



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

**Chronic Pulmonary Aspergillosis National Service**

**The National Aspergillosis Centre**

**Annual Report 2016-2017**



**A European Centre of Excellence in Medical Mycology**

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**Cover photo** - the members of the NHS Mycology Reference Laboratory, Manchester.

## 1 General Overview and highlights

This report covers the eighth full year of this National Aspergillosis Centre (NAC), commissioned as a Highly Specialised Service within the NHS. The number of new patients with chronic pulmonary aspergillosis (CPA) increased annually to 2012/13 and remains steady; 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, 111 in 2015/16 and 121 in 2016/17. Sixty patients died and 29 were discharged from service, leaving a total of 425 on service from England and Scotland and an additional 12 patients from Wales, 1 patient from Northern Ireland and 1 from the Isle of Man on April 1<sup>st</sup> 2017. This represents a 6.7% growth (8.8% growth in prior year). Non-CPA patients with aspergillosis are also being referred in larger numbers, a total of 396 in 2016/17. The overall expenditure has fallen slightly as voriconazole has come off patent.

The NAC and its partner the NHS Mycology Reference Centre, Manchester (MCRM) were awarded Medical Mycology Centre of Excellence status by the European Confederation of Medical Mycology in January 2017, the first such centre in the world.

A major audit of 2 years of 206 new referrals (April 2013-March 2015) showed that initial therapy was continued for 12 months in only 48% of the total cohort. Change of therapy was observed in 32% of patients and discontinuation in 29% (adverse events, azole resistance or failure of therapy or a combination). At 12 months, median survival was 94%. The rate of emergence of resistance during therapy was 13% for itraconazole compared to 5% for voriconazole. Bronchial artery embolisation was done in 9 patients and lobectomy in 7 patients. Seventeen patients required at least one course of antifungal therapy. Multiple other audits were undertaken.

The plan to utilise n-of-1 trials of posaconazole and isavuconazole for those intolerant or failing itraconazole and voriconazole has been successful as 38 patients were trialled on posaconazole and 23 on isavuconazole.

Manchester was successful in its bid to host an NIHR Biomedical Research Unit, with a grant of £28.5M over 5 years. Infection, and especially fungal infection and aspergillosis, is one of the topic areas included.

There were 45 papers and book chapters published in calendar year 2016 many of direct relevance to patients with CPA and pulmonary aspergillosis, including the diagnostic value of having physiotherapists in clinic generating sputum samples (with resistant fungi identified, critical for guiding therapy), the diagnostic performance of 6 different commercial *Aspergillus* antibody tests, response rates to courses of AmBisome for CPA and a description of the newly discovered manifestation of *Aspergillus* nodules.

2 Activity

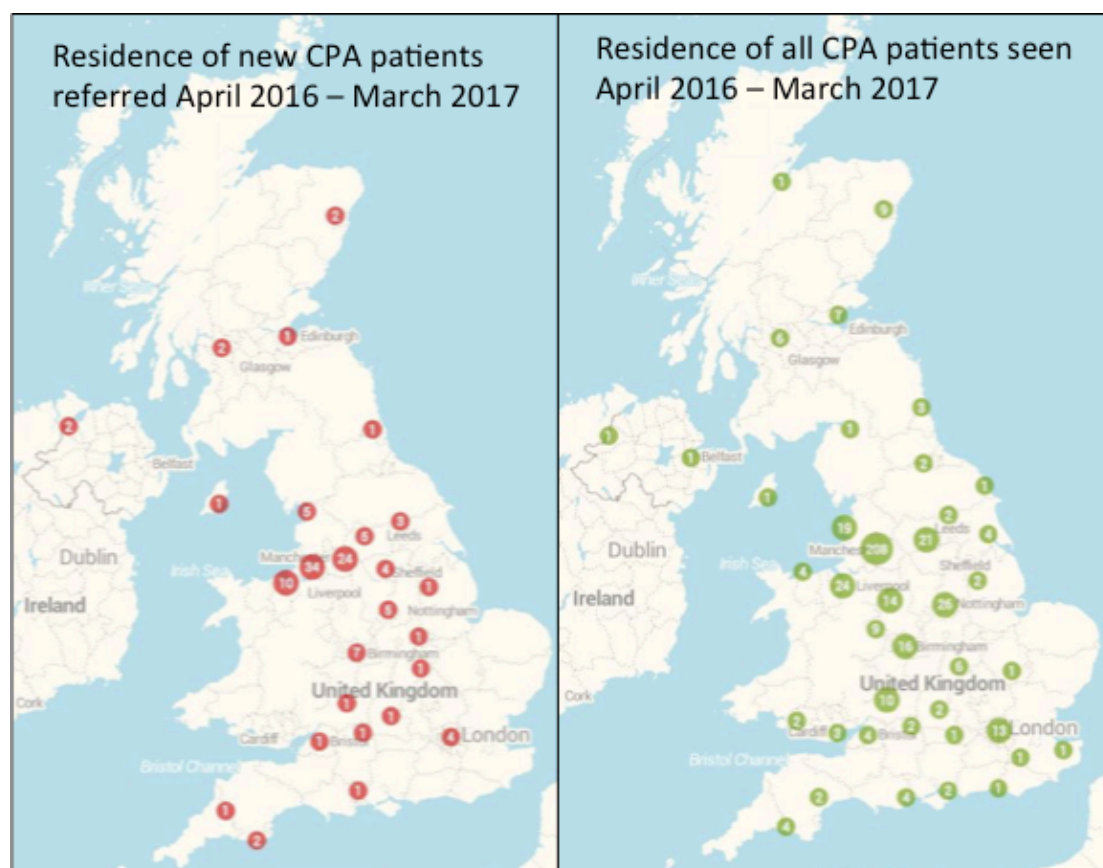
The total referrals, inpatient stays, procedures, death and caseload in 2016/17 were as follows:

