	35	30	25	29	26	28	35	28	27	30	32	34	N	359
New Patients Testing	14	7	5	5	6	12	9	12	9	12	15	13	Y	119
Outpatient - Follow-Up Attendances	108	144	124	116	139	118	128	131	91	133	101	144	N	1,477
Caseload - Band 1	129	128	128	127	128	127	125	127	133	138	146	150	Y	150
Caseload - Band 2	159	160	163	164	161	164	171	174	179	177	180	175	Y	175
Caseload - Band 3	24	25	25	24	25	25	24	25	23	24	24	25	Y	25
Occupied Bed Days	86	15	65	27	32	17	105	50	109	44	67	197	Y	814
Inpatient Discharges	5	4	3	3	1	4	6	4	7	5	5	11	N	58
IV Homecare (OPAT) (days)	0	8	0	27	0	0	0	0	0	0	0	0	N	35
Surgical Resection	0	1	0	1	1	0	0	0	0	1	0	0	Y	4
Embolisations	2	1	1	1	0	1	3	1	2	1	1	1	Y	15
Patient Death	3	5	1	6	5	6	4	2	7	4	2	4	N	49
Discharge from Service	2	3	3	1	3	0	3	0	0	0	2	4	N	21

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

Of the 359 new 'aspergillosis' referrals from England and Scotland (increase of 13.2%) during the year 2014/15, 119 (33.1%) had CPA, very similar to the previous year (125 patients). There were seven inpatient admissions, which included two internal referrals, one of whom died. Among the outpatient referrals, the mean time from referral to being seen was 6 weeks (Appendix 2); appointments longer than 10 weeks were 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 5.5 weeks, which is an improvement on the previous year. Appendix 2 shows the area of residence, date of referral and date of appointment. In addition the service cares for 13 patients from Wales. Two patients from Ireland were discharged from service during the year.

There has been a growth in Band 1 numbers from 127 to 150 patients, Band 2 patient numbers have grown from 159 to 175, and Band 3 from 24 to 25 patients. These shifts include 49 deaths (51 the previous year) and 21 discharges from service (16 the previous year). Four patients were presumptively cured with surgery. Fifteen underwent bronchial artery embolization.

Admission days were again substantially lower at 814, with 35 patient days at home on IV therapy. Compared with 2012/3, this is almost a 50% reduction from 1,613 days in hospital. Our presumption is that is attributable to active immunization with Prevanar 13 and Menitorix, reducing some pneumococcal and *Haemophilus* infections. Intensive oral antifungal therapy with therapeutic drug monitoring also mimimises breathrough aspergillosis.

3 Mycology Reference Centre, Manchester

The Mycology Reference Centre Manchester (MRCM) has completed its sixth year of operations. There have been numerous developments and continued growth in its portfolio of tests and activities, and as well as major contributions to the University of Manchester taught Masters level degrees in Medical Mycology and Medical Microbiology.

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 second 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 offered as three-week CPD courses accredited by the Royal College of Pathologists.
4. Marked increase (87%) in requests for Aspergillus PCR tests on NAC patients
5. Income: internal and external: increase of 4.3% compared to 2013-2014
6. Income: environmental monitoring business unit: income in excess of £30,000
7. 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
    - Department of Microbiology, Clinical Sciences Building
    - ENT Theatres: ventilation system upgrade
    - Catheter Laboratories
    - Completion of Paediatric OPD Courtyard Project
    - New Bronchoscopy Unit
    - Burns Unit
    - Cardiac MRI Scanner Building
    - Endoscopy drying cabinets and environment
    - Fire Detector Upgrade works
    - Fire stopping works
    - Hybrid Theatre Project: 12 months
        - CF/Pearce Ward
        - Doyle Ward
        - TDC/Endoscopy Recovery Suite
8. Establishment of a Mould Surveillance Service for assessing the homes of NAC and Respiratory Medicine patients, UHSM
9. Other services for non-CPA patients:
    - Real-time PCR for Pneumocystis DNA

- 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.

2) Representation on national and international committees:

- EUCAST Antifungal Susceptibility Testing Committee as a Collaborating Laboratory
- Public Health England Standards for Microbiology Investigations Steering Committee
- British Society for Medical Mycology
- International Society for Human and Animal Mycology

3) Research activities:

- Consolidation of test portfolio offered for the benefit of CPA patients:
    - Ongoing evaluation of a lateral flow device (ISCA Diagnostics/OLM Medical) for the detection of an Aspergillus exoantigen in sputum from CPA patients
    - Ongoing experience regarding sensitivity testing on *Aspergillus* isolates to include terbinafine, anidulafungin, caspofungin, micafungin and a new azole antifungal, isavuconazole
    - Real-time PCR for Aspergillus in respiratory secretions and blood
    - Molecular identification of fungi, including unusual *Aspergillus* species. This is a nation-wide service
    - Ongoing evaluation of automated DNA extraction robots in order to respond to the dramatic increase in PCR assay requests
    - Completed evaluation of improved methods for detection of anti-*Aspergillus* antibodies: ELISA for *Aspergillus* IgG and indirect haemagglutination for *Aspergillus* precipitins
    - 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*
    - Publications 2013: 15 (Appendix 5) including treatment and diagnostic guidelines commissioned by the European Society for Clinical Microbiology and Infectious Diseases.

4) Training:

- Completion of four year training programmes for two trainee Clinical Scientists funded by NHS NW SLA. One has been appointed as a Band 7 Clinical Scientist in Edinburgh Royal Infirmary. One appointed to a five-year Higher Specialist Scientific Training post at Manchester Royal Infirmary
- Completion of a three-year Healthcare Scientist training programme under the Department of Health's Modernisation of Scientific Careers scheme.

- UCL/BSMM distance learning Masters in Medical Mycology: one staff member enrolled
- Individual CPD modules of University of Manchester Masters in Medical Mycology, in collaboration with MRCM approved by Royal College of Pathologists and each awarded 25-27 credits
- Contributions to the development of an on-line histopathology of fungal infections training course, in collaboration with the University of Manchester, Leading International Fungal Education (www.LIFE-Worldwide.org - UK charity).
- Host to four University of Manchester PhD students
- Award of two IBMS registration portfolios. The MRCM is a designated IBMS training laboratory.
- Enrolment of one of the laboratory's Medical Laboratory Assistants on a NVQ course in Pathology
- Host to two University of Bradford one-year work experience students
- Host to trainees from around the UK
- Host to two oversees visitors for training and collaboration:
    - Dr Subhosmito Chakrabarty (Kolkata)
    - Dr Rita Oladele (Lagos)

4) Challenges:

- Ongoing maternity leaves, leave entitlements of staff, and part-time returns to work
- Dramatic increase in work-load in the absence of an adequate workforce.

4 Clinical service developments and personnel

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

1) 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 (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)
Wei-Juan Zhang in Infectious Diseases (50%)
Dr Wilson Cheng, Educational Fellow (50%)
Ms Deborah Kennedy, Specialist Nurse (40%)
Mrs Georgina Powell, Specialist Nurse (80%)
Ms Stephanie Poliensa, Specialist Nurse (50%)
Mr Philip Langridge, Senior Specialist Physiotherapist (50%)
Miss Reyenna Sheehan, Specialist Physiotherapist (20%)
Dr Iain Page, Clinical Fellow (100%)

Dr Gemma Hayes, Clinical Fellow (100%)
Mrs Christine Harris, NAC manager (100%)
Dr Graham Atherton, Senior Clinical Information Architect (Patient engagement) 25%
Mrs Maxine Redshaw (50%)
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.

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

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 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 PCT funded patients with other forms of aspergillosis. There was a problem in delivery last year and no new patients were registered. We had a meeting with Healthcare at Home in February 2015 to discuss recommencement of the service and it was agreed that initially we would only register urgent patients and then gradually send small numbers to be registered to the service. This would allow the service to adjust to the extra numbers and to allow HAH time to bring in additional staff. This has worked well and HAH are now fully operational.

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 is much more sensitive than culture and can be used as a proxy for detecting resistance and clinical failure. It has also proved helpful to assess patient status and advise accordingly if they are too ill to attend. Testing has been extended to high volume cultures to improve the culture yield for susceptibility testing.

