

**NHS National Commissioning Group - Highly Specialised Services**

**Chronic Pulmonary Aspergillosis National Service**

**The National Aspergillosis Centre**

**Annual Report 2015-2016**



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**Cover photo** shows a PET scan and CT transverse image of one patient with chronic pulmonary aspergillosis. The colour image shows high intensity radio-labelled glucose uptake at the apex of the left lung indicating high metabolic activity, which may be seen in lung cancer or infection, in this case CPA. The CT scan shows the left apex replaced by a cavity with highly irregular interior walls representing fungal growth on the interior of the thick-walled cavity, and some additional material within the cavity, which is also fungal growth that has detached from the cavity wall. There is marked pleural thickening as well. The right apex shows some fibrosis which is not illuminated on the PET scan.

## 1 General Overview and highlights

This report covers the seventh full year of this nationally commissioned service. The number of new patients with chronic pulmonary aspergillosis (CPA) increased annually to 2012/13 and has now levelled off; 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, and 111 in 2015/16. Sixty seven patients died and 20 were discharged from service, leaving a total of 398 on service from England and Scotland and an additional 13 patients from Wales on April 1<sup>st</sup> 2016. This represents an 8.8% growth (9.4% growth in prior year). Non-CPA patients with aspergillosis are also being referred in larger numbers, a total of 346 in 2015/16.

The plan to utilise n-of-1 trials of posaconazole (and now isavuconazole) has been successful in that 34 of 78 patients trialled remained on the therapy and the remainder did not benefit and/or were intolerant. One application was made to NHSE for long term therapy but this was declined. Two patients that were on long term therapy have now come off and one remains on treatment.

The Mycology Reference Centre continues to process increasing numbers of samples, notably for aspergillus PCR (87% increase). Antifungal resistant rates in *A. fumigatus* remain above 10%.

In March 2016, the 7th Advances Against Aspergillosis international meeting was held in Manchester, with 350 attendees. News of the meeting reached 8 million viewers via BBC Breakfast Time, BBC NW Tonight, BBC News, BBC local radio throughout the north west of England and ex-pat communities in Spain. Stories were also run in the Guardian, The Sun, The Mirror and Good Housekeeping magazine. A greater emphasis on reaching out to the public is bearing fruit in terms of general awareness.

UK guidelines on the investigation and diagnostic testing of patients with fungal diseases were published in Lancet Infectious Diseases. In January 2016, clinical guidelines for the diagnosis and management of CPA were published jointly by the European Society for Clinical Microbiology and Infectious Diseases and the European Respiratory Society. This is the first ever set of management guidelines for CPA.

The whole Manchester research group (fungi@manchester) published 57 papers and book chapters including some key observations including extremely high levels of the neutrophil chom attractant PPBP found in monocytes in CPA patients. In 2015, estimated country burdens of serious fungal diseases including chronic and allergic aspergillosis were published for 20 countries. A call for all populations to have access to fungal disease diagnostics and antifungal treatments was issued by the Global Action Fund for Fungal Infections in May 2015, an NGO closely linked to the National Aspergillosis Centre.

## 2 Activity

The total referrals, inpatient stays, procedures, death and caseload in 2015/16 were as follows:

Activity Measure / Currency	Month Activity												Contract Currency Y/N	Annual Plan †	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	28	23	35	53	46	40	50	45	37	29	35		36	N
New Patients Testing	7	4	10	11	14	12	12	7	10	11	6	7	Y	80	111
Outpatient - Follow-Up Attendances	97	140	123	141	129	105	88	87	89	134	135	78	N	1,200	1,346
Caseload - Band 1	155	149	148	147	150	157	159	163	166	173	172	173	Y	100	173
Caseload - Band 2	177	185	194	195	195	193	191	200	192	191	191	190	Y	150	190
Caseload - Band 3	24	22	22	22	22	20	22	21	22	23	23	25	Y	20	25
Occupied Bed Days	139	9	145	41	228	154	54	9	79	20	37	66	Y	1,500	981
Inpatient Discharges	6	2	7	3	9	7	4	2	3	3	5	5	N	120	56
IV Homecare (OPAT)	0	0	0	0	20	29	0	0	0	0	0	0	N	0	49
Surgical Resection	1	0	0	0	1	1	0	0	1	0	0	0	Y	4	4
Embolisations	1	1	0	1	1	0	1	0	0	0	0	0	Y	10	5
Patient Death	8	5	4	4	4	4	7	5	8	8	7	3	N		67
Discharge from Service	1	1	0	2	3	4	5	0	1	1	2	0	N	16	20

\* The NCG fund patients from England and Scotland only

# Appendix 1 shows the Banding criteria used

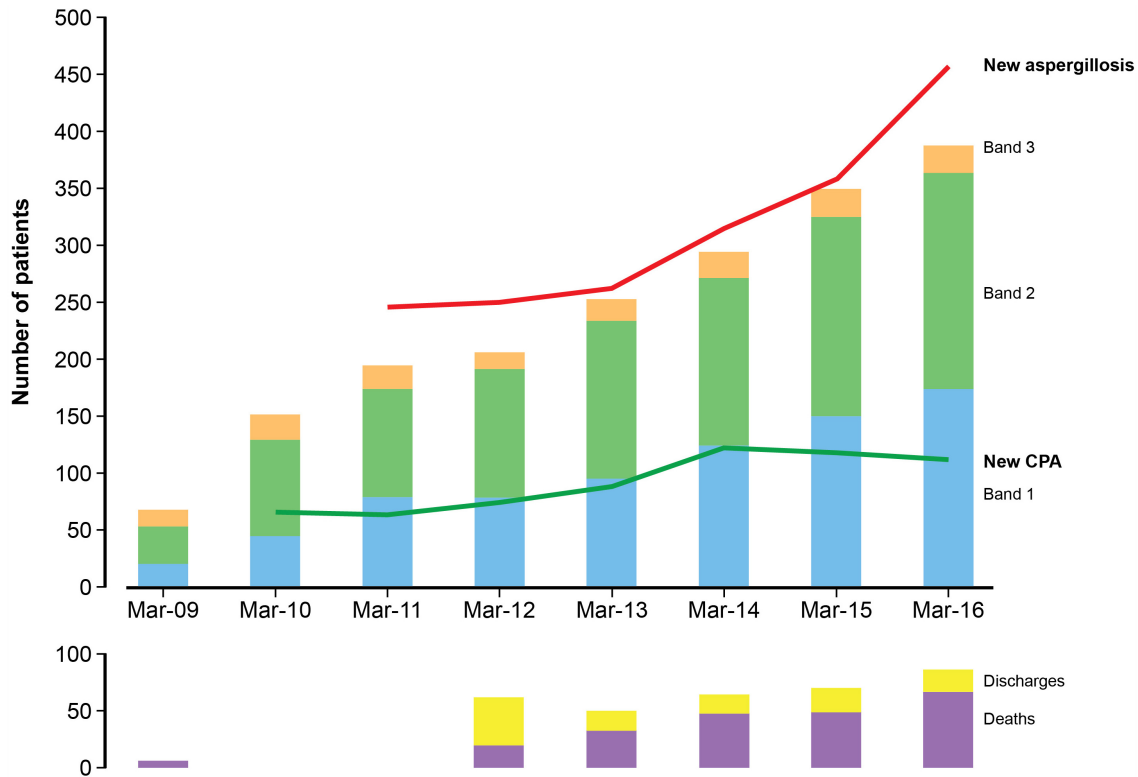
Of the 457 new 'aspergillosis' referrals from England and Scotland (increase of 27.3%) during the year 2015/16, 111 (24.2%) had CPA, very similar to the previous 2 years (125 and 119 patients). Among the outpatient referrals, the mean time from referral to being seen was 6 weeks (Appendix 2), including 10 patients who rescheduled their appointments or did not attend initially. This is similar to the previous year. Appendix 2 shows the area of residence, date of referral and date of appointment. These numbers include 2 referrals and care for 16 patients from Scotland. In addition the service had 3 referrals from Wales and cared for 16 Welsh patients. There were no patients referred from Northern Ireland. Twelve referred patients died within the year.