Activity Measure / 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	YTD Actual
Referrals	37	37	42	37	49	39	36	38	60	38	55	49	517
New Patients Testing	8	12	10	11	12	8	6	9	14	10	10	11	121
Outpatient - Follow-Up Attendances	172	115	116	143	132	145	114	129	115	133	116	155	1,585
Caseload - Band 1	178	174	173	172	176	178	178	174	174	173	178	168	168
Caseload - Band 2	186	190	197	202	206	211	214	212	213	222	218	238	238
Caseload - Band 3	25	25	26	25	25	24	23	22	23	23	22	19	19
Occupied Bed Days	189	21	92	45	28	67	99	82	56	22	99	106	906
Inpatient Discharges	9	1	5	7	4	8	7	5	7	4	7	9	73
IV Homecare (OPAT)	0	0	101	31	31	53	82	31	31	31	31	13	435
Surgical Resection	0	0	0	0	0	0	1	0	0	1	0	1	3
Embolisations	3	0	1	6	0	1	1	0	2	2	2	2	20
Patient Death	4	3	5	4	1	7	5	10	3	8	7	3	60
Discharge from Service	2	6	1	2	0	2	1	5	2	0	5	3	29

\* The NCG fund patients from England and Scotland only

# Appendix 1 shows the Banding criteria used

Of the 517 new ‘aspergillosis and related infectious diseases’ referrals from England and Scotland (increase of 8.8%) during the year 2016/17, 121 (23.4%) had CPA, very similar to the previous 3 years (125, 119 and 117 patients). The locations of the CPA



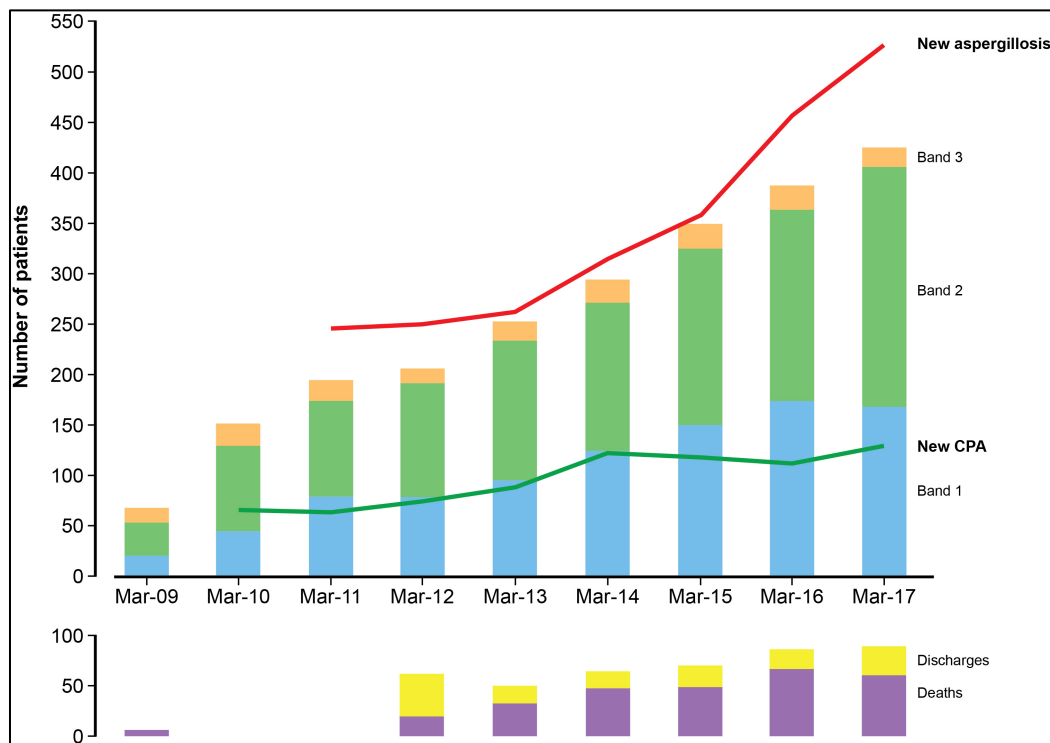
referrals and all patients seen are shown in the maps, and displayed as heatmaps in Appendix 3. Among the outpatient referrals, the mean time from referral to being seen was 8 weeks (Appendix 2), including 6 patients who rescheduled their appointments or were too unwell to attend. Four referrals were directly admitted to hospital for an opinion first. Appendix 2 shows the area of residence, date of referral and date of

appointment. These numbers include 2 referrals from Northern Ireland, 4 Scotland, 5 Welsh and 1 patient from the Isle of Man (admission) There were nine direct admissions, one of whom died during that admission. Overall 12 referred patients died within the year. Seven patients had been under our care with another form of aspergillosis and transformed their disease into CPA.