6) Home nursing

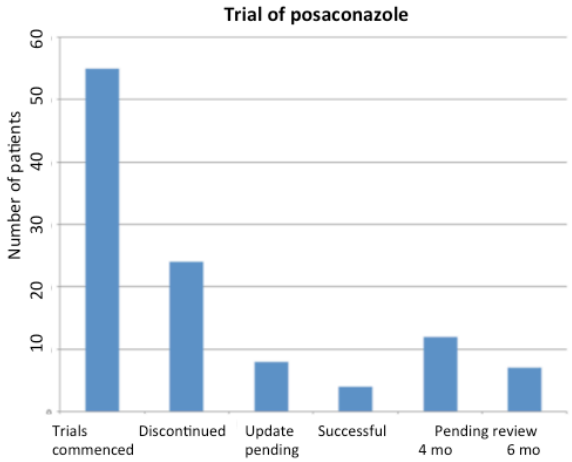
Home nursing follow up service for CPA patients at home has been discontinued. The quality of service delivered by Healthcare at Home was too variable to be useful.

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. Together with the MRC dyspnoea score the 2014/15 data is presented in Appendix 4.

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

New guidelines were introduced following discussions with NCG to use posaconazole on an individual trial basis. Patients are required to successfully meet the criteria set out by NCG of 3Kg weight gain and decrease in SGRQ score of 12 points by six months. Failure to meet these targets requires the patient to stop therapy. An audit of progress for February 2015 showed that 55 patients had commenced a trial of posaconazole, of whom 24 had discontinued and 4 had successfully completed a trial. The remainder were pending appropriate assessments. Of those who discontinued, 12 had significant adverse reactions at 4 months and 3 at 6 months, 5 had died and 4 had failed the criteria for success.



Extended courses of AmBisome or micafungin was also agreed for three patients in whom oral medication had failed and there was good evidence of improvement with a shorter course of IV therapy.

5 Audits

1. Time to appointment

Most patients were booked for an appointment within 6 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.

There were 11 deaths in year of the new patient referrals. Ten patients were not counted in the waiting time because they were late diagnoses or transition of disease.

Obviously when urgent cases are booked in, this pushes back routine appointments. A new fortnightly new patient clinic has been added to the service to help reduce the wait time for the increased number of new referrals to the centre. Distance and transport continue to be a problem for many patients that are referred to the centre which often adds to the delay in getting their appointment booked. Many patients have complained that the journey is not only costly but difficult to make when they are so unwell. In addition some patients cannot make the journey in one day and require accommodation which adds to the overall cost of their visits. While the patients 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.

For patients who could not make the journey but clearly required a management plan advice was sent to their local consultant in the interim until such time the patient could find a way to attend an appointment in Manchester.

2. Clinical audits

Several clinical audits have been undertaken in 2014/15. Most of these have been completed:

- Pneumococcal and haemophilus vaccination
- Chronic fibrosing pulmonary aspergillosis case series presented at ECCMID 2015, being written up
- CPA/ atypical mycobacterial coinfection. Database complete, need to analyse case series.
- Posaconazole trials (see section 4.8)
- Aspergillus PCR (write up complete)
- CF genotype in ABPA (ongoing)
- Induced sputum yield of Aspergillus PCR and culture (completed, submitted for publication)
- Aspergillus nodules and masses (submitted for publication)
- Single and multiple dose AmBisome efficacy and side effects for CPA (submitted for publication)
- Survival in CPA patients (Submitted for publication)
- ABPA to CPA transition (submitted, under revision)

- Gamma interferon production deficiency (Completed, presented, being written up by Addenbrookes).

6 Patient and public engagement

1. Community booklet.

A new community booklet has been produced that is now distributed to all patients who do not have access to a computer. 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 allows readers to know what is happening in the service and with other patients and carers. It includes news items, recipes, puzzles, tips for breathing, physio and travel. It also provides contact numbers for social groups. It is also circulated in the clinic area so that patients can read while in the waiting room or take home.

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 50% of our patients fall into this category it is gratifying that we are seeing 25 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.

2. Aspergillus Website @ *www.aspergillus.org.uk*

The Aspergillus Website is most used resource for patients & carers to access information about aspergillosis in its many forms. The Aspergillus Website had visitors from 179 countries in the first quarter of 2015. A newsletter is sent to ~25,000 emails monthly, and a separate patients' newsletter is also written. Prior NAC patient surveys have suggested that it is only accessed by approximately 51% (2012) then 54% (2013) and 57% (2014) of our patients. By the start of 2014 we had implemented a new website structure that allows easier use of the patient's part of the website (www.nacpatients.org.uk/) which seemed to have a positive impact but by early 2015 the proportion of our patients who had visited the website had fallen slightly to 47%. This might have been caused by one or more of the following:

- The rest of the Aspergillus Website was transitioning to the new structure during 2014, causing some disruption
- Some of the activity that used to be done on the patients website has now been 'outsourced' to our Facebook groups (500 participants) and our NHS aspergillosis community (490 participants) (http://www.nhs.uk/Conditions/Aspergillosis/Pages/Introduction.aspx) and thus is not counted in the current survey.
- Community booklet and monthly newsletter handed out in clinic supplanting the need for the website.

The success of the new website structure in engaging those who browse the internet using handheld devices is illustrated in the following table:

Proportion of total users accessing via mobile devices May 2015:	Aspergillus Website aspergillus.org.uk	Patients Website nacpatients.org.uk
Smartphones	23%	24%
Tablets	10%	19%
Total	33% (22% in Dec 2014)	43% (38% in Nov 2013)

Of those who looked at the website, satisfaction was 100%.

3. 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 encourages face to face social support between patients & carers. The meeting was attended by 10% of all patients who responded to the patient's survey in 2015 whereas 7% attended in 2014 and 6% in 2012. 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. The meeting is attended by 8 – 12 people each month and we regularly (most months) see new attendees taking the opportunity to meet with us. The meetings are lead and organised by Dr Graham Atherton and Chris Harris.

One comment from participants was the inability of nurses to attend the meeting since the move to Fridays was a drawback. We have addressed that need by moving the meeting to the first Friday in the month (from Feb 2015) and this has resulted in a nurse attending 3 meetings in 2015.

The subjects covered and their on-line links are listed below. More recent meeting recordings have had to be moved from their former host (Slideshare) to our patients website. As of July 2015 they had been accessed over 42,000 times on Slideshare and a further 10,000 (2014-15) in their new location.

March 2015	NCG Commissioner	Funding meeting for NAC	0' 00' 00secs	0' 26' 45secs
February 2015	Debbie Kennedy (Specialist Nurse in Aspergillosis)	Antifungal drugs and their management	0' 26' 45secs	end
	Graham Atherton	Antifungal Interactions, Spring booklet, London Marathon		
		Entire Meeting	0' 31' 40secs	0' 48' 40secs
December	Graham Atherton	Christmas Quiz		

2014				
		Entire meeting		
November 2014	MSc Students	Personal introductions to Medical Mycology in many different countries	0' 00' 00secs	0' 24' 20secs
	Evelyn	Her own story & why this group is worthwhile for patients		
	Graham Atherton	Entire meeting		1' 16' 25secs
October 2014	Graham Atherton	Diagnosing aspergillosis	0' 00' 00secs	
	Graham Atherton	Entire Meeting		1' 35' 45secs
September 2014	Danielle Yuill	Giving patients & carers a VOICE	0' 00' 00secs	0' 33' 00secs
	Chris Harris	Healthier together, CallPlus, Ring & Ride	0' 33' 00secs	0' 46' 45secs
	Graham Atherton	Entire Meeting		1' 35' 45secs
August 2014	Chris Harris	Self help: a letter from a patient	0' 00' 00secs	1' 31' 39secs
	William Kidd	Damp homes & health: Help from the Institute of Specialist Surveyors & Engineers (www.isse.org.uk)		1' 31' 39secs
	Graham Atherton	Entire Meeting	0' 00' 00secs	54' 15secs
July 2014	Graham Atherton	Heatwaves: Precautions, Antifungal drug resistance in the environment	54' 15secs	1' 11' 30secs
	David Denning	Managing our deaths better		1' 27' 30secs
	Led by Graham Atherton	Entire Meeting	0' 00' 00secs	10' 05secs
June 2014	Chris Kosmidis	Side effects of long term steroid use	10' 05secs	1' 44' 5secs

	Graham Atherton	Open the windows: A poetry and music awareness event
	Led by Graham Atherton	Entire Meeting
May 2014	Paul Bowyer	Latest NAC research results: ABPA
May 2014	Chris Harris	Travel Tips
May 2014	Graham Atherton	Several topics including discussions on defective sunblocks, recent developments in diagnostics & treatment and beginning discussion on end of life planning for chro respiratory patients.
	Graham Atherton	Entire Meeting
April 2014	Graham Atherton	Offline community building (Newsletter)
April 2014	Chris Harris	5th Anniversary of the National Aspergillo Centre
April 2014	Led by Graham Atherton	Entire meeting

4. 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 in 2012 was to encourage the setting up of regional support groups run by volunteer patients and we now have eight 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. We recently found a new leader for the Bristol Group, set up a new group in Scotland and are about to set up a group in Australia!