There has been a growth in Band 1 numbers from 150 to 173 patients, Band 2 patient numbers have grown from 175 to 190, and Band 3 was steady at 25 patients (see banding at Appendix 1). These shifts include 67 deaths (49 the previous year) and 16 discharges from service (21 the previous year). At the end of year, 398 patients were on service from England and Scotland, compared with 363 in the previous year (8.8% growth). Four patients were presumptively cured with surgery and 5 underwent bronchial artery embolization.

Admission days were increased on the prior year – from 814 to 981, with 49 patient days at home on IV therapy.

We have plotted the outpatient activity over the 7 years of the National Aspergillosis Centre operations in the figure below. The green line represents gradually increasing numbers of aspergillosis referrals, and the gap between that line and the actual CPA patients indicates that many alternative diagnoses are made, such as allergic

bronchopulmonary aspergillosis, *Aspergillus* bronchitis, various forms of *Aspergillus* rhinosinusitis and invasive aspergillosis.



### 3 Mycology Reference Centre, Manchester (Director Prof Malcolm Richardson)

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 third 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  $\beta$ -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* precipitating 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*
- 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](http://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 overseas 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.
- Laboratory space, increase necessary to accommodate 12 staff

**4 Clinical service developments and personnel**

The NAC has completed its seventh 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 Infectious Diseases in Global Health (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)

Luke Cannon, CT2 in Infectious Diseases (50%)

Dr Shomik Sibartie, 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 Maria Gamaletsou, Clinical Fellow (100%)

Dr Gemma Hayes, Clinical Fellow (100%)

Mrs Christine Harris, NAC manager (100%)

Dr Graham Atherton, Senior Clinical Information Architect (Patient engagement) 40%

Mrs Maxine Redshaw (50%)

Ms Marian Webster (50%)

Ms Debbie Kirby, Medical Secretary (50%)

Mrs Megan Hildrop Clerical Assistant (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.

**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.

**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.

**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. The delivery service has been extended to PCT funded patients with other forms of aspergillosis. This service has been extended to include isavuconazole in the last 12 months.

#### 5) Postal bloods and sputum

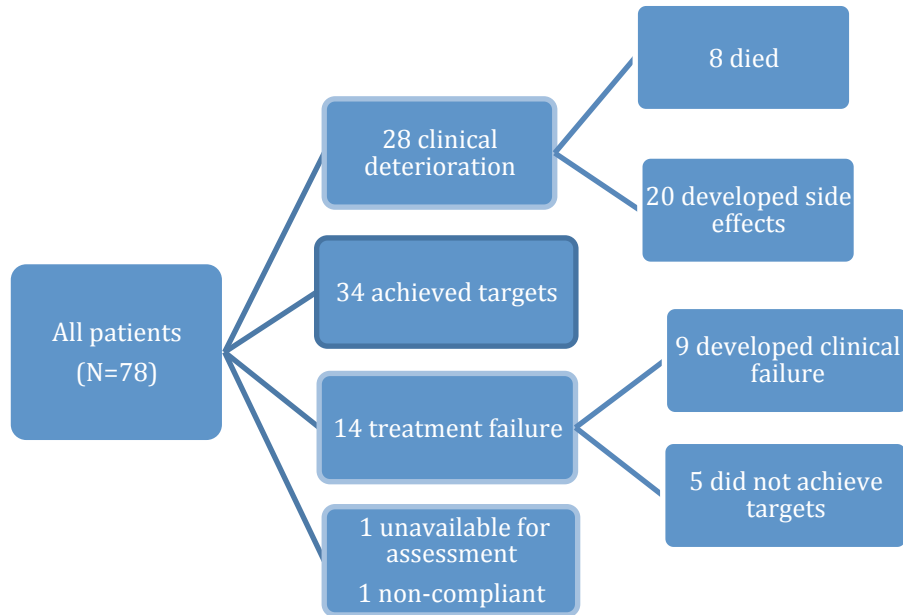
The postal blood and sputum service works well for following up antifungal drug levels between clinics, and getting much higher quality and volume samples. As *Aspergillus* PCR on sputum is not available elsewhere in the country, some of these samples are also transported in the post. PCR is much more sensitive than culture and can be used as a proxy for detecting resistance and clinical failure. An increasing number of high volume cultures to improve the culture yield for susceptibility testing come in through postal packs.

#### 6) 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. Together with the MRC dyspnoea score the 2014/15 data is presented in Appendix 4. This was further augmented by an assessment of fatigue which has a major impact on quality of life.

#### 7) n-of-1 trials of posaconazole for third or fourth line antifungal therapy

We have now fully evaluated the new guidelines to use posaconazole on an individual trial basis, 'n-of-1' trials. 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 The outcome for 78 patients is shown in the figure.



This trial has been presented as a poster twice and the paper is nearly ready for submission.

## 5 Audits

### 1. Time to appointment and shared care

Most patients were booked for an appointment within 6 weeks. However, some appointments were longer mostly due to patients rescheduling appointments or not attending.

Ten patients died within the year after being seen for for the first time and overall 67 patients died on service, up from the prior year. This probably reflects a combination of late diagnosis and referral, highly complex patients with azole resistance and drug intolerance, and severe underlying disease.

There continues to be considerable shared care arrangements, especially for patients requiring IV courses of therapy near their home. If the patients is under our care, and the local consultant is willing to administer AmBisome or micafungin, we sanction and pay for this. This is one of the reasons why our admission days are relatively low for the increasing volume of work. Our own OPAT service has only helped a small number of CPA patients, because of the issues of distance.

### 2. Clinical audits

Several clinical audits have been undertaken in 2015/16. Most of these have been completed:

- Chronic fibrosing pulmonary aspergillosis case series finalised and submitted
- CPA/ atypical mycobacterial coinfection. (Database complete, need to analyse case series)
- Posaconazole n of 1 trials (see section 4.8)

- *Aspergillus* PCR (write up complete)
- Azole resistance rates in *A. fumigatus* and antifungal stewardship (in writing phase)
- CF genotype in ABPA (data entry complete, manuscript in preparation)
- Impact of fatigue in CPA on quality of life (paper published)
- Induced sputum yield of *Aspergillus* PCR and culture (published)
- *Aspergillus* nodules and masses (published)
- Single and multiple dose AmBisome efficacy and side effects for CPA (published online)
- Survival in CPA patients (Resubmitted after 2 revisions)
- Gamma interferon production deficiency (Completed, presented, being written up by Addenbrookes)
- Gamma interferon therapy (40 patients, in progress).