There has a slight fall in Band 1 numbers from 172 to 168 patients, Band 2 patient numbers have grown from 190 to 238, and Band 3 numbers have declined from 25 to 19 patients (see banding at Appendix 1). These shifts include 60 deaths (67 the previous year) and 29 discharges from service (16 the previous year). At the end of year, 425 patients were on service from England and Scotland, compared with 398 in the previous year (9.3% growth), as well as 18 patients from Wales and 1 from the Isle of Man. Three patients were presumptively cured with surgery and 20 underwent bronchial artery embolization, some because of poorly controlled disease attributable to azole resistance.

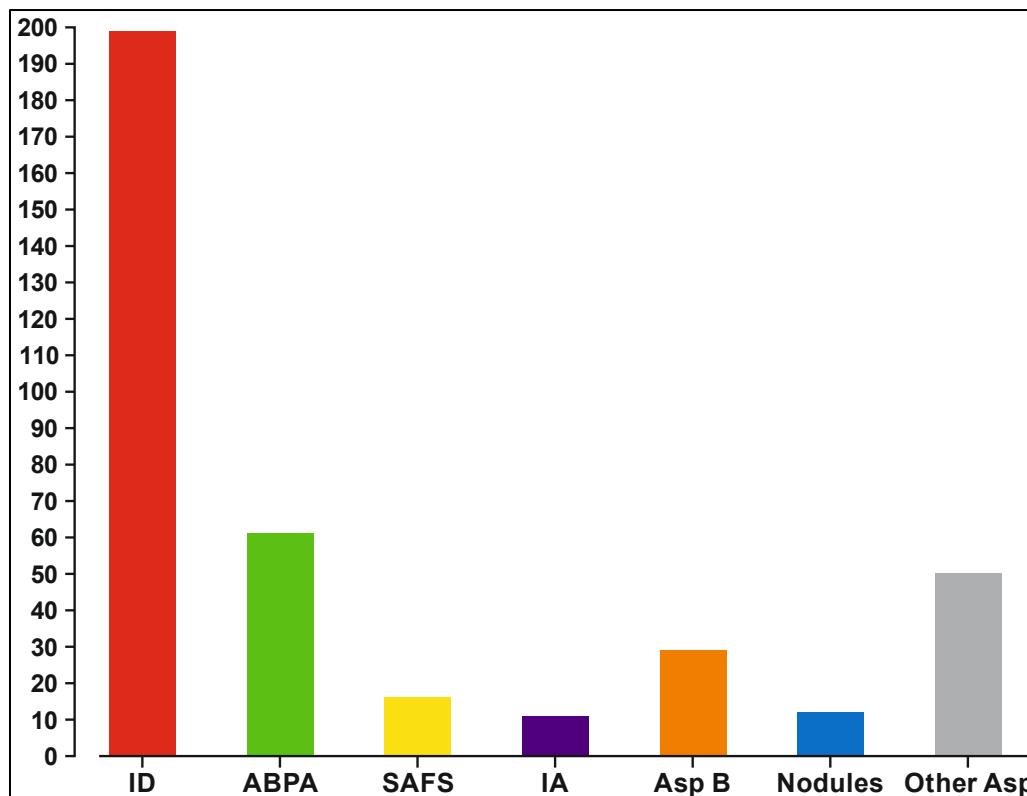
Admission days were similar to the prior year – from at 906 from 981, bed days with an increase in days at home on IV therapy from 49 to 73.

We have plotted the outpatient activity over the 8 years of the National Aspergillosis Centre operations in the figure below. The red line represents gradually increasing numbers of aspergillosis and related infectious diseases referrals, and the gap between that line and the actual CPA patients indicates that many alternative diagnoses are made. These are shown in the histogram below.



The distribution of new patients who do not have CPA but are seen by the same medical and nursing team is shown below. Of particular note, the number of other forms of aspergillosis are shown including allergic bronchopulmonary aspergillosis

(ABPA), severe asthma with fungal sensitisation (SAFS), invasive aspergillosis (IA), Aspergillus bronchitis (Asp B), Aspergillus nodules (Nodules). Under other forms of aspergillosis are included fungal rhinosinusitis, otitis, onychomycosis, building sickness syndrome and primary community acquired *Aspergillus* pneumonia. The ID column reflects patients with a broader differential diagnosis such as mycobacterial infection, other complex fungal disease, transplant assessments etc.



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

The NHS Mycology Reference Centre Manchester (MRCM) has completed its seventh 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.

In January 2017, the MRCM in partnership with the National Aspergillosis Centre (NAC) became the first clinical – diagnostic service to be recognised as a Centre of Excellence for the diagnosis and treatment of aspergillosis and other fungal infections, achieving the top Diamond status. The inauguration of the European Confederation of Medical Mycology (ECMM) Centre of Excellence scheme took place at the University Hospital of South Manchester in January 2017. The ceremony included presentations highlighting the work being done by Trust and University of Manchester scientists working in the NAC and MRCM and culminated in the presentation of the award to



Professor Malcolm Richardson, Director of the MRCM and Professor David Denning, Director of the NAC. The MRCM, in partnership with the NAC, are the first recipients of this award. It recognises our collaboration in establishing a better understanding of the medical issues related to mycology.