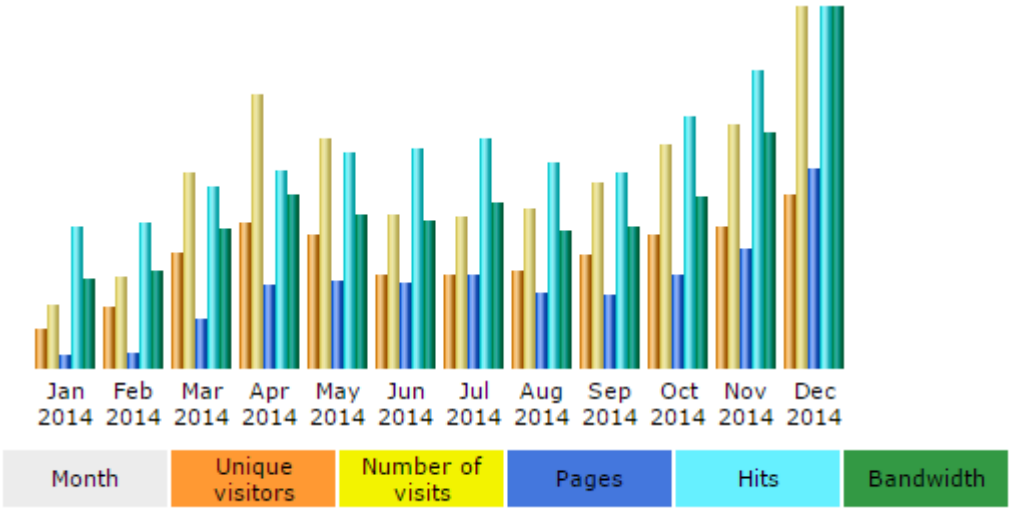
Each group advertises its presence with the local medical organisations, performing two services: offering a service to medical professionals as well as patients and increasing awareness of aspergillosis nationally. Each group is dependent upon its leader to be well enough and have the time & energy 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. This has been problematic as groups find that their meeting places don't provide good enough internet connections, so more work is needed to start this up – possibly a single national 'Skype' session that all groups can publicise and provide contact points for but most will attend from home.

The 2015 patient's survey showed that 49% of people were aware of our regional support groups, which is encouraging as is the 14% (10% 2014) who want more information about setting one up. 10% (5% 2014) have gone so far as to make contact with a group.

4. Patients' communities

The new Patient's Website [www.nacpatients.org.uk] has received steadily increasing traffic since its redesign, last figures being 13,000 unique visitors (26,000 visits) in December 2014. This website is the gateway to several communities and is also making progress in encouraging the creative arts, a collection of which is made available on the website.



There are long standing online communities on Yahoo! (1106) and Facebook (504 members and very active), NHS Choices Aspergillosis Community (486 members) as well as 512 LinkedIn members (Aspergillus and Aspergillosis Group).

5. Phone buddies

Graham Atherton and Chris Harris completed a training course on Befriending and Mentoring so that they could introduce a new "buddy service" and support and guide anyone who wished to offer that service. We provide a phoneline since December 2014 for patients & carers to use for instances when they have no computer access or prefer to use a phone and speak to someone who can help. This phoneline is manned by patient/carer volunteers who report steady interest.

7 Research outputs, other published research summary

1. Papers and book chapters

Amongst the 38 papers and book chapters published in calendar year 2014, there were several areas of direct relevance to patients with CPA and pulmonary aspergillosis. These were:

1. Genetics of CPA

In 2 papers using candidate gene approaches, several important genetic abnormalities have been identified in CPA patients including distinctive single nucleotide polymorphisms in several immune genes including interleukins 1 and 15 and several other immune receptors (refs 8 and 11).

2. Lab processing of samples

A small detailed study of sputum and bronchoalveolar lavage samples from patients with aspergillosis showed PCR to be more sensitive than culture, high volume culture to have any chance of growing aspergillus and sputum to have stronger PCR signals than BAL fluids (ref 2). This needs confirmation elsewhere, but is likely to change how samples are handled in routine laboratories.

3. Azole resistance

Two position papers reviewed the use of azole fungicides in agriculture in driving azole resistance in *Aspergillus*, and the implications of voriconazole resistance for selection of initial therapy for life-threatening aspergillosis (Refs 1 and 30). As voriconazole is ~20% more active (in terms of reduce mortality) than amphotericin B and echinocandins, the rate of resistance has to be quite high to justify a shift in primary therapy recommendations. The rate of azole resistance in UK fields sprayed with azoles was 2.1% and 0% in Manchester (ref 18).

4. Epidemiology

We provided estimates of the number of patients with CPA in India (290,000 patients after TB alone) and in Nigeria (120,000) cases (refs 12 and 17). We also estimated the number of adult patients with cystic fibrosis and allergic bronchopulmonary aspergillosis (ABPA) and *Aspergillus* bronchitis worldwide (6,675 and 11,000 respectively) (ref 10). ABPA may be more common in India, and estimates varied from 0.12 to 6 million, with the best estimate at 1.4 million (ref 17). We also reviewed the epidemiological data for severe asthma with fungal sensitisation (SAFS) and a conservative estimate of 6.5 million is likely (ref 6).

2. Abstracts

Several abstracts were submitted and/or presented:

European Conference on Clinical Microbiology and Infectious Diseases (ECCMID), Copenhagen 2015

Aspergillus nodule; a less common manifestation of Chronic Pulmonary Aspergillosis.

Muldoon, E.G. Page, I. Bishop, P. Denning, D.W.

Objectives

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 purpose of this study is to review the presentation, radiology and histological features of nodules caused by *Aspergillus spp*.

Methods

Thirty four patients with nodular *Aspergillus* disease were identified from patients attending our specialist Chronic Pulmonary Aspergillosis clinic. Patients with cavitating lung lesions, with or without fibrosis and those with aspergillomas were excluded. Patients with a diagnosis of invasive aspergillosis were also excluded. Demographic data, laboratory data and radiologic findings were recorded on each patient, in addition to their clinical presentation.

Results

Thirty four patients with pulmonary nodules and supportive features diagnostic of aspergillosis (histology and/or laboratory findings) were identified. The mean age of the patients was 58 years (range 27-80). Eighteen (53%) were men. The mean Charleston co-morbidity score was 3.3 (0-7). Smoking status was documented in 24 patients; 19 (79%) were current or former smokers. None of the patients was in receipt of immunosuppressive drugs. Of 30 patients who were investigated mannose binding lectin deficiency, 12/30 (40%) were deficient. Ten patients (30%) did not have an elevated *Aspergillus* IgG, results were not available for one patient, and only 10 patients had elevated *Aspergillus* precipitins. Nineteen patients (55%) had a single nodule identified on computerised tomography (CT), the remaining patients had up to 7 nodules present. The mean size of the nodules was 2.1cm (range 1.0-5.5cm), none had cavitation radiographically. The upper lobes were most commonly involved, being involved in 29 (85%) of patients. Only one patient had significant lymphadenopathy on CT. Histology was available for 25 patients, 17 underwent lung biopsy. Biospy findings were; evidence of fibrosis, granulation tissue and visualisation of fungal hyphae. On presentation, thirty patients (88%) complained of cough, 24 (70%) complained of dyspnoea, 11 (32%) complained of weight loss, and 5 (15%) complained of haemoptysis.