## 6 Patient and public engagement

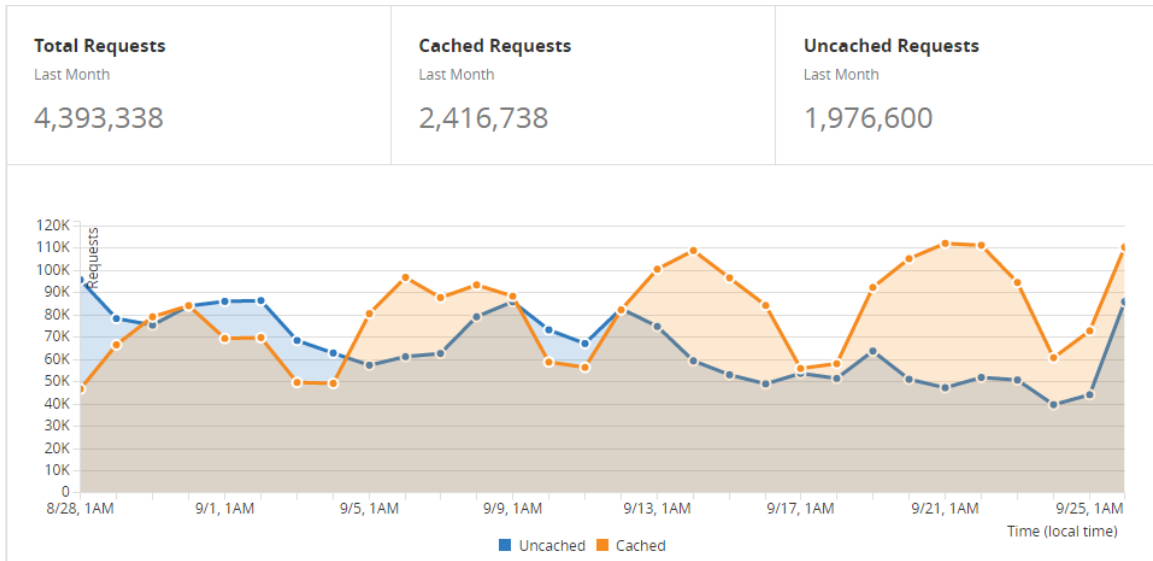
### 1. Community booklet.

A community booklet is produced and distributed to all patients who do not have access to a computer, informally at clinic. The group of patients & carers that attend the monthly support meeting at NAC play an integral role in developing and publishing the NAC community booklet each quarter. 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.

### 2. Aspergillus Website @ [www.aspergillus.org.uk](http://www.aspergillus.org.uk)

The Aspergillus Website is the most comprehensive source of information about Aspergillus and the diseases it causes available on the internet. There are extensive sections for clinicians, scientists and laypeople (patients) including comprehensive collection of treatment protocols covering 43 distinct therapeutic areas and all approved antifungal drug SPC's & PIL/VIPIL's. We also provide information on evidence supporting other unapproved non-herbal treatments. We provide simple access to over 9,800 scientific articles (including a unique collection of 815 historical articles) and well over 14,400 conference abstracts from 1974 onwards.

The Aspergillus Website is listed at number 1, 1, 1 and 2 in Google.co.uk, number 4, 3, 4 and 4 in Google.com, number 2, 2, 7, 2 in Bing and Yahoo! for 'aspergillus', 'ABPA' 'aspergillosis' and 'aspergilloma' respectively. If 'aspergillus' is searched in Google, there are over 6 million results. The Aspergillus Website had 65,682 unique visitors in a typical month and the Website for Patients 11,109. About 43% of visits are using smaller devices. China has overtaken the USA as the country from which we get most visits, and numbers of visits have surged to over 200,000 per month.



Usage by country is depicted here:

Locales				
Locales		Pages	Hits	Bandwidth
China	cn	164,337	219,072	4.36 GB
United States	us	123,167	282,420	7.23 GB
Great Britain	gb	9,052	26,533	432.91 MB
Unknown	ip	4,548	14,270	266.45 MB
France	fr	2,294	4,846	124.93 MB
Canada	ca	1,936	5,188	93.85 MB
Australia	au	1,393	3,766	44.01 MB
Mexico	mx	1,261	3,638	37.89 MB
Brazil	br	1,258	39,593	950.71 MB
Spain	es	1,130	3,867	58.18 MB
Italy	it	1,077	2,656	72.59 MB
Netherlands	nl	782	2,114	43.06 MB
Argentina	ar	707	2,611	38.04 MB
Japan	jp	662	2,985	81.51 MB
Russian Federation	ru	469	1,784	49.16 MB
South Korea	kr	459	1,421	44.72 MB
Turkey	tr	430	849	12.10 MB
New Zealand	nz	336	1,718	24.72 MB
Hong Kong	hk	313	813	7.13 MB
Philippines	ph	312	1,992	46.72 MB
Norway	no	307	668	8.18 MB
Germany	de	307	1,567	20.10 MB
Sweden	se	238	1,354	106.78 MB
Finland	fi	199	689	5.22 MB
Portugal	pt	184	578	19.15 MB
Vietnam	vn	179	543	11.67 MB
South Africa	za	162	990	10.29 MB
Taiwan	tw	161	602	15.50 MB
Hungary	hu	156	429	18.73 MB
Ukraine	ua	150	159	2.81 MB
Czech Republic	cz	138	716	4.39 MB
Seychelles	sc	119	119	1.14 MB

Our weekly blog ([www.aspergillusblog.blogspot.com](http://www.aspergillusblog.blogspot.com)) has 5-7000 page requests per month this year and has recently passed 250,000 page accesses since it began in 2007.

Monthly newsletters from the Aspergillus Website are sent out to over 24,000 (free) subscribers. This figure is driven by newly registered members seeking to access our secure 'articles'. There are ~45,000 people registered on The Aspergillus Website (40% medics, 29% scientists, 8% vets and 23% laypeople).

### 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 is attended by 8 – 15 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.

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 36,000 (early 2016) in their new location.

April 2015	Malcolm Richardson	Tour of diagnostics labs	0' 00' 00secs	0' 26' 45secs
May 2015	Chris Kosmidis	<a href="#"><u>Q &amp; A session</u></a>	0' 26' 45secs	end
June 2015	Graham Atherton & Chris Harris	<a href="#"><u>Biomes, Diagnostics &amp; Travel Tips</u></a>		
July 2015	Gemma Hayes	<a href="#"><u>Aspergillosis, Asthma &amp; ABPA: Where we are and where we are going.</u></a>	0' 31' 40secs	0' 48' 40secs
	Chris Harris	<a href="#"><u>Skype consults &amp; creative writing</u></a>		
August 2015	Alan Savage	<a href="#"><u>Home Care, health and use of social resources in the local community</u></a>		
	Chris Harris	<a href="#"><u>Poetry</u></a>		
	Graham Atherton	<a href="#"><u>Planning Autumn Booklet</u></a>		
September 2015	Phil Langridge	<a href="#"><u>The variety and use of positive expiratory pressure devices to aid mucus clearance</u></a>	0' 00' 00secs	0' 24' 20secs
	Graham Atherton	<a href="#"><u>fungi@MANCHESTER</u></a>		
October 2015	Maria Gamaletsou	<a href="#"><u>Introduction to the background of our new medic</u></a>		
	Graham Atherton	<a href="#"><u>ERS 2015 &amp; Take the Active Option</u></a>		

	Chris Harris	Group Poem
November 2015	Chris Kosmidis	<a href="#"><u>Introduction to Isavuconazole: a new antif drug</u></a>
	Graham Atherton	<a href="#"><u>Patients &amp; carer discussion</u></a>
December 2015	Graham Atherton	<a href="#"><u>Christmas Quiz</u></a>
February 2016	Graham Atherton	<a href="#"><u>Shortened Meeting</u></a>
March 2016	Ritesh Agarwal MD	Sinusitus & ABPA
	Richard Moss MD	Allergic Aspergillosis & Cystic Fibrosis
	Darius Armstrong-James FRCP	NAC Satellite Clinic in London
	Stuart Levitz MD	Fungal Vaccines
	Jeanette Boyd	European Lung Foundation
	Vicky Barber	British Lung Foundation
	Led by Graham Atherton	<a href="#"><u>Entire meeting</u></a>

#### 4. Community structure

Our online communities have been very popular since 2000 but our patient surveys indicated that up to half of our patients did not have access to a computer which denied them access to our expensive resources online. Our support community is thus a combination of online and offline meetings & resources.