A) Primary activities and developments:

1. Approval of a business case to UHSM, underwritten by NHS England to develop a DNA sequencing service (pyrosequencing) to detect mutations that confer resistance to azole antifungal drugs directly in respiratory samples. Following an intensive period of methods development and validation the service analysed its first clinical samples in January 2017.
2. Ongoing validation and familiarisation of new tests in the Centre's portfolio.
3. For the first time hosting University of Manchester work placement students – highly successful placement year for both students
4. Highly successful completion of the fourth year of a Masters degree in Medical Mycology, in collaboration with the University of Manchester.
5. The overall increase in workload since 2009 is approximately 400%.
6. Active participation in weekly Infectious Diseases MDTs – presentation of new clinical diagnostic findings and discussion of complex patients
7. Membership of the UHSM Antimicrobial Committee and Lead role for Antifungal stewardship.
8. Clinical and laboratory audits –
  - Comparison of *Aspergillus* galactomannan index with PCR signal in sputum from patients with CPA
  - Posaconazole formulations influence antifungal drug levels in CPA patients
  - Fungal glucan-guided antifungal stewardship
  - High-volume sputum culture for the improved detection of *Aspergillus* spp.
9. Participation in weekly programme of educational meetings, alternating between invited speakers, research, clinical and audit meetings.
10. Income: internal and external: increase of 4% compared to 2015-2016.
11. Income: environmental monitoring business unit: income in excess of £20,000
12. Second year of a Mould Surveillance Service for assessing the homes of NAC and Respiratory Medicine patients, UHSM
13. Other services for non-CPA patients:
  - Sustained demand for the  $\beta$ -1,3-D-glucan ELISA test (Fungitell): a panfungal assay for fungal cell wall glucan, including *Aspergillus* and *Candida*, offered nationwide
  - Environmental monitoring (air sampling and dust analysis) of the homes of patients with sarcoidosis and extrinsic allergic alveolitis (hypersensitivity pneumonitis)

B) Representation on national and international committees:

1. EUCAST Antifungal Susceptibility Testing Committee as a Collaborating Laboratory
2. Standards for Microbiology Investigations (SMI) Steering Committee and Bacteriology Working Group
3. British Society for Medical Mycology

4. International Society for Human and Animal Mycology
5. Public Health England English surveillance programme for antimicrobial utilisation and resistance (ESPAUR)
6. Academy of the European Confederation of Medical Mycology
7. British Society for Antimicrobial Chemotherapy Grants committee
8. Testing laboratory for UK NEQAS for Microbiology – Mycology identification and susceptibility schemes
9. Test centre for all Fungal PCR Initiative (FPCRI) schemes – fungal PCR for *Aspergillus*, *Candida*, *Pneumocystis*, Mucorales and tissue

C) Research activities:

Consolidation of test portfolio offered for the benefit of CPA patients:

- The use of beta-D-glucan, PCR and other diagnostic tests in antifungal stewardship
- Ongoing experience regarding sensitivity testing on *Aspergillus* isolates to include terbinafine, micafungin and the new azole antifungal, isavuconazole
- Real-time PCR for *Aspergillus* spp. in respiratory secretions and blood
- Molecular identification of fungi, including unusual *Aspergillus* species. This is a nation-wide service
- Completed evaluation and implementation of an automated DNA extraction robot in order to respond to the dramatic increase in PCR assay requests
- Monitoring of NAC/CPA patients houses, workplaces for *Aspergillus*

D) Publishing activities 2016:

- 15 research papers, reviews and book chapters on *Aspergillus*-related topics and fungal infections in general (see Appendix 5) - highlights:
  - The first isolation of the pan-azole-resistant *Aspergillus fumigatus cyp51A* TR46/Y121F/T289A mutant in a UK patient
  - Bagpipe players lung, top 5% Altmetric score
  - *Candida auris* biofilms, top 5% Altmetric score
- iBook: Illustrated Cases in Medical Mycology, iTunes store, 149 downloads.

E) Training:

- UCL/BSMM distance learning Masters in Medical Mycology: one staff member enrolled
- Contributions to the development of an on-line histopathology of fungal infections training course ([www.microfungi.net](http://www.microfungi.net)), 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
- Host to one University of Manchester MD student
- Host to medical microbiology trainees
- Institute Pasteur, Paris – lectures
- Lecturing on University of Leeds Masters in Bioscience
- Host to overseas visitors for training and collaboration: Dr Luqman Satti (Pakistan)

F) Presentations and global outreach:



- Society for Indian Human and Animal Mycologists meeting (SIHAM, Shimla)
- British Society for Medical Mycology meeting
- INFORM: ISHAM Regional Meeting in collaboration with Gilead Sciences (Dubai) meeting
- Departments of Haematology, UK
- Departments of Clinical Microbiology, UK
- Filmed lectures: Gilead Antifungal Information Network
- Federation of Infection Sciences (FIS, Edinburgh)
- Controversies in Fungal Infection meeting (London)
- Advances Against Aspergillosis meeting (Manchester)
- 1<sup>st</sup> Symposium in Systemic Fungal Infections (Lagos)
- Symposium on Systemic Fungal Infections (Taipei)
- 7<sup>th</sup> National Conference on Systemic Fungal Infections (Beijing)