Conclusion

Pulmonary nodules are a less common manifestation of aspergillosis in immunocompetent patients. Their natural history is not yet defined, although in this series many of the patients presented with cough alone. These nodules may be difficult to distinguish from other lung pathology on CT findings alone.

Comparative efficacy of five *Aspergillus*-specific IgG ELISAs for the diagnosis of Chronic Pulmonary Aspergillosis (CPA)

1 – Page, Iain Dunsmuir – Institute of Inflammation and Repair, The University of Manchester, UK, Manchester Academic Health Science Centre, UK, National Aspergillosis Center, University Hospital South Manchester, UK

2 – Kwizera, Richard – Institute of Inflammation and Repair, The University of Manchester, UK, Infectious Diseases Institute, Mulago Hospital, Kampala, Uganda.

3 - Richardson, Malcolm - Institute of Inflammation and Repair, The University of Manchester, UK[a], Manchester Academic Health Science Centre, UK[b], National Aspergillosis Center and Mycology Reference Centre, University Hospital South Manchester, UK[c]

4 - Denning, David W - Institute of Inflammation and Repair, The University of Manchester, UK[a], Manchester Academic Health Science Centre, UK[b], National Aspergillosis Center, University Hospital South Manchester, UK[c]

Objectives

Chronic pulmonary aspergillosis (CPA) is a fatal condition that is estimated to effect 2-3 million people worldwide. Measurement of *Aspergillus*-specific IgG is central to the diagnosis of CPA, alongside clinical and radiological features. In-house assays are in use in some referral centers, but cannot be easily reproduced in other laboratories. Various assays are commercially produced. Such assays might provide consistently reliable results that are reproducible across many areas.

Our major aim was to compare the efficacy of five commercial assays for the diagnosis of CPA in an untreated population. We also noted that the diagnostic cut-offs for these assays were largely determined in mixed groups of aspergillosis patients and may not be optimal for the diagnosis of CPA. Hence, we aimed reconsider the appropriateness of existing diagnostic cut-offs for these assays in our patient population.

Methods

We tested sera from 250 patients with untreated CPA at the UK National Aspergillosis Center. Diagnosis of CPA was taken from clinical notes and required appropriate symptoms, radiological changes and microbiological evidence of infection. 100 sera from adolescent Ugandan blood donors were tested as controls.

Intra-assay variability was measured for each assay by repeating a single test 20 times. *Aspergillus*-specific IgG was measured on all sera by five methods. ImmunoCAP was also performed during routine diagnostic work-up. We performed ROC curve analysis to compare the efficacy of each assay for CPA diagnosis. We suggest new diagnostic cut-offs for each assay and describe sensitivity and specificity with these cut-offs.
Results

Co-efficient of variation (CoV), Receiver-operator curve area under curve (ROC AUC) and sensitivity and specificity for each test are shown in table 1.

ROC curves are shown in figure 1.
Conclusions

The Siemens Immunolite assay has statistically superior efficacy to all other assays where ROC analysis was possible, for the diagnosis of CPA. It also has superior sensitivity to

the ImmunoCAP assay, which is widely used in Europe. Its high sensitivity and specificity mean that it can be used with confidence for the diagnosis of CPA, when clinical and radiological features are also present.

TEST	CoV	Median *Aspergillus*-specific IgG in healthy controls (n=100)	Median *Aspergillus*-specific IgG in CPA cases (n=250)	Maximum *Aspergillus*-specific IgG in CPA cases (N=250)	ROC AUC (95% confidence interval)	New proposed diagnostic cut-off	Sensitivity with new cut-off	Specificity with new cut off
Siemens	3.4%	4 mg/L	390 mg/L	7660 mg/L	0.99 (0.981 - 0.999)	10 mg/L	95.6%	98%
Serion	23.2%	6 U/ml	133 U/ml	3436 U/ml	0.972 (0.957 - 0.986)	35 U/ml	90.4%	98%
Genesis	11.1%	7 U/ml	60 U/ml	930 U/ml	0.902 (0.872 - 0.933)	16 U/ml	78.4%	97%
Dynamiker	12.1%	34 U/ml	126 U/ml	6118 U/ml	0.918 (0.890 - 0.946)	70 U/ml	75.2%	98%
ImmunoCAP						*40 mg/L*	87.6%	
Precipitins							59%	100%

Evaluation of Fungiplex Surface-Enhanced Raman Scattering PCR Assay for the Detection of Aspergillus in Sputum

Emma Ann Davies[1], Rikesh Masania[1], Jennifer Dougan[2], Lily Novak-Frazer[3], Emma Stirling[2], Ross Stevenson[2], David Denning[4], Malcolm Richardson[1].

[1]Mycology Reference Centre Manchester, Manchester, United Kingdom.
[2]Renishaw Diagnostics Limited, Glasgow, United Kingdom.
[3]University of Manchester, Manchester, United Kingdom.
[4]National Aspergillosis Centre, Manchester, United Kingdom.

Culture of respiratory samples for *Aspergillus spp.* is substantially less sensitive than either antigen detection or PCR. PCR is still underrepresented in clinical laboratories. A semi-automated PCR surface-enhanced Raman scattering (SERS) Fungiplex assay for the detection of both *Aspergillus* and *Candida* spp., capable of differentiating drug resistant species, has recently been launched commercially. Whilst extensive validation work has been carried out for this assay on blood samples, limited data are available for respiratory samples. This study was designed to evaluate sputum samples as processed through the RenDx platform for use in the diagnosis and management of respiratory aspergillosis. Eighty sputum samples were collected prospectively from patients with proven/probable chronic pulmonary aspergillosis and analysed for the presence of *Aspergillus* and *Candida* sp using the Fungiplex assay [Renishaw Diagnostics Limited, Glasgow, UK].

Results were compared to culture performed as per Public Health England SMIB57: Investigation of bronchoalveolar lavage, sputum and associated specimens.
A total 12/14 (85%) culture positive samples were detected using Fungiplex. Of the two undetected, one sample contained an *Aspergillus sp*not covered by the primer sets. A total 27/66 (40%) culture negative samples tested positive by Fungiplex, of these 14/27 (52%) were on active treatment which may account for the perceived false positivity. *Candida* positivity was observed in 18/80 (23%) samples. A further explanation for perceived false positivity may be the difference in sample volume analysed by each method with culture utilising 1µl of a 1 in 500 dilution of treated sputum and nucleic acid extraction for Fungiplex utilising 1.6ml of treated sample.
The currently observed results suggest Fungiplex may have superior sensitivity to culture, especially in those patients who are undergoing active treatment. Whilst the clinical utility as a standalone test for sputum samples remains unclear,results suggest the test can be beneficial when used alongside other relevant diagnostics.