The community is supported in several ways:

##### Online

- Our (Facebook & Yahoo!) worldwide communities are very active with 2000 participants
- The NHS Choices online community for Aspergillosis has 700 participants
- NACPatients.org.uk website (averaging 4000 visitors per month)
- Local online Facebook groups (14 groups, 8 in the UK serving 50 - 70 people)
- Facebook group specifically for carers

- The Professional LinkedIn members (Aspergillus and Aspergillosis Group) has over 400 members and 120 are in the related ‘Damp Buildings and Human Health’ LinkedIn group.
- Monthly meeting viewed live & by recordings (250-450 viewings per month in 2016)

#### Offline

- Monthly meeting at National Aspergillosis Centre (NAC) attended by 10-20 per month. This meeting offers social support and also a series of talks on a wide variety of subjects aimed at helping patients self manage, reducing anxiety, explaining some of the tests we do at NAC and outlining encouraging research progress.
- 120 community booklets, written quarterly are given out per month. This publication contains seasonal advice, informative articles and artwork & recipes contributed by the patient's community. Regular meetings are held to get patient & carers opinions on how we should update the booklets.
- Monthly newsletter issued to every patient attending clinic (250 per month).
- A series of 13 information leaflets are available and handed out in clinic by clinical staff as required for new and existing patients
- ‘Buddy’ phone support manned by patients (15 - 20 participants)

#### 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 phonenumber 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 phonenumber is manned by patient/carer volunteers who report steady interest.

#### 6. Public awareness

Promoting awareness of aspergillosis and the National Aspergillosis Centre is particularly important as we suspect that many thousands of people remain undiagnosed. This results in people not being appropriately treated and the national statistics for serious fungal disease remain low in the UK and abroad. Consequently government health & research funding is low. Improving awareness helps make far more people in the UK aware of aspergillosis and the National Aspergillosis Centre, improving the chances that more cases of aspergillosis will be looked for and found.

However awareness could be counterproductive if it is not linked to good information and advice. Our patients & carers’ community can help to spread awareness in the UK (and abroad) and provide links back to our resources, maximising the benefit.

Personal stories from patients & carers always have a high impact when told by the media. Combined with support from NAC they regularly make an important contribution to national TV and print/website news outlets, most recently during the 7th Advances Against Aspergillosis meeting in Manchester where we reached 8 million viewers via

BBC Breakfast Time, BBC NW Tonight, BBC News, BBC local radio throughout the north west of England and ex-pat communities in Spain<sup>1</sup>. Stories were also run in the Guardian, The Sun, The Mirror and Good Housekeeping magazine. The NAC has engaged 2 public relations companies to assist getting key health and educational messages out.

On a more individual scale our informed patients & carers do a great job spreading awareness every day via our online communities and through local groups and fundraising events as well as to their doctors and other medical staff.

## 7 Research outputs, other published research summary

### 1. Papers and book chapters

Amongst the 57 papers and book chapters published in calendar year 2015, there were several areas of direct relevance to patients with CPA and pulmonary aspergillosis. These were:

- UK guidelines on the investigation and diagnostic testing of patients with fungal diseases were published in Lancet Infectious Diseases [1].
- In January 2016, clinical guidelines for the diagnosis and management of CPA were published jointly by the European Society for Clinical Microbiology and Infectious Diseases and the European Respiratory Society [2]. This is the first ever set of management guidelines for CPA.
- Extremely high levels of the neutrophil chemoattractant PPBP are found in monocytes in CPA patients [3]. This is indicative of major ongoing inflammation in patients with CPA.
- A review of aspergillosis was published in Thorax [4] and many of our referring physicians commented that they found this most helpful.
- A consensus group discussed and offered an opinion of the management of patients with azole resistant aspergillosis [5], a common problem in those treated with oral azoles long term.
- Progression from ABPA to CPA was documented in detail in 20 patients cared for at the NAC, including the time frames [6].
- Poor antibody response to *S. pneumoniae* and a muted response to immunisation with Pneumovax was documented [7]. This prompted a shift to using 2 doses of Prevanar 13 vaccine to protect our patients from recurrent infection.
- UpToDate is a key resource for doctors across the world. Both chapters on CPA in this online searchable encyclopaedia of medical practice are updated 6 monthly [8,9]
- Estimated country burdens of serious fungal diseases including chronic and allergic aspergillosis were published for 20 countries [Appendix 5]. A call for all populations to have access to fungal disease diagnostics and antifungal treatments was issued by the Global Action Fund for Fungal Infections in May 2015 [10], an

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<sup>1</sup> 7th Advances Against Aspergillosis, Manchester, UK 3-5th March 2016. **Aspergillus Website** <http://www.aspergillus.org.uk/content/7th-advances-against-aspergillosis-manchester> accessed 26th May 2016.



NGO closely linked to the National Aspergillosis Centre. This call included a focus on CPA complicating pulmonary tuberculosis across the world.

#### Key papers related to CPA:

1. Schelenz S, Barnes RA, Barton RC, Cleverley JR, Lucas SB, Kibbler CC, Denning DW. British Society for Medical Mycology: Diagnostic standards for the management of serious fungal diseases. *Lancet Infect Dis* 2015;15:461-474.
2. Denning DW, Cadranel J, Beigelman-Aubry C, Ader, F, Chakrabarti A, Blot S, Ullman A, Dimopoulos G, Lange C, European Society for Clinical Microbiology and Infectious Diseases and European Respiratory Society. Chronic pulmonary aspergillosis – Rationale and clinical guidelines for diagnosis and management. *Eur Resp J* 2016; 47:45-68.
3. Smith NL, Bromley MJ, Denning DW, Simpson A, Bowyer P. Elevated levels of the neutrophil chemoattractant pro-platelet basic protein in macrophages from individuals with chronic and allergic aspergillosis. *J Infect Dis* 2015;211:651-60.
4. Kosmidis C, Denning DW. The clinical spectrum of pulmonary aspergillosis. *Thorax* 2015;70:270-277. (Republished in *Postgrad Med J* 2015;91:403-10.)
5. Verweij PE, Ananda-Rajah M, Andes D, Arendrup MC, Brüggemann RJ, Chowdhary A, Cornely OA, Denning DW, Groll AH, Izumikawa K, Kullberg BJ, Lagrou K, Maertens J, Meis JF, Newton P, Page ID, Seyedmousavi S, Sheppard DC, Viscoli C, Warris A, DonnellyJP. International expert opinion on the management of infection caused by azole-resistant *Aspergillus fumigatus*. *Drug Res Updates* 2015;21-22:30-40.
6. Lowes D, Chishimba L, Greaves M, Denning DW. Progression from asthma to ABPA to chronic pulmonary aspergillosis. *Resp Med* 2015;109:1509-15.
7. Kosmidis C, Powell G, Borrow R, Morris J, Alachkar H, Denning DW. Response to pneumococcal polysaccharide vaccination in patients with chronic and allergic aspergillosis. *Vaccine* 2015;33:7271-5.
8. [www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-chronic-pulmonary-aspergillosis](http://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-chronic-pulmonary-aspergillosis)
9. [www.uptodate.com/contents/treatment-of-chronic-pulmonary-aspergillosis](http://www.uptodate.com/contents/treatment-of-chronic-pulmonary-aspergillosis)
10. Global Action Fund for Fungal Infections. 95-95 by 2025. Improving outcomes for patients with fungal infections across the world; A roadmap for the next decade. May 2015 <http://www.gaffi.org/roadmap/>

#### 2. Advances Against Aspergillosis

The 7<sup>th</sup> Advances Against Aspergillosis meeting was held at Manchester Central, March 3<sup>rd</sup> to 5<sup>th</sup>, 2016. There were 352 attendees, from over 30 countries who discussed *Aspergillus* and aspergillosis over 3 days. [www.advancesagainstaspergillosis.org/2016/](http://www.advancesagainstaspergillosis.org/2016/)



In addition to the main plenary sessions, breakfast meetings were held which included a 'challenging cases' slot on CPA, delivered by the NAC consultants. There were 128 abstracts submitted and displayed, including the first ever disclosure of a new antifungal destined for inhalation – PC945. This and other new antifungals from F2G Ltd and Cidara were the focus of a press release<sup>2</sup>.