#### **4 Clinical service developments and personnel**

The NAC has completed its eighth 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 Paschalis Vergidis (5 PAs) (from October 2016)

Dr Ibrahim Hassan, Consultant in Microbiology (1 PA)

Dr Riina Richardson, Consultant in Oral Microbiology & Infectious Diseases (4 PAs)

Dr Ruth Tunney, CT2 in Infectious Diseases (50%)

Dr Samihah Moazam, Educational Fellow (50%)

Ms Deborah Kennedy, Specialist Nurse (40%)

Mrs Jenny White, Specialist Nurse (60%)

Ms Dawn Capey, Specialist Nurse (50%)

Ms Sarah Morris, Specialist Nurse (50%)

Mr Philip Langridge, Senior Specialist Physiotherapist (50%)

Miss Reyenna Sheehan, Specialist Physiotherapist (20%)

Dr Isabel Rodriguez Goncer, 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%

Mr Azad Aziz, New antifungals Clinical Trials Manager (100%)

Miss Alison Smith (50%)

Ms Marian Webster (50%)

Medical Secretary (50%) – vacant

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) Antifungal therapy at a distance

Healthcare at Home continue to deliver high cost antifungal medicine to patients at home, reducing some clinic visits and improving service to patients.

An increasing number of patients are receiving intravenous antifungal therapy close to home. Sometimes this is arranged through our OPAT team and delivered at home or on a day case unit locally, and sometimes as inpatients with NAC guidance. All these local courses of therapy are reimbursed to the prescribing unit from NAC. This is one of the reasons why our admission days are relatively low for the increasing volume of work.

#### 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 barely available elsewhere in the country, sample delivery to the MCRM in the post is an important component of care. PCR is more sensitive than culture and can be used as a proxy for detecting resistance and clinical failure. Some of these samples end up undergoing pyrosequencing to detect resistance. An increasing number of high volume cultures to improve the culture yield for susceptibility testing come in through postal packs. Significant results and new cases of azole resistance are discussed in the weekly MDT.

#### 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 scores, weights and *Aspergillus* IgG antibody levels, the 2016/17 data is presented in Appendix 4.

#### 7) N-of-1 trials of posaconazole or isavuconazole 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. This paper has been submitted for publication. We have also adopted this style of n-of-1 trials for isavuconazole. In the year April 2016 to March 2017, 38 patients were trialled on posaconazole and 23 on isavuconazole.

## 5 Audits

### 1. Time to appointment and shared care

Most patients were booked for an appointment within 8 weeks (Appendix 2). However, some appointments were longer mostly due to patients rescheduling appointments or not attending due to illness

Twelve patients died within the year after being seen for for the first time and overall 57 patients died on service, down on the 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.

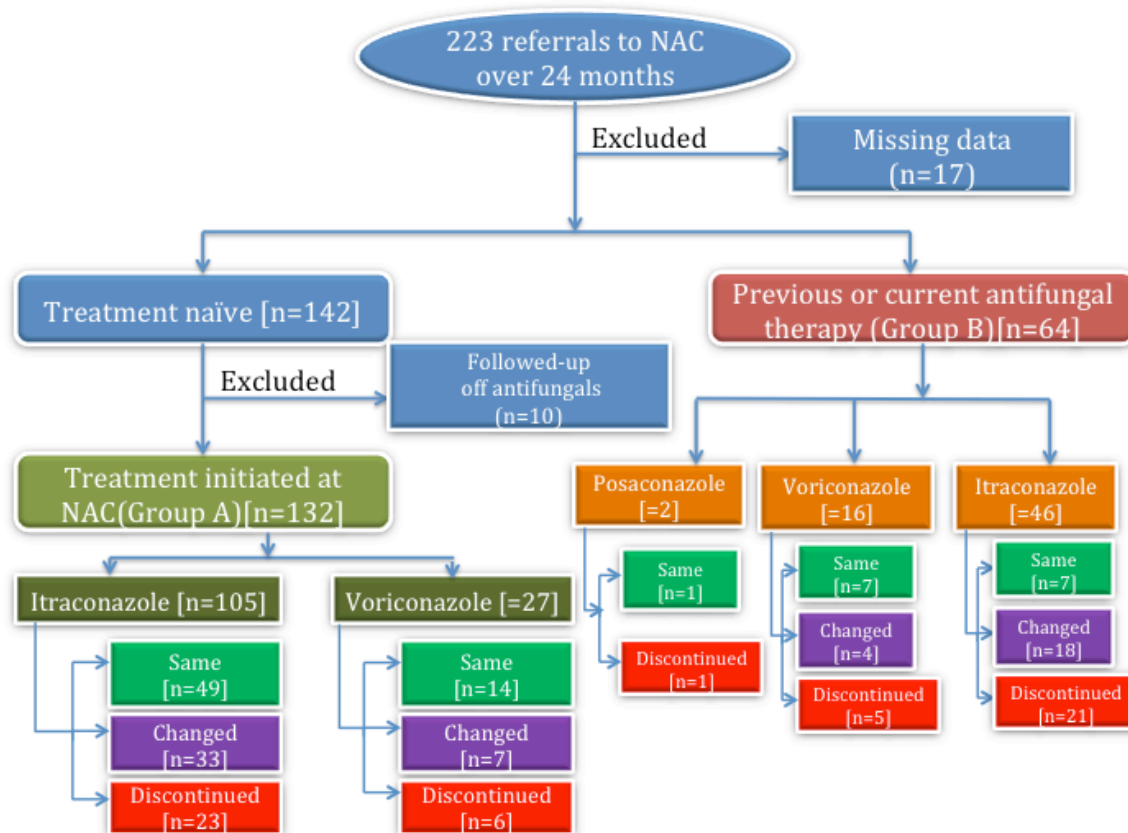
### 2. Clinical audits

Prior audits which have been published in 2016/17 include:

- Al-shair K, Muldoon EG, Morris J, Atherton GT, Kosmidis C, Denning DW. Characterisation of fatigue and its substantial impact on health status in a large cohort of patients with chronic pulmonary aspergillosis (CPA). *Resp Med* 2016;114:117-22.
- Langridge P, Sheehan R, Denning DW. Microbial yield from physiotherapy assisted sputum production in respiratory outpatients. *BMC Pulm Med* 2016;16:23.
- Kosmidis C, Newton PJ, Muldoon EG, Denning DW. Chronic fibrosing pulmonary aspergillosis: a cause of "destroyed lung" syndrome. *Infect Dis (Lond)*. 2017;49:296-301.
- Muldoon EG, Sharman A, Page ID, Bishop P, Denning DW. *Aspergillus* nodules; another presentation of chronic pulmonary aspergillosis. *BMC Pulm Med* 2016; 16:123.
- Bongomin F, Harris C, Foden P, Kosmidis C, Denning DW. Innate and adaptive immune defects in chronic pulmonary aspergillosis. *J of Fungi* 2017;2:26.
- Fayemiwo S, Moore CB, Foden P, Denning DW, Richardson MD. Comparative performance of *Aspergillus* galactomannan ELISA and PCR in sputum from patients with ABPA and CPA. *J Microbiol Method* 2017;140:32-39.

We undertook a comprehensive audit of 2 years of referrals with CPA to assess overall impact of therapy. This was presented as a poster at ECCMID in April 2017 and is in the final stages of preparation as a paper. We retrospectively evaluated treatment outcomes, including change in quality of life scores (St George's QoL questionnaire), weight and *Aspergillus*-specific IgG at 6 and 12 months following initiation of therapy in a cohort of 196 CPA patients referred to the UK National Aspergillosis Centre (NAC), Manchester between April 2013 and March 2015. Data was extracted on azole therapy prior to, or at the time of referral, and subsequent changes in therapy, including rates and rationale for discontinuation, and mortality.

The 12 month switches of therapy are summarised in the figure below, Group A being treatment naïve when seen and Group B having been treated previously:



Initial therapy was continued for 12 months in 48% of the total cohort (78 patients). Change of therapy was observed in 32% of patients (62) and discontinuation in 29% (56 patients). Azole discontinuation rates were higher in Group B (34%) than in Group A (21%) ( $p = 0.003$ ), indicative of a more challenging group of patients from a therapy perspective. At 12 months, there was no difference in median survival between group A and group B (95% vs. 91%,  $p = 0.335$ ). The rate of emergence of resistance during therapy was 13% for itraconazole compared to 5% for voriconazole. Bronchial artery embolisation was done in 9 patients and lobectomy in 7 patients. Thirty five (33%) patients developed adverse events to itraconazole over the 12-month period, with 15 (43%) requiring discontinuation of therapy. Ten (37%) patients developed adverse events to voriconazole, five severe enough to require discontinuation of voriconazole therapy. During the 12 months, 26 patients (18 from Group A and 8 from Group B) were switched to posaconazole and were evaluated for response at 4 and 6 months. All patients who were changed to posaconazole stayed on therapy for the remainder of the 12 months of observation, although some were discontinued subsequently. Seventeen patients required at least one course of antifungal therapy.

Other clinical audits undertaken in 2016/17 included:

- Seventy-eight n-of-1 trials of oral posaconazole for chronic pulmonary aspergillosis
- Relapse after discontinuation of antifungal therapy in CPA

- Isavuconazole levels and side effects in non-immunocompromised patients treated for chronic pulmonary aspergillosis
- Steady state serum levels of posaconazole on tablets versus oral liquid formulation
- Application of ISHAM guidance on ABPA diagnosis to a clinical cohort at specialist clinic
- High-volume sputum culture for the diagnosis of pulmonary aspergillosis
- Comparison of the performance of conventional culture, high-volume culture and quantitative real-time polymerase chain reaction in the diagnosis of pulmonary aspergillosis
- Emergence of echinocandin resistance in a patient with chronic pulmonary aspergillosis
- Does positive *Aspergillus* PCR predict azole resistance?