Fibrosis as a complication of chronic pulmonary aspergillosis

C. Kosmidis, P. Newton, E. Muldoon, D.W. Denning

The National Aspergillosis Centre- University Hospital of South Manchester, The University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom

Objectives: Chronic Pulmonary Aspergillosis (CPA) is a chronic, progressive condition affecting patients with underlying lung pathology. It impacts significantly on quality of life and mortality. A subset of patients with CPA has been observed to develop significant fibrosis, termed chronic fibrosing pulmonary aspergillosis (CFPA). The causes, course and prognosis of these patients have not been characterised. We aimed to define the clinical implications and prognosis of patients with fibrosis complicating CPA.
Methods: We retrospectively identified patients with CPA followed in our specialty clinic who developed significant fibrosis by reviewing their medical notes. We defined CPA as the presence of positive *Aspergillus* serology and evidence of *Aspergillus* in respiratory samples (by culture, PCR or galactomannan), accompanied by compatible findings on chest imaging. CFPA was defined as evidence of pulmonary parenchymal (not pleural) fibrosis on biopsy or presence of extensive fibrosis on imaging (chest X-Ray or computed tomography) in a patient with CPA. We recorded the demographic characteristics, underlying conditions, time to development of fibrosis, laboratory parameters, clinical course after CFPA was diagnosed, response to treatment and outcome.
Results: We identified 8 patients with CFPA; five were female. Mean age (range) was 59.25 (37-73) years. In 5 patients, fibrosis was already evident when CPA was diagnosed and in three it evolved after diagnosis of CPA in patients not on antifungals. Fibrosis was histologically confirmed in 3 patients; fungal hyphae were seen in one. Previously treated tuberculosis was the underlying condition in three patients, atypical mycobacterial

infections in three and previous chest surgery (for cancer or pneumothorax) in two. The predominant radiological finding was extensive or complete opacification of one lung, with volume loss and presence of cavities, usually with minimal contralateral involvement. One or more aspergillomas were present in 7 patients. CFPA usually developed over some weeks or months, but in one case within a month. Serial imaging revealed sparing of the contralateral lung in all cases. Response to antifungal agents was variable, and azole resistant strains were isolated in 4 cases on treatment. Interferon was used in one patient with a satisfactory response. Three patients died 1-3 years after developing fibrosis whereas 5 were alive for up to 10 years on follow up. Two cases were treated with a surgical procedure (lobectomy and pneumonectomy) and both developed complications (empyema and recurrence of aspergilloma in chest
cavity, respectively).
Conclusion: CFPA is an uncommon manifestation of chronic aspergillosis that may already be present when CPA is recognised or may develop in patients not on antifungals. Fibrosis is usually unilateral, extensive and does not spread to the contralateral lung. Prognosis is variable, as some patients may exhibit stable radiological appearances over several years, whereas some may deteriorate more rapidly.

Annual meeting of the Chartered Society for Physiotherapy, Birmingham

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

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

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.

Nebulised/ Bronchoscopically-instilled N-acetylcysteine for mucoid impaction

Langridge PJ, Denning DW

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

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

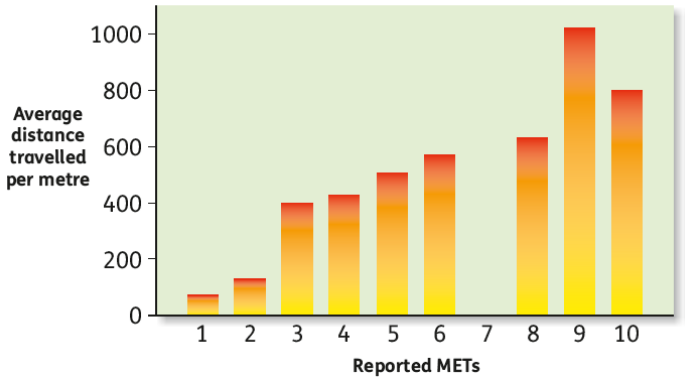
Subsequently, nebulised 20% NAC has been delivered by the Aspergillosis service respiratory physiotherapists using a PariSprint® nebuliser. A challenge test was conducted to ensure patient safety, and no adverse events were reported/observed
Conclusion
Instillation of NAC at bronchoscopy could resolve 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.

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

Langridge PJ

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

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.

International Society for Human and Animal Mycology, Melborne

Chronic Pulmonary Aspergillosis (CPA) frequently complicates pulmonary TB – interim results of a cross-sectional survey.

Page, Iain Dunsmuir – Institute of Inflammation and Repair, The University of Manchester, UK, Manchester Academic Health Science Centre, UK, National Aspergillosis Center, University Hospital South Manchester, UK

Onyachi, Nathan – Gulu Regional Referral Hospital, Uganda.

Opira, Cyprian – St. Mary's Hospital, Lacor, Gulu region, Uganda.

Opwonya, John – Department of Tuberculosis and Leprosy control, Gulu District Health Office, Uganda.

Sawyer, Richard - University Hospital South Manchester, UK

Hosmane, Sharath - University Hospital South Manchester, UK

Kneale, Matthew - National Aspergillosis Center, University Hospital South Manchester, UK

Richardson, Malcolm - Institute of Inflammation and Repair, The University of Manchester, UK[a], Manchester Academic Health Science Centre, UK[b], National Aspergillosis Center and Mycology Reference Centre, University Hospital South Manchester, UK[c]

Denning, David W - Institute of Inflammation and Repair, The University of Manchester, UK[a], Manchester Academic Health Science Centre, UK[b], National Aspergillosis Center, University Hospital South Manchester, UK[c]

CPA has a 5-year mortality of up to 85%. The global 5-year period prevalence of CPA is estimated at 0.8 to 1.3 million cases. The Siemens *Aspergillus* specific IgG assay has a specificity of 98% and sensitivity of 96% for the diagnosis of CPA.

400 adults who completed treatment for pulmonary tuberculosis in the last 7 years were recruited. Patients underwent clinical assessment, chest x-ray and *Aspergillus*-specific IgG measurement in 2012. 18 months later 283 of these patients were re-surveyed with repeat CXR. CT scan was also performed in patients with raised *Aspergillus*-specific IgG or suspicion of aspergilloma on CXR. GeneXpert tuberculosis PCR test was performed on all patients who could provide a sputum sample.

Likely CPA was diagnosed in a patient who has ALL of the following; 1 – Cough or haemoptysis of 1 month duration, 2 – Raised levels of *Aspergillus*-specific IgG, 3 – either progressive cavitation on serial CXR OR cavities with paracavitary fibrosis or aspergilloma on CT scan.

Table - Frequency of pulmonary aspergillosis

Condition	Number of cases	Frequency n=282	95% CI
CCPA	14	5%	2.9 – 8%
CFPA	2	0.7%	0.1 - 2.3%
CPA (includes CCPA + CFPA)	16	5.7%	3.4 – 8.8%
Simple aspergilloma	2	0.7%	0.1 – 2.3%
All pulmonary aspergillosis	**18**	**6.4%**	**4 – 9.4%**

CCPA – chronic cavitary pulmonary aspergillosis, CFPA – chronic fibrosing pulmonary aspergillosis.

There was no significant difference in CPA prevalence between the HIV positive and negative groups, although a non-significant trend to increased CPA in the HIV negative group was noted (p-value 0.08). 3 cases of active pulmonary tuberculosis were identified, none in the pulmonary aspergillosis group.

CPA is common complication of pulmonary tuberculosis. It represents a major public health issue. Effective treatment is available with cheap, generic Itraconazole and surgery. Diagnosis and treatment programs should now be investigated, defined and implemented as soon as possible.

8 Statutory reports

MRSA

No cases of MRSA were reported.

C. difficile infection

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

No HIRS reported

No SUI's were reported.

Complaints

There was one formal complaint made. This related to a delay in the patients clinic letter reaching her GP. This problem was resolved by the department and the Trust.

9 Future developments

The developments planned for 2014/15 were (and commented on):

- Recruitment of an additional nurse to support the growing number of patients. Not enough resource in the Trust to support this
- Implementation of an antibiotic at home service (OPAT), to include antifungal therapy. Implemented and growing, with one full time nurse and a second to be recruited. About 200 beds days saved across the Trust per month. Some CPA patints have used our OPAT, or another hospital's OPAT service.
- Merging of the infection specialities at UHSM into one administrative group. Not happened, because of the massive numbers of other more critical changes ongoing.
- Implementation of the Aspergillus IgG antibody comparison findings in the MRCM. The work is concluded and once published (paper submitted) will form a discussion about appropriate cut-offs.
- Development of a routine azole resistance service using pyrosequencing in the MRCM, and then clinical validation (2 year process). Business planning stalled, and now picked up again.

Developments planned for 2015/16 included:

- Decision about utility of offering routine sputum galactomannan assay – a superficial audit suggests the test over-reads, and may not reflect Aspergillus load in the airways.
- Introduction of isavuconazole, as a second or third-line therapy for CPA, using the same evaluation methodology now used for posaconazole.
- Implementation of a routine azole resistance service using pyrosequencing in the MRCM, and then clinical validation (2 year process).

- Introduction of Skype or Facetime nurse appointments, preceded by postal sputum and blood testing, to reduce travelling costs and increae appointment intervals.
- Planning for the recruitment of an additional consultant to contribute to the growth of the service.
- Support of a nascent infectious diseases service at the Brompton Hopsital with occasional joint clinics for complex aspergillosis cases.