Several papers from this meeting will be published in Medical Mycology as a permanent record of the meetings. Prior meetings have resulted in 229 published papers in 7 supplements.

## 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 SUI's were reported.

### Complaints

None

### HIRS alerts

One was related to incorrect drug labelling.

## 9 Future developments

The developments planned for 2015/16 were (**and commented on**):

- 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. **No straightforward cutoff, but very high levels suggestive of active infection. Poor quality samples (mucoïd, salivary) are falsely negative.**
- Introduction of isavuconazole, as a second or third-line therapy for CPA, using the same evaluation methodology now used for posaconazole. **Introduced using 'n-of-1' trials as for posaconazole.**
- Implementation of a routine azole resistance service using pyrosequencing in the MRCM, and then clinical validation (2 year process). **Development and validation in progress, not yet operational.**
- Introduction of Skype or Facetime nurse appointments, preceded by postal sputum and blood testing, to reduce travelling costs and increase appointment intervals. Successfully introduced and found to be useful. **The relevant nurse has just left (after 7 years), so will be a delay until new appointees sufficiently trained to do this.**

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<sup>2</sup> <http://www.manchester.ac.uk/discover/news/manchester-fungal-disease-conference/>

- Planning for the recruitment of an additional consultant to contribute to the growth of the service. **New consultant appointed and starting in October 2016. Expertise in fungal infections and transplant ID.**
- Support of a nascent infectious diseases service at the Brompton Hospital with occasional joint clinics for complex aspergillosis cases. **One joint clinic. Many cases, handled internally.**

Developments planned for 2016/17 include:

- As multiple new experimental antifungals are in phase 1 or phase 2 development, recruitment of a clinical trials manager to orchestrate the multiple approvals required.
- Four antifungal developments being investigated are for CPA patients: primary therapy with isavuconazole, injection of a novel highly active azole antifungal into aspergillomas, weekly IV therapy as salvage therapy and possibly another oral salvage therapy.
- Manchester-wide Single Hospital Service discussions ongoing about the merger of Central Manchester FT and UHSM FT, as well as integrating all the infection services.
- Increased clinic, nursing and medical capacity is planned.
- Doubling of undergraduate teaching by UHSM ID team, to both year 3 and year 4.
- Recruitment of another academic with an interest in aspergillosis to further develop the research with what is now a globally unique cohort of patients and service.
- Plan to hold UK-wide video meetings via Skype, enabling patients & carers to participate with patient meetings using a standard telephone line rather than a computer.

## Appendix 1

### Categorisation of complexity (Banding)

#### Stage 1

- Ambulant and independent
- No evidence of antifungal resistance
- No treatment or treatment with itraconazole capsules

#### Stage 2

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

#### Stage 3

- Antifungal azole resistance documented and/or
- Long term nebulised or IV antibiotic treatment required (bronchiectasis, Pseudomonas colonisation) and/or
- Wheelchair bound and/or
- HIV infected and/or
- Severe hepatic or renal disease

**Appendix 2**  
**Referral to appointment time audit - April 2015 – March 2016**

Patient level data

**Appendix 3**

**Quality of life (SGRQ) and MRC dyspnoea scores for new referrals 2015/16**

Patient level data

## Appendix 4

### NAC Patient Survey 2016 – Summary

All patients attending every clinic in for the four weeks during February 2016 were asked to complete this survey. 166 responded to the survey which this year we have presented as a single survey combining all three weekly clinics.

#### Q1. First Visit

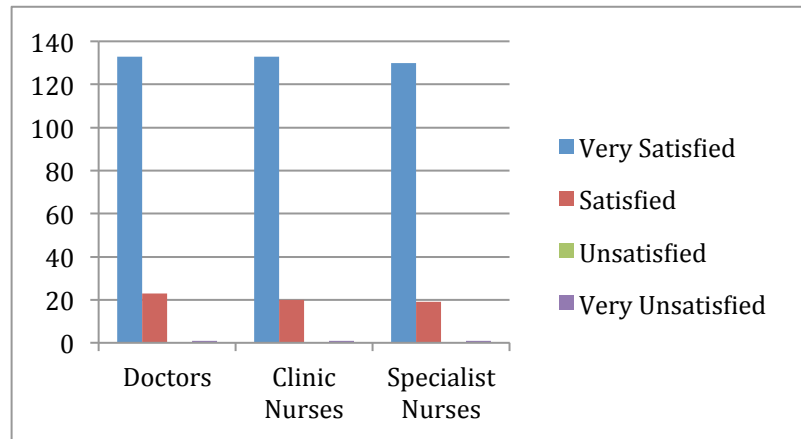
98% patients completing the survey had attended clinic before

#### Q2. Waiting time

95% were satisfied or better with all waiting times (broken down into Reception, Doctor, Nurses, Blood tests, Pharmacy, X-ray and Lung Function). Slight weaknesses are identified in waiting times for Doctors and Pharmacy (1.5% and 2% unsatisfied or worse respectively).

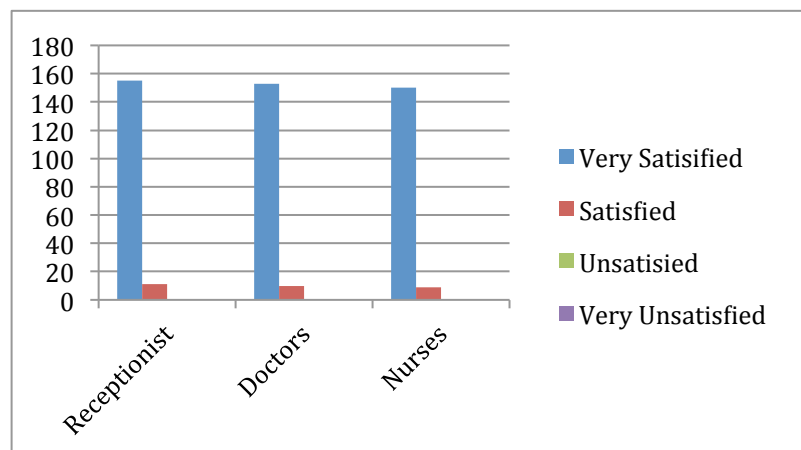
#### Q3. Courtesy

Courtesy from all receptionists, medical and nurse team members are exemplary.



#### Q4. Quality of care

Quality of care from all medical team members was highly rated with only one person unsatisfied.



**Q5. Contact from a member of the NAC team**

There has been a notable rise in the number of patients being contacted by a member of the NAC team with 49% now having been contacted versus 32% in 2015. 24 comments on the quality of support show that 22 (96%) had an overwhelmingly positive experience, two had been contacted to correct problems with blood sampling and one considered advice given *“has been inconsistent and unhelpful”*. In 2015 98% had been satisfied or better.

**Q6. Specialist physiotherapists**

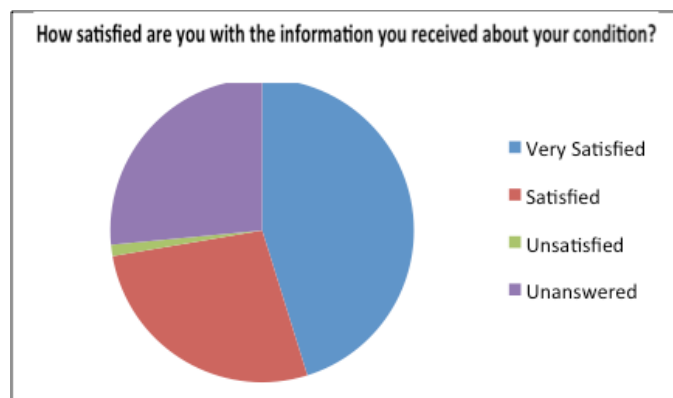
The proportion of patients attending our physiotherapy service is unchanged with 100% satisfied and all comments reinforcing universal approval of both staff members.