## 6 Patient and public engagement

### 1. Community booklet.

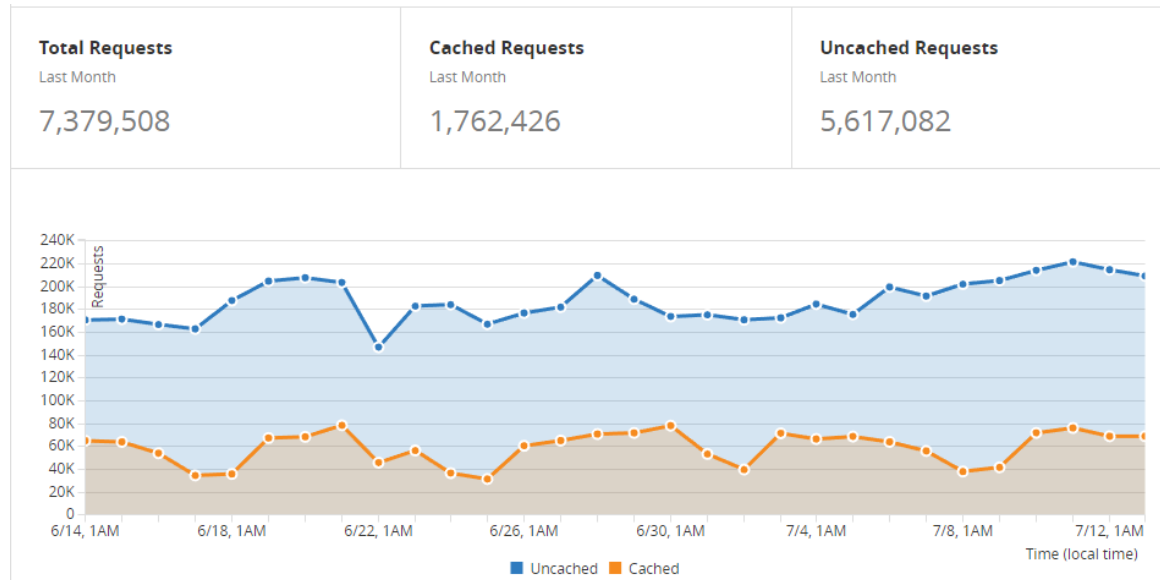
A community booklet is produced and 1000 per year distributed to all patients who do not have access to a computer, informally at clinic. The group of patients & carers that attend the monthly support meeting at NAC play an integral role in developing and publishing the NAC community booklet each quarter. 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. The Aspergillus Website @ [www.aspergillus.org.uk](http://www.aspergillus.org.uk) and [www.nacpatients.org.uk](http://www.nacpatients.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 a 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 11,500 scientific articles (including a unique collection of 829 historical articles) and well over 14,450 conference abstracts from 1974 onwards. A separate linked website for patients and carers provided answers to multiple questions in lay language.

The Aspergillus Website is listed at number 1, 1, 1 and 3 in Google.co.uk, number 1, 4, 1 and 5 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 7 million results. The Aspergillus Website had 80,000 unique visitors in a typical month and the Website for Patients 10,500 visits. About 46% of visits are using smaller devices. USA has overtaken China as the country from which we get most visits with UK and India in the next 2 places, and numbers of requests for website data have surged to over 7,000,000 per month, approximately 160,000 page requests in June 2017.

Monthly newsletters from the Aspergillus Website are sent out to over 22,000 (free) subscribers. This figure is driven by newly registered members seeking to access our secure ‘articles’. There are ~46,000 people registered on The Aspergillus Website (40% medics, 29% scientists, 8% vets and 23% laypeople).



Usage by country is depicted here (1<sup>st</sup> May – June 30 2017):

Country ?	Sessions ? ↓	Pages / Session ?
	72,383 % of Total: 100.00% (72,383)	3.28 Avg for View: 3.28 (0.00%)
1.  United States	19,949 (27.56%)	2.94
2.  United Kingdom	12,346 (17.06%)	3.88
3.  India	6,305 (8.71%)	2.71
4.  Australia	2,433 (3.36%)	2.90
5.  Canada	2,033 (2.81%)	2.74
6.  China	2,020 (2.79%)	1.60
7.  Netherlands	1,278 (1.77%)	2.86
8.  Brazil	1,231 (1.70%)	4.14
9.  Germany	1,156 (1.60%)	3.26
10.  Japan	936 (1.29%)	3.10

### 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 most months we see new attendees taking the opportunity to meet with us. The meetings are led and organised by Dr Graham Atherton and Chris Harris.

The subjects covered are available at [www.nacpatients.org.uk/monthly\\_meeting](http://www.nacpatients.org.uk/monthly_meeting) and include

- Dr Paul Bowyer on why some people get ABPA when most of us don't,
- Eating well by following the Mediterranean Diet,
- Allergy to salicylic acid by Dr Susana Marinho,
- 3 dimensional in vitro models of epithelia and immune cells lining human airways by Parul Chandorkar,
- Patient involvement in NAC clinical trials by Dr Azad Aziz,
- When a lung transplant might be an option for aspergillosis patients by UHSM Transplant Team,
- Other subjects covered include the use of mindfulness to control stress, anxiety and promote better health in the chronically ill, prevention of stress and depression and new antifungal drugs in development.