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

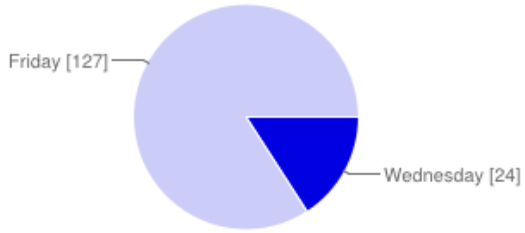
- Significant impairment of respiratory function, sufficient to impair activities of daily living, but ambulant
  and/or
- Concurrent anti-mycobacaterial treatment
  and/or
- Failed or developed toxicity to itraconazole capsules
  and
- No evidence of azole antifungal resistance

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

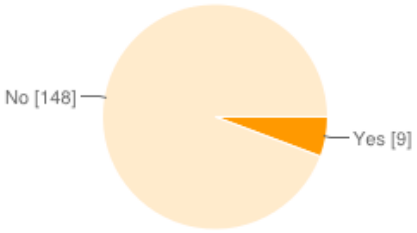
Appendix 2
National Aspergillosis Centre patients' survey

Which day did you attend the clinic?



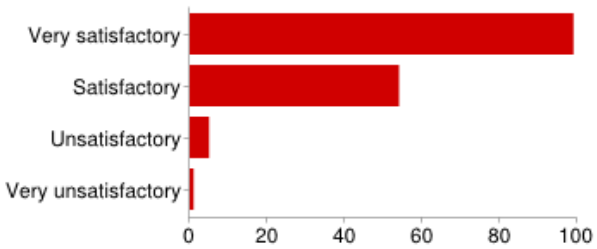
Wednesday	**24**	16%
Friday	**127**	84%

Is this your first visit to the National Aspergillosis Centre?



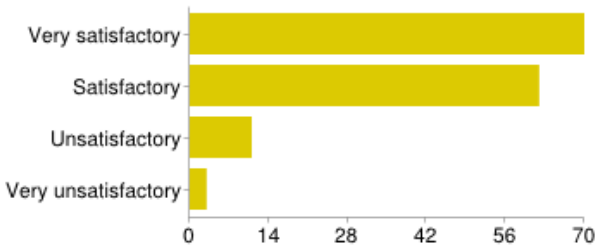
Yes	**9**	6%
No	**148**	94%

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



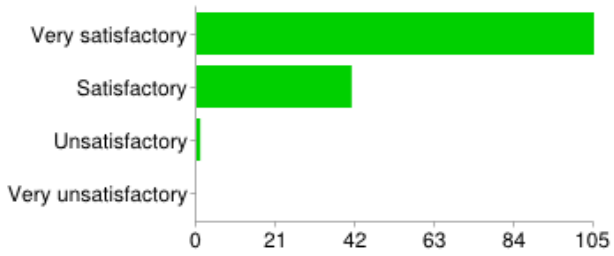
Very satisfactory	**99**	62%
Satisfactory	**54**	34%
Unsatisfactory	**5**	3%
Very unsatisfactory	**1**	1%

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



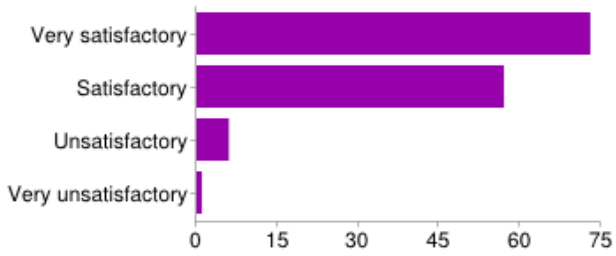
Very satisfactory	**70**	48%
Satisfactory	**62**	42%
Unsatisfactory	**11**	8%
Very unsatisfactory	**3**	2%

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



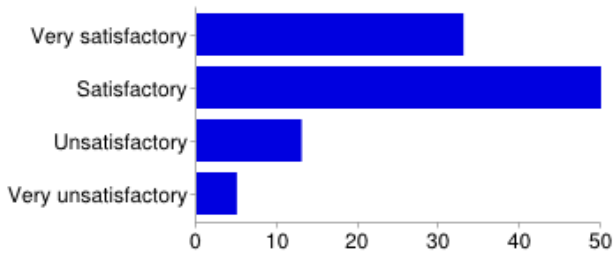
Very satisfactory	105	71%
Satisfactory	41	28%
Unsatisfactory	1	1%
Very unsatisfactory	0	0%

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



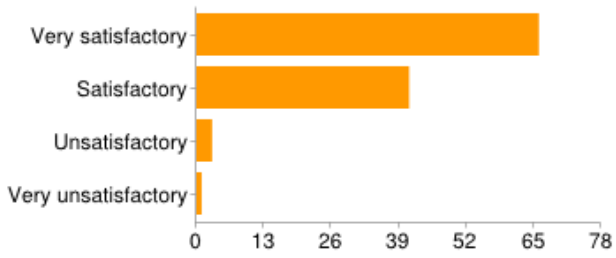
Very satisfactory	73	53%
Satisfactory	57	42%
Unsatisfactory	6	4%
Very unsatisfactory	1	1%

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



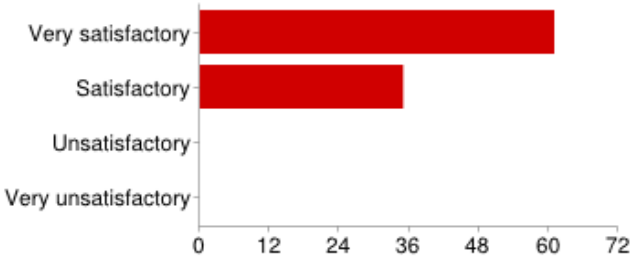
Very satisfactory	33	33%
Satisfactory	50	50%
Unsatisfactory	13	13%
Very unsatisfactory	5	5%

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



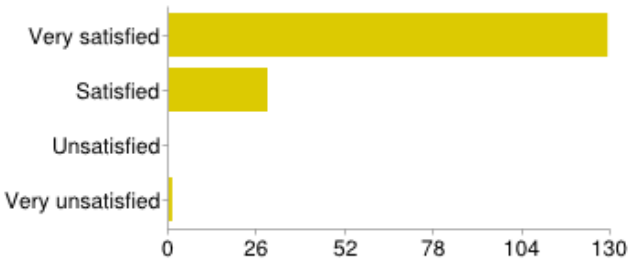
Very satisfactory	66	59%
Satisfactory	41	37%
Unsatisfactory	3	3%
Very unsatisfactory	1	1%

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



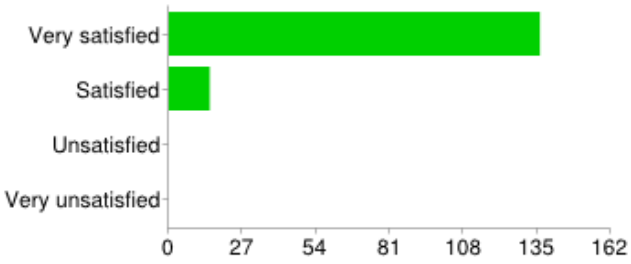
Very satisfactory	**61**	64%
Satisfactory	**35**	36%
Unsatisfactory	**0**	0%
Very unsatisfactory	**0**	0%

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



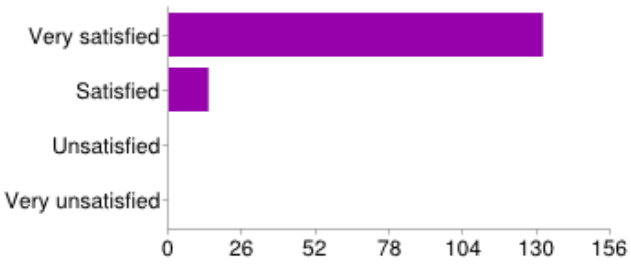
Very satisfied	**129**	81%
Satisfied	**29**	18%
Unsatisfied	**0**	0%
Very unsatisfied	**1**	1%