**Q7 and 8. Written information about your condition?**

More people (62%) have received written information compared with 2015 (55%) though there seems to be room for improvement in

- the consistency of type of information received (some only recollect seeing the community booklets, some newsletters, while others are seeing none)
- the quality of information (*“still don’t fully understand all aspects of the condition”*)
- the frequency of receiving information (*“Some years ago”*)
- the range of information (*“If I ever need surgery”*)
- accessibility or availability (*“Have requested to do previously, but not received any”* and *“I get information from other hospitals after clinic visit. Never from here.”*)

NOTE that only 16 out of 168 people left comments in this section and only 8 (5%) of these highlighted the issues listed above. Satisfaction levels on information received were >95%.

**Q9. Potential symptoms regarding your illness or medication**

More patients (61%) remembered having been told about symptoms to watch out for at home regarding adverse effects compared with 2015 (48%), most comments from patients showing good awareness of this issue.



**Q10. Answers from questions to doctors**

The clarity of answers from our doctors received 93% approval (98% of those who responded to the question) with one negative comment: *“Doctors on ward spoke above me and did not listen to me – I felt they spoke at me and not to me”* and one that may provide food for thought for further improvement: *“sometimes I forget to ask anything till I am on my way home”*.

**Q11 & 12. Wythenshawe Hospital (UHSM)**

40% of patients asked had been inpatients at Wythenshawe Hospital and of these 97% were very happy or better with how they were treated while on a ward. The only negative comment concerned the difficulties getting discharged at weekends. 90% (97% of those who responded to the question) would recommend UHSM to family and friends. Large numbers (69) of comments in this section with only 2 negative *“Purse taken twice – records filled in incorrectly not listened to”* and *“6 months between appointments when a UHSM Doctor said 4 months”*.

Many (67) others ranged from *“Excellent treatment”* and *“For the NAC services as best in country. Prof Denning and team are worth the round trip”* to importantly *“In every situation I knew what was happening”* and *“Care and friendliness.”*

**Q13. Postal service for drug levels and sputum samples**

Comment (40) on the postal service for drug levels and sputum samples were very positive with one writing about how important this service was to them. Several comments were suggestions for improvement:

- Better envelopes
- Containers are not a good fit in order box
- It is easy from your end, but I found it difficult to get blood taken on my end
- Make the little plastic sample pouch much larger than the samples sent
- Blood packs could be sent more quickly
- Clearer paper work and guidance for 3rd parties taking blood samples
- When I asked for pills to be sent out for me as I was running out (and did), I was told this was not possible by a nurse
- There could be more communication with the GP surgery as they always tell me this is outside of their standard practice

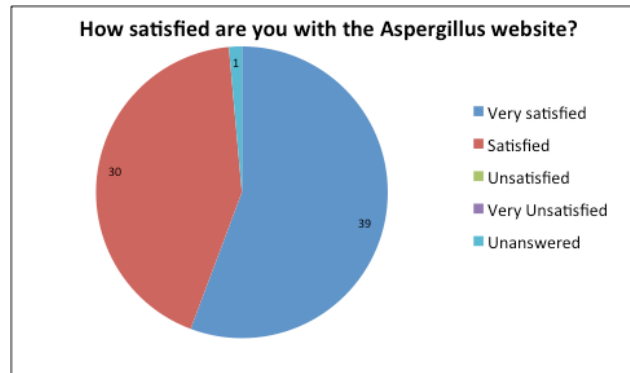
- When I have been sent items, the envelope has arrived damaged on at least two occasions
- Didn't know of this service

#### Q14. Anti-fungal drugs delivery

There is universal approval for antifungal drug delivery service, no criticisms of the current service.

#### Q15. Aspergillus website

The proportion of patients visiting the Aspergillus Website is up slightly compared to 2015 to 45% and approval is 100%. Comments of those who do not visit the website are mainly divided between those who have no computer access (50%) and those who do not want to know more about their illness (30%). 1 comment considered that the website was too complex for them to understand revealing a need to make the patients section of the website more prominent.



#### Q16. Patient information leaflets

Suggestions for new information leaflets requested more information on diet, breathing apparatus, the range and value of exercise, the benefits of each drug.

#### Q17-20. Patients meetings.

7% of those responding to the question had attended one of the monthly patients meetings compared with 9% in 2015 which suggests a reduction in active interest though attendance numbers at each meeting is stable at 10-14 per month.

Comments(9) of those who do attend are very positive *"I always go to meetings - they are the most informative"*, *"They are very good. I have learnt more from meetings than anywhere else"* and *"The patient meetings are very helpful; it's a great chance to speak to others with this condition"*. One or two negative comments reflect difficulties with travel distance.

50% of those who did not attend the meeting did not do so because of inconvenience (and thus presumably would be interested in attending) – over 90% of these due to the distance required to travel to the meeting. The remaining 50% who did not attend had no current interest in attending (*"not needed"*, *"not useful"*, *"happy as I am"*).

In 2015 the same reasons for not attending predominated but more (59%) did not attend due to inconvenient time or distance. This increase in convenience may be due to us switching the meeting to Fridays (when the main clinic takes place) and additional efforts made to arrange patient's clinic time to the same day as the meetings.

Our meeting are streamed live in the internet and have been viewed by 7% of patients. Recordings of our meetings have been viewed by 17% (13% in 2015) of patients who responded.

**In conclusion 7% go to the meeting, 7% watch live and 17% watch a recording, so a total of 31% of patients view the meeting in some form.**

57% were aware of our regional support groups (up from 44% in 2015) but only 5% had made contact with a group. The main reasons given for not contacting were:

- Distance – 19 (29%)
- Time – 10 (15%)
- Not needed – 22 (33%)

#### **Q21. Hospital transport**

4% of patients used hospital transport, all were satisfied or better.

#### **Q22. Clinical Research**

70% were happy to participate in clinical research, all of these were satisfied or better with procedures and consent process.

### **General comments (25 in all) about NAC service**

Mostly positive, **some constructive**

1 - I have had great care with every aspect of the hospital. 2 – I hope I attend a meeting this Year. 3 – If I have an appointment with one doctor, I do not want to see another. 4 – Great care from staff, always excellent service. 5 – Very satisfied with care and help. 6 – Since I first visited the NAC, I have been impressed by the standard and quality of the care from all staff here. I appreciate the efforts that have been made to improve my condition. 7 – You are doing a great job – thank you! 8 – Nursing staff are wonderful and always treat you with kindness and respect. The doctor never rushes you. 9 – Been on no meds for months now. 10 – The care, attention, professionalism at clinic and between clinics is excellent. 11 – **There was some confusion over my latest clinic date.** 12 - **I had a letter informing me of an appointment that did not match the records / schedule.** 13- I try not to think of the problems as much as possible, so I don't read up on it. 14 – I have only been to the clinic once and saw Dr N. Who I thought was

excellent. 15- Care given was very good from the centre. Would be good if clinic appointment reports could be sent out to patients if requested. 16 – Very satisfied with everything. 17 – Very satisfied with treatment. 18 – All the staff are lovely. 19 – I have been very happy with my care at Wythenshawe hospital. 20 – The last time we were here, we had a telephone request to attend the clinic. No one here new about it and we ended up waiting for 3 hours. 21 – Find there is always a delay receiving clinic letters following meeting the consultants. 22 – Apart from one unsatisfactory consultation (first one). 23 – Very happy with the aspergillosis centre. 24 – NAC provides an excellent service – the staffs are first class. 25 – Thank goodness NAC is here. Best doctors and nurses and thanks to graham for keeping us all informed online! Saved my life getting the proper treatment for my aspergillosis.