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



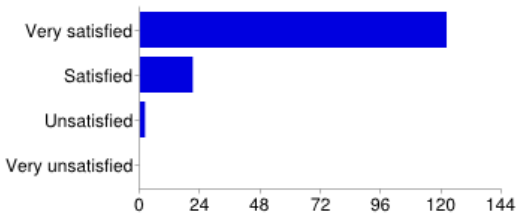
Very satisfied	**136**	90%
Satisfied	**15**	10%
Unsatisfied	**0**	0%
Very unsatisfied	**0**	0%

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



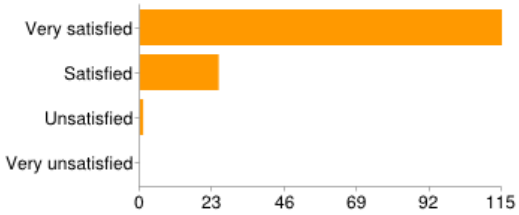
Very satisfied	**132**	90%
Satisfied	**14**	10%
Unsatisfied	**0**	0%
Very unsatisfied	**0**	0%

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



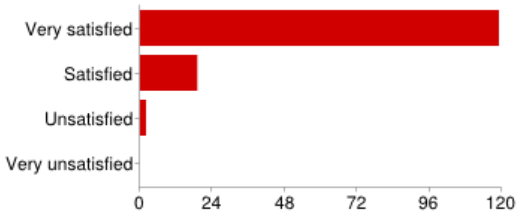
Very satisfied	122	84%
Satisfied	21	14%
Unsatisfied	2	1%
Very unsatisfied	0	0%

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



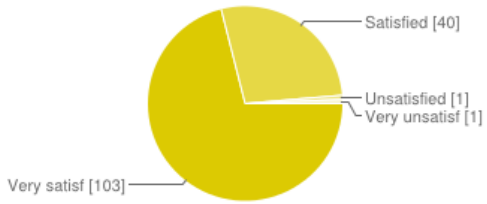
Very satisfied	115	82%
Satisfied	25	18%
Unsatisfied	1	1%
Very unsatisfied	0	0%

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?

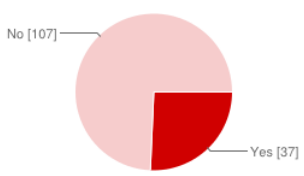


Very satisfied	103	71%
Satisfied	40	28%
Unsatisfied	1	1%
Very unsatisfied	1	1%

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

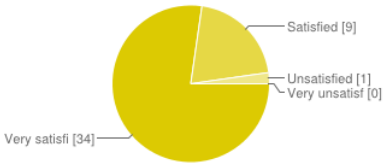
Very helpful and professional | Always friendly & helpful | Specialist aspergillosis nurse is a great support | Very satisfied helped me with all my questions | I received excellent support and advice | Very helpful with my meds | Lost appointment card advised of visit date | Very satisfied overall | 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%

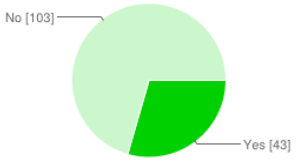
Any comments on the care provided to you by the specialist physiotherapists?

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?

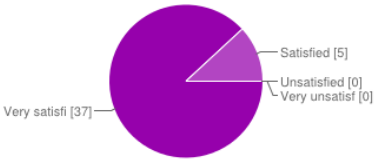


Yes	43	29%
No	103	71%

If yes, who was it?

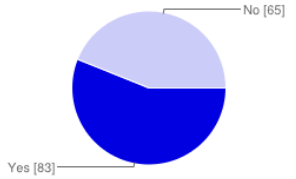
Graham Atherton | Georgina | Debbie | Kate or Kaz | Deborah | Ward nurse | Debbie/Georgina | Debbie & Georgina | Pippa | Georgina and Debbie | Georgina/Debbie | Not sure

And how satisfied were you with this support?



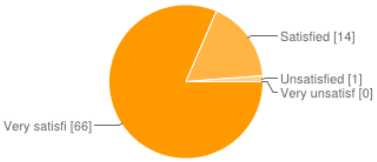
Very satisfied	37	88%
Satisfied	5	12%
Unsatisfied	0	0%
Very unsatisfied	0	0%

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 (2014)

1. Bowyer P, Denning DW. Fungicides and triazole resistance in *Aspergillus*. **Pest Manag Sci** 2014;70:173-8.

2. Fraczek MG, Kirwan MB, Moore CB, Morris J, Denning DW, Richardson MD. Volume dependency for culture of fungi from respiratory secretions and increased sensitivity of Aspergillus quantitative PCR. **Mycoses** 2014;57:69-78.

3. Nowaseb V, Gaebc E, Fraczek MG, Richardson MD, Denning DW. The frequency of *Pneumocystis jirovecii* in sputum samples of HIV and TB patients received at the Central Reference Laboratory in Windhoek, Namibia. **J Infect Dev Ctries** 2014; 8:349-57.

4. Muldoon EG, Denning DW. Prophylactic echinocandin - is there a subgroup of Intensive care unit patients who benefit? **Clin Infect Dis** 2014;58:1227-9.

5. Brown GD, Meintjes G, Kolls JK, Gray C, Horsnell W; Working Group from the EMBO-AIDS Related Mycoses Workshop, Achan B, Alber G, Aloisi M, Armstrong-James D, Beale M, Bicanic T, Black J, Bohjanen P, Botes A, Boulware DR, Brown G, Bunjun R, Carr W, Casadevall A, Chang C, Chivero E, Corcoran C, Cross A, Dawood H, Day J, De Bernardis F, De Jager V, De Repentigny L, Denning D, Eschke M, Finkelman M, Govender N, Gow N, Graham L, Gryschek R, Hammond-Aryee K, Harrison T, Heard N, Hill M, Hoving JC, Janoff E, Jarvis J, Kayuni S, King K, Kolls J, Kullberg BJ, Lalloo DG, Letang E, Levitz S, Limper A, Longley N, Machiridza TR, Mahabeer Y, Martinsons N, Meiring S, Meya D, Miller R, Molloy S, Morris L, Mukaremera L, Musubire AK, Muzoora C, Nair A, Nakiwala Kimbowa J, Netea M, Nielsen K, O'hern J, Okurut S, Parker A, Patterson T, Pennap G, Perfect J, Prinsloo C, Rhein J, Rolfes MA, Samuel C, Schutz C, Scriven J, Sebolai OM, Sojane K, Sriruttan C, Stead D, Steyn A, Thawer NK, Thienemann F, Von Hohenberg M, Vreulink JM, Wessels J, Wood K, Yang YL. AIDS-related mycoses: the way forward. **Trends Microbiol** 2014;22:107-9.

6. Denning DW, Pashley C, Hartl D, Wardlaw, A, Godet C, Del Giacco, Delhaes L, Sergejeva S. Fungal allergy in asthma–state of the art and research needs. **Clin Transl Allergy** 2014;4:14.

7. Wheat LJ, Nguyen MH, Alexander BD, Denning D, Caliendo AM, Lyon GM, Baden LR, Marty FM, Clancy C, Kirsch E, Noth P, Witt J, Sugrue M, Wingard JR. Long-term stability at -20°C of *Aspergillus* galactomannan in serum and bronchoalveolar lavage specimens. **J Clin Microbiol** 2014;52:2108-11.

8. Smith NL, Bowyer P, Simpson A, Hankinson J, Denning DW. A prominent role for IL1 pathway and IL15 in susceptibility to chronic cavitary pulmonary aspergillosis. **Clin Microbiol Infect** 2014;20(8):O480-8.

9. Jones AM, Horsley A, Denning D. What is the importance of classifying *Aspergillus* disease in cystic fibrosis patients? **Exp Rev Resp Med** 2014 May 29:1-4.

10. Armstead J, Morris J, Denning DW. Multi-country estimate of different manifestations of aspergillosis in cystic fibrosis. **PLoS One** 2014;9:e98502.

11. Smith NS, Bowyer P, Simpson A, Hankinson J, Denning DW. Reduced expression of TLR3, TLR10 and TREM1 by macrophages in CCPA, and novel genetic associations of VEGFA, DENND1B and PLAT with this disease. **Clin Microbiol Infect** 2014; 20:O960-8.