## Appendix 5

**Publications from the Fungi@Manchester Group (2015)**

1. Smith NL, Bromley MJ, Denning DW, Simpson A, Bowyer P. Elevated levels of the neutrophil chemoattractant pro-platelet basic protein in macrophages from individuals with chronic and allergic aspergillosis. **J Infect Dis** 2015;211:651-60.
2. Muldoon EG, Switkowski K, Tice A, Snyderman DR, Allison GM. A national survey of infectious disease practitioners on their use of outpatient parenteral antimicrobial therapy (OPAT). **Infect Dis (Lond)**. 2015;47:39-45.
3. Muñoz A, Bertuzzi M, Bettgenhaeuser J, Iakobachvili N, Bignell EM, Read ND. Different Stress-Induced Calcium Signatures Are Reported by Aequorin-Mediated Calcium Measurements in Living Cells of *Aspergillus fumigatus*. **PLoS One**. 2015;10:e0138008.
4. Bleichrodt RJ, Vinck A, Read ND, Wösten HA. Selective transport between heterogeneous hyphal compartments via the plasma membrane lining septal walls of *Aspergillus niger*. **Fungal Genet Biol**. 2015;82:193-200.
5. Juvvadi PR, Muñoz A, Lamoth F, Soderblom EJ, Moseley MA, Read ND, Steinbach WJ. Calcium-Mediated Induction of Paradoxical Growth following Caspofungin Treatment Is Associated with Calcineurin Activation and Phosphorylation in *Aspergillus fumigatus*. **Antimicrob Agents Chemother**. 2015 Aug;59(8):4946-55.
6. Kosmidis C, Denning DW. The clinical spectrum of pulmonary aspergillosis. **Thorax** 2015;70:270-277. (Republished in **Postgrad Med J** 2015;91:403-10.)
7. Tanaka RJ, Boon NJ, Vrcelj K, Nguyen A, Vinci C, Armstrong-James D, Bignell E. In silico modeling of spore inhalation reveals fungal persistence following low dose exposure. **Sci Rep**. 2015;5:13958.
8. Denning DW, Ghnan N, Kwizera R, Osmanov A. Comment on: Susceptibility breakpoints and target values for therapeutic drug monitoring of voriconazole and *Aspergillus fumigatus* in an in vitro pharmacokinetic/pharmacodynamic model. **J Antimicrob Chemother** 2015;70:633.
9. de Hoog SG, Haase G, Charturvedi V, Walsh TJ, Meyer W, Boekhout T, Chakrabarti A, Chowdhary A, Cole G, Cornely O, Crous P, de Queiroz Telles F, d'Enfert C, Denning DW, Dyer P, Frisvad J, Garcia-Hermoso D, Geiser D, Gräser Y, Guarro G, Ellis D, Kwon-Chung KJ, Lass-Floerl C, Levitz S, Li R, JMeis J, Mitchell A, O'Donnell K, Perfect J, John Pitt J, Samson R, Sutton D, Taylor J, Tintelnot K, Vitale R, Voigt K, White T, Xi L, and Lackner M. Name changes in medically important fungi and their implication on clinical practice. **J Clin Microbiol** 2015;53:1056-62.
10. Rodriguez-Tudela JL, Alastruey-Izquierdo A, Gago S, Cuenca-Estrella M, León C, Miro JM, Nuñez Boluda A, Ruiz Camps I, Sole A, Denning DW. Burden of serious fungal infections in Spain. **Clin Microbiol Infect** 2015;21:183-9.
11. Schelenz S, Barnes RA, Barton RC, Cleverley JR, Lucas SB, Kibbler CC, Denning DW. British Society for Medical Mycology: Diagnostic standards for the management of serious fungal diseases. **Lancet Infect Dis** 2015;15:461-474.

12. Denning DW, Bromley MJ. How to bolster a sparse antifungal pipeline. **Science** 2015;347:1414-6.
13. Dorgan E, Denning DW, McMullan R. Burden of fungal disease – Ireland. **J Med Microbiol** 2015;64:423-6.
14. Chishimba L, Langridge P, Powell G, Niven RM, Denning DW. Efficacy and safety of nebulised amphotericin B in severe asthma with fungal sensitisation and allergic bronchopulmonary aspergillosis. **J Asthma** 2015; 52:289-95.
15. Namvar S, Warn P, Farnell E, Bromley M, Fraczek M, Bowyer P, Herrick S. *Aspergillus fumigatus* proteases, Asp f 5 and Asp f 13, are essential for airway inflammation and remodelling in a murine inhalation model. **Clin Exp Allergy**. 2015;45:982-93.
16. Robertson DP, Keys W, Rautemaa-Richardson R, Burns R, Smith AJ. Management of severe acute dental infections. **Br Med J**. 2015;350:h1300.
17. Global Action Fund for Fungal Infections. 95-95 by 2025. Improving outcomes for patients with fungal infections across the world; A roadmap for the next decade. May 2015 <http://www.gaffi.org/roadmap/>
18. Page ID, Richardson MD, Denning DW. Antibody testing in aspergillosis - quo vadis?. **Med Mycol** 2015;53:417-39.
19. Sakko M, Tjäderhane L, Sorsa T, Hietala P, Rautemaa R. Antimicrobial 2-hydroxyisocaproic acid (HICA) and chlorhexidine resist inactivation by dentine. **Int Endod J**. 2015 May 6. doi: 10.1111/iej.12465.
20. Marttila E, Uittamo J, Rusanen P, Lindqvist C, Salaspuro M, Rautemaa R. Site-specific acetaldehyde production and microbial colonization in relation to oral squamous cell carcinoma and oral lichenoid disease. **Oral Surg Oral Med Oral Pathol Oral Radiol**. 2015;119:697-9.
21. Thomas S, Ghosh J, Porter J, Cockcroft A, Rautemaa-Richardson R. Periodontal disease and late-onset aortic prosthetic vascular graft infection. **Case Rep Vasc Med**. 2015;2015:768935.
22. van der Linden JW, Arendrup MC, Warris A, Lagrou K, Pelloux H, Hauser PM, Chryssanthou E, Mellado E, Kidd SE, Tortorano AM, Dannaoui E, Gaustad P, Baddley JW, Uekötter A, Lass-Flörl C, Klimko N, Moore CB, Denning DW, Pasqualotto AC, Kibbler C, Arikian-Akdagli S, Andes D, Meletiadis J, Naumiuk L, Nucci M, Melchers WJ, Verweij PE. Prospective multicenter international surveillance of azole resistance in *Aspergillus fumigatus*. **Emerg Infect Dis** 2015;21:1041-4.
23. Denning DW. The ambitious '95-95 by 2025' roadmap for the diagnosis and management of fungal diseases. **Thorax** 2015;70:613-4.
24. Ben-Ami R, Denning DW. Estimating the burden of fungal diseases in Israel. **Israel Med Assc J** 2015;17:374-9.
25. Hedayati MT, Azimi Y, Droudinia A, Mousavi B, Ahmadi A, Khalilian A, Hedayati N, Denning DW. Prevalence of chronic pulmonary aspergillosis in patients with tuberculosis from Iran. **Eur J Clin Microbiol Infect Dis** 2015;34:1759-65.
26. Gugnani H, Denning DW. The burden of serious fungal infections in Dominican Republic. **J Infect Pub Health** 2016;9:7-12.

27. Thomas S, Hassan I, Barker J, Ashworth A, Barnes A, Fedor I, Feddy L, Hayes T, Malagon I, Stirling S, Szentgyorgyi L, Mutton K, Richardson M. Chronic mould exposure as a risk factor for severe community acquired pneumonia in a patient requiring extra corporeal membrane oxygenation. **Respir Med Case Rep.** 2015;15:39-41.
28. Bertuzzi M, Schrettl M, Alcazar-Fuoli L, Cairns TC, Muñoz A, Walker L, Herbst S, Cheverton A, Kalchschmidt J, Chen D, Liu H, Fedorova ND, Armstrong-James D, Munro C, Read ND, Filler SG, Espeso EA, Nierman WC, Haas H, Bignell EM (2014) The pH-responsive PacC transcription factor of *Aspergillus fumigatus* governs epithelial entry and tissue invasion during pulmonary aspergillosis. *PLoS Pathog* **10**: e1004413
29. Sili U, Bilgin H, Masania R, Eryuksel E, Cimsit NC, Ayranci G, Richardson M, Korten V. Successful treatment of an invasive fungal infection caused by *Talaromyces* sp. with voriconazole. **Med Mycol Case Rep.** 2015;8:21-3.
30. Jayasekera PI, Denning DW, Perera PD, Fernando A, Kudavidanage S. The burden of serious fungal infections in Sri Lanka. **Sri Lankan J Infect Dis** 2015;5:73-85.
31. Badiane AS, Ndiaye D, Denning DW. Burden of serious fungal infection in Senegal. **Mycoses** 2015: 58 (Suppl. S5):63–69.
32. Parkes-Ratanshi R, Achan B, Kwizwera R, Kambugu A, Meya D, Denning DW. The Burden of fungal disease in Uganda; What we know and how we can fill our knowledge gaps using cryptococcal disease research in Uganda as a model. **Mycoses** 2015: 58 (Suppl. S5):85-93.
33. Shrestha Khwakhali U, Denning DW. Burden of serious fungal infections in Nepal. **Mycoses** 2015: 58 (Suppl. S5):45-50.
34. Osmanov A, Denning DW. Burden of serious fungal infections in Ukraine. **Mycoses** 2015;58 (Suppl. S5):94–100.
35. Beardsley J, Denning DW, Chau NV, Yen NTB, Crump JA, Day JN. Estimating the burden of fungal disease in Vietnam. **Mycoses** 2015: 58 (Suppl. S5):101–106.
36. Mortensen KL, Denning DW, Arendrup MC. The burden of fungal disease in Denmark. **Mycoses** 2015: 58 (Suppl. S5):15–21.
37. Faini D, Maokola W, Furrer H, Hatz C, Battegay M, Tanner M, Denning DW, Letang E. Burden of serious fungal infections in Tanzania. **Mycoses** 2015: 58 (Suppl. S5):70–79.
38. Sinkó J, Sulyok M, Denning DW. Burden of serious fungal diseases in Hungary. **Mycoses** 2015: 58 (Suppl. S5):29–33.
39. Chrdele A, Mallatova N, Vašáková M, Haberd J, Denning DW. Burden of serious fungal infections in the Czech Republic. **Mycoses** 2015: 58 (Suppl. S5):6–14.
40. Klimko N, Kozlova Y, Khostelidi S, Shadrivova O, Borzova Y, Burygina E, Vasilieva N, Denning DW. The burden of serious fungal infections in Russia. **Mycoses** 2015: 58 (Suppl. S5):58-62.

41. Ruhnke M, Groll A, Mayser P, Ullmann A, Rickerts V, Mendling V, Hof H, Denning DW. Burden of fungal infections in Germany. **Mycoses** 2015; 58 (Suppl. S5):22–28.
42. Taj-Aldeen SJ, Chandra P, Denning DW. Burden of fungal infections in Qatar. **Mycoses** 2015; 58 (Suppl. S5):51–57.
43. Corzo-León DE, Armstrong-James D, Denning DW. Burden of serious fungal infections in Mexico. **Mycoses**, 2015; 58 (Suppl. S5):34–44.
44. Lagrou K, Maertens J, van Even E, Denning DW. Burden of Serious Fungal Infections in Belgium. **Mycoses**, 2015; 58 (Suppl. S5):1–5.
45. Denning DW, Gugnani H. Burden of serious fungal infections in Trinidad and Tobago. **Mycoses**, 2015; 58 (Suppl. S5):80–84.
46. Brasier AR, Zhao Y, Spratt HM, Wiktorowicz JE, Ju H, Wheat LJ, Baden L, Stafford S, Wu Z, Issa N, Caliendo AM, Denning DW, Soman K, Clancy CJ, Nguyen MH, Sugrue MW, Alexander BD, Wingard JR. Improved detection of invasive pulmonary aspergillosis arising during leukemia treatment using a panel of host response proteins and fungal antigens. **PLoS One** 2015;10:e0143165.
47. Bussink HJ, Bignell EM, Múnera-Huertas T, Lucena-Agell D, Scazzocchio C, Espeso EA, Bertuzzi M, Rudnicka J, Negrete-Urtasun S, Peñas-Parilla MM, Rainbow L, Peñalva MÁ, Arst HN Jr, Tilburn J. Refining the pH response in *Aspergillus nidulans*: a modulatory triad involving PacX, a novel zinc binuclear cluster protein. **Mol Microbiol.** 2015;98(6):1051-72.
48. Verweij PE, Ananda-Rajah M, Andes D, Arendrup MC, Brüggemann RJ, Chowdhary A, Cornely OA, Denning DW, Groll AH, Izumikawa K, Kullberg BJ, Lagrou K, Maertens J, Meis JF, Newton P, Page ID, Seyedmousavi S, Sheppard DC, Viscoli C, Warris A, DonnellyJP. International expert opinion on the management of infection caused by azole-resistant *Aspergillus fumigatus*. **Drug Res Updates** 2015;21-22:30-40.
49. Lowes D, Chishimba L, Greaves M, Denning DW. Progression from asthma to ABPA to chronic pulmonary aspergillosis. **Resp Med** 2015;109:1509-15.
50. Otu AA, Ochang E, Oladele R, Denning DW. If not pulmonary tuberculosis, what else could it be? **Afr J Resp Med** 2015;11:19-21.
51. Kosmidis C, Powell G, Borrow R, Morris J, Alachkar H, Denning DW. Response to pneumococcal polysaccharide vaccination in patients with chronic and allergic aspergillosis. **Vaccine** 2015;33:7271-5.
52. Gugnani H, Denning DW. The burden of serious fungal infections in Jamaica by literature and modelling. **West Ind Med J** 2015;64:245-249.
53. [www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-chronic-pulmonary-aspergillosis](http://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-chronic-pulmonary-aspergillosis)
54. [www.uptodate.com/contents/treatment-of-chronic-pulmonary-aspergillosis](http://www.uptodate.com/contents/treatment-of-chronic-pulmonary-aspergillosis)
55. Denning DW. Aspergillosis. Eds Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J. Harrison's Principles of Internal Medicine. 19<sup>th</sup> ed. McGraw-Hill, New York, 2015. Chapter 204. Pp 1345-1349.
56. Clemons KV and Richardson MD. Pathways and routes of natural exposure to fungal infection. In: Environmental Mycology in Public Health, 1st Edition. Eds. C.



Viegas, A. Pinheiro, R. Sabino, S. Viegas, J. Brandão, C. Veríssimo. Academic Press, 2015.

57. Richardson MD and Rautemaa RMK. Aspergillus and Aspergillosis. In: Molecular Biology of Food and Water Borne Mycotoxigenic and Mycotic Fungi. Edited by: RRM Paterson, Taylor and Francis, London, 2015.