12. Oladele R, Denning DW. Burden of serious fungal infection in Nigeria. **West Afr J Med** 2014;33:107-14.

13. Zumla A, Memish ZA, Maeurer M, Bates M, Mwaba P, Al-Tawfiq JA, Denning DW, Hayden FG, Hui DS. Emerging novel and antibiotic resistant respiratory tract Infections – New drug development and therapeutic options. **Lancet Infect Dis** 2014;14:1136-1149.

14. Ellenbogen J, Denning DW, Cooke RP, Skinner DW, Lesser T, Javadpour M. Use of posaconazole for cerebral aspergillosis in an immunocompetent patient: Case report and literature review. **J Clin Neurosci** 2014;21:1825-7.

15. Smith NL, Denning DW. Interferon Gamma genetic and epigenetic variants – options for better patient selection and immunotherapy. **Immunology** 2014;143:499-511.

16. Barnes RA, Gow NA, Denning DW, May RC, Haynes K; British Society of Medical Mycology. Antifungal resistance: more research needed. **Lancet** 2014;384:1427. (letter).

17. Agarwal R, Denning DW, Chakrabarti A. Estimation of the burden of chronic and allergic pulmonary aspergillosis in India. **PLoS One** 2014;9:e114745.

18. Bromley MJ, Muijlwujk G, Fraczek MG, Robson G, Verweij PE, Denning DW, Bowyer P. Occurrence of azole resistant species of *Aspergillus* in the UK environment. **J Global Resist** 2014; 2: 276-279.

19. Bertuzzi M, Schrettl M, Alcazar-Fuoli L, Cairns T, Muñoz A, Walker L, Herbst S, Safari M, Cheverton A, Chen D, Liu H, Saijo S, Fedorova N, Armstrong-James D, Munro C, Read N, Filler S, Espeso E, Nierman W, Haas H, Bignell E. The pH-responsive PacC transcription factor of Aspergillus fumigatus governs epithelial entry and tissue invasion during pulmonary aspergillosis. **PLoS Pathog** 2014;10(10):e1004413.

20. Gonçalves A, Cordeiro J, Monteiro J, Muñoz A, Correia-de-Sá P, Read N, Videira A. Activation of a TRP-like channel and intracellular Ca2+ dynamics during phospholipase-C-mediated cell death. **J Cell Sci** 2014;127(Pt 17):3817-29.

21. Lichius A, Goryachev A, Fricker M, Obara B, Castro-Longoria E, Read N. CDC-42 and RAC-1 regulate opposite chemotropisms in *Neurospora crassa*. **J Cell Sci** 2014;127(Pt 9): 1953-65.

22. Muñoz A, Chu M, Marris P, Sagaram U, Kaur J, Shah D, Read N. Specific domains of plant defensins differentially disrupt colony initiation, cell fusion and calcium homeostasis in *Neurospora crassa*. **Mol Microbiol** 2014;92(6):1357-74

23. Cornely OA, Arikan-Akdagli S, Dannaoui E, Groll AH, Lagrou K, Chakrabarti A, Lanternier F, Pagano L, Skiada A, Akova M, Arendrup MC, Boekhout T, Chowdhary A, Cuenca-Estrella M, Freiberger T, Guinea J, Guarro J, de Hoog S, Hope W, Johnson E, Kathuria S, Lackner M, Lass-Flörl C, Lortholary O, Meis JF, Meletiadis J, Muñoz P, Richardson M, Roilides E, Tortorano AM, Ullmann AJ, van Diepeningen A, Verweij P, Petrikkos G. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. **Clin Microbiol Infect** 2014;20:5-26.

24. Chowdhary A, Meis JF, Guarro J, de Hoog GS, Kathuria S, Arendrup MC, Arikan-Akdagli S, Akova M, Boekhout T, Caira M, Guinea J, Chakrabarti A, Dannaoui E, van Diepeningen A, Freiberger T, Groll AH, Hope W, Johnson E, Lackner M, Lagrou K, Lanternier F, Lass-Flörl C, Lortholary O, Meletiadis J, Muñoz P, Pagano L, Petrikkos G, Richardson MD, Roilides E, Skiada A, Tortorano AM, Ullmann AJ, Verweij PE, Cornely OA, Cuenca-Estrella M. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of systemic phaeohyphomycosis: diseases caused by black fungi. **Clin Microbiol Infect** 201;20:47-75.

25. Tortorano AM, Richardson M, Roilides E, van Diepeningen A, Caira M, Munoz P, Johnson E, Meletiadis J, Pana Z-D, Lackner M, Verweij P, Freiberger T, Cornely OA, Arikan-Akdagli S, Dannaoui E, Groll AH, Lagrou K, Chakrabarti A, Lanternier F, Pagano L, Skiada A, Akova M, Arendrup MC, Boekhout T, Chowdhary A, Cuenca-Estrella M, Guinea J, Guarro J, de Hoog S, Hope W, Kathuria S, Lortholary O, Meis JF, Ullmann AJ, Petrikkos G, Lass-Flörl C. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: F*usarium* spp., *Scedosporium* spp. and others. **Clin Microbiol Infect** 2014;20: 27-46.

26. Marttila E, Jarvensivu A, Sorsa T, Grenier D, Richardson M, Kari K, Tervahartiala, Rautemaa R. Intracellular localisation of *Treponema denticola* chymotrypsin-like proteinase in chronic periodontitis. **J Oral Microbiol** 2014;6.

27. Alcazar-Fuoli L, Cairns T, Lopez J, Zonja B, Pérez S, Barceló D, Igarashi Y, Bowyer P, Bignell E. A modified recombineering protocol for the genetic manipulation of gene clusters in *Aspergillus fumigatus*. **PLoS One**, 2014;9(11): e111875

28. Huber F, Bignell E. Distribution, expression and expansion of *Aspergillus fumigatus* LINE-like retrotransposon populations in clinical and environmental isolates. **Fungal Genet Biol** 2014;64:36-44.

29. Moore CB, Richardson MD. 12 Infections Caused by Mucorales. **Human Fungal Pathogens** 2014;205-228. Springer Berlin Heidelberg.

30. Denning DW, Bowyer P. Voriconazole resistance in *Aspergillus fumigatus*: should we be concerned? **CID** 2014;57(4):521-523

31. Nieminen M, Hernandez M, Novak-Frazer L, Kuula H, Ramage G, Bowyer P, Warn P, Sorsa T, Rautemaa R. DL-2-hydroxyisocaproic acid attenuates inflammatory responses in a murine *Candida albicans* biofilm model. **Clin Vaccine Immunol** 2014;21(9):1240-5.

32. Nieminen M, Novak-Frazer L, Rautemaa W, Rajendran R, Sorsa T, Ramage G, Bowyer P, Rautemaa R. A novel antifungal is active against *Candida albicans* biofilms and inhibits mutagenic acetaldehyde production in vitro. **PLoS One** 2014;9(7):e101859.

33. Sakko M, Moore C, Novak-Frazer L, Rautemaa V, Sorsa T, Hietala P, Järvinen A, Bowyer P, Tjäderhane L, Rautemaa R 2-hydroxyisocaproic acid is fungicidal for *Candida* and *Aspergillus* species. **Mycoses** 2014;57(4):214-21.

34. Orsborne C, Hardy A, Isalska B, Williams SG, Muldoon EG. Acidovorax oryzae catheter-associated bloodstream infection. **J Clin Microbiol** 2014;52(12):4421-4.

35. Allison GM, Muldoon EG, Kent DM, Paulus JK, Ruthazer R, Ren A, Snydman DR. Prediction model for 30-day hospital readmissions among patients discharged receiving outpatient parenteral antibiotic therapy. **Clin Infect Dis** 2014;58(6):812-9.

36. http://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-chronic-pulmonary-aspergillosis (2011-)

37. http://www.uptodate.com/contents/treatment-of-chronic-pulmonary-aspergillosis (2011-)

38. Denning DW. Aspergillosis. Eds Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J. Harrison's Principles of Internal Medicine. 19th ed. McGraw-Hill, New York, 2015. Chapter 204. Pp 1345-1349.