### 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 2,100 participants
- The NHS Choices online community for Aspergillosis has 1,070 participants
- [www.nacpatients.org.uk](http://www.nacpatients.org.uk) website (averaging 4,000 visitors per month)
- Local online Facebook groups (15 groups, 9 in the UK serving 50 - 70 people)
- Facebook group specifically for carers
- The Professional LinkedIn members (Aspergillus and Aspergillosis Group) has over 500 members and 130 are in the related 'Damp Buildings and Human Health' LinkedIn group.
- Monthly meeting viewed live & by recordings (250-450 viewings per month in 2017)

#### 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

We provide a phone line 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 phone line is manned by patient/carers 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. 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 and key publication findings

### 1. Papers and book chapters

Amongst the 45 papers and book chapters published in calendar year 2016, there were several areas of direct relevance to patients with CPA and pulmonary aspergillosis.

These were:

- Following on from the European clinical guidelines for the diagnosis and management of CPA (1) US guidelines under the aegis of the Infectious Diseases Society of America were also published (2).
- The diagnostic value of having physiotherapists in clinic generating sputum samples was clearly documented, both for bacterial infection, but also for aspergillosis, with many resistant strains identified (3).
- The diagnostic performance of 6 different commercial *Aspergillus* antibody tests was compared, with the best performing for CPA at a sensitivity exceeding 95% with a high specificity against blood donors (4).
- The free online and app database for antifungal drug interactions was highlighted in a letter (5).
- The response rates to courses of AmBisome for CPA was published and residual nephrotoxicity found in 15% of patients (6).
- The newly discovered manifestation of *Aspergillus* nodules was described for the first time (7).
- The lack of access and in some countries excessive cost of antifungal agents was documented in a global 3 year study (8).
- Estimated country burdens of serious fungal diseases including chronic and allergic aspergillosis were published for 4 more countries [Appendix 5].

### 2. Key papers related to CPA:

1. 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.
2. Patterson TF, Thompson GW, Denning DW, Fishman J, Hadley S, Herbrecht R, Kontoyiannis DP, Marr KA, Morrison VA, Nguyen MH, Segal BH, Steinbach WJ, Stevens DA, Walsh TJ, Wingard JR, Young J-AH, Bennett JE, Practice guidelines for the diagnosis and management of aspergillosis: 2015

- Update by the Infectious Diseases Society of America. Clin Infect Dis 2016 63:e1-e60. (Executive summary - Clin Infect Dis 2016;63:433-42.)
3. Langridge P, Sheehan R, Denning DW. Microbial yield from physiotherapy assisted sputum production in respiratory outpatients. BMC Pulm Med 2016;16:23.
  4. Page ID, Richardson MD, Denning DW. Comparative diagnostic performance of six Aspergillus-specific IgG assays for the diagnosis of chronic pulmonary aspergillosis. J Infect 2016;72:240-9.
  5. Bartholomew J, Banfield S, Atherton GT, Denning DW. Antifungal therapy: adverse drug–drug interactions database and Smartphone APPs. J Antimicrob Chemother 2016 71:2062 (Letter).
  6. Newton PJ, Harris C, Denning DW. Impact of AmBisome therapy on chronic pulmonary aspergillosis. J Infect 2016;73:485-95.
  7. Muldoon EG, Sharman A, Page ID, Bishop P, Denning DW. *Aspergillus* nodules; another presentation of chronic pulmonary aspergillosis. BMC Pulm Med 2016; 16:123.
  8. Kneale M, Bartholomew JS, Davies E, Denning DW. Global access to antifungal therapy and its variable cost. J Antimicrob Chemother 2016; 71:359-606.
  9. [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)
  10. [www.uptodate.com/contents/treatment-of-chronic-pulmonary-aspergillosis](http://www.uptodate.com/contents/treatment-of-chronic-pulmonary-aspergillosis)

Manchester was successful in its bid to NIHR for a Biomedical Research Centre, which has 7 themes, one respiratory, and including infection. The five year grant is for £28.5M and includes specific areas of research in CPA and other forms of aspergillosis, including genetics and microbiome work.

There are six new antifungal agents in clinical development. The NAC is being proactive in working with industry to develop studies that could lead to the first approval of an antifungal agent for CPA (as none have been prospectively studied in phase 2 or phase 3 development to date). These agents include novel (ie non-azole) compounds with excellent activity against *Aspergillus* spp.

## 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

One complaint from relatives of patient who died. Response sent to family.

### HIRS alerts

No HIRS submitted.

## 9 Future developments

Developments planned for 2016/17 included (outcomes):

- 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. **Azad Aziz in post**
- 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. **First study will recruit in 2017.**
- 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. **Merger likely in Autumn 2017**
- Increased clinic, nursing and medical capacity is planned. **Additional rooms found for some clinics**
- Doubling of undergraduate teaching by UHSM ID team, to both year 3 and year 4. **Implemented and will be fully operational from August 2017**
- 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. **Advertised in June 2017, but no suitable applicants applied.**
- 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. **Ongoing.**

The developments planned for 2017/18 are:

- Implementation of year 1 of the NIHR BRC research plan in infection.
- Implementation of direct detection of azole resistance by pyrosequencing into routine clinical service.
- International Fungal Disease Awareness week (August 14th week 2017) being promulgated by the Centers for Disease Control, Atlanta with the NAC playing a full part.
- Eighth Advances Against Aspergillosis Meeting to be held in Lisbon (February 1-3rd, 2018), and a Portuguese patient's meeting is planned.
- A primary therapy study of isavuconazole for CPA funded by industry. Other new antifungal developments are in the planning phase.

## 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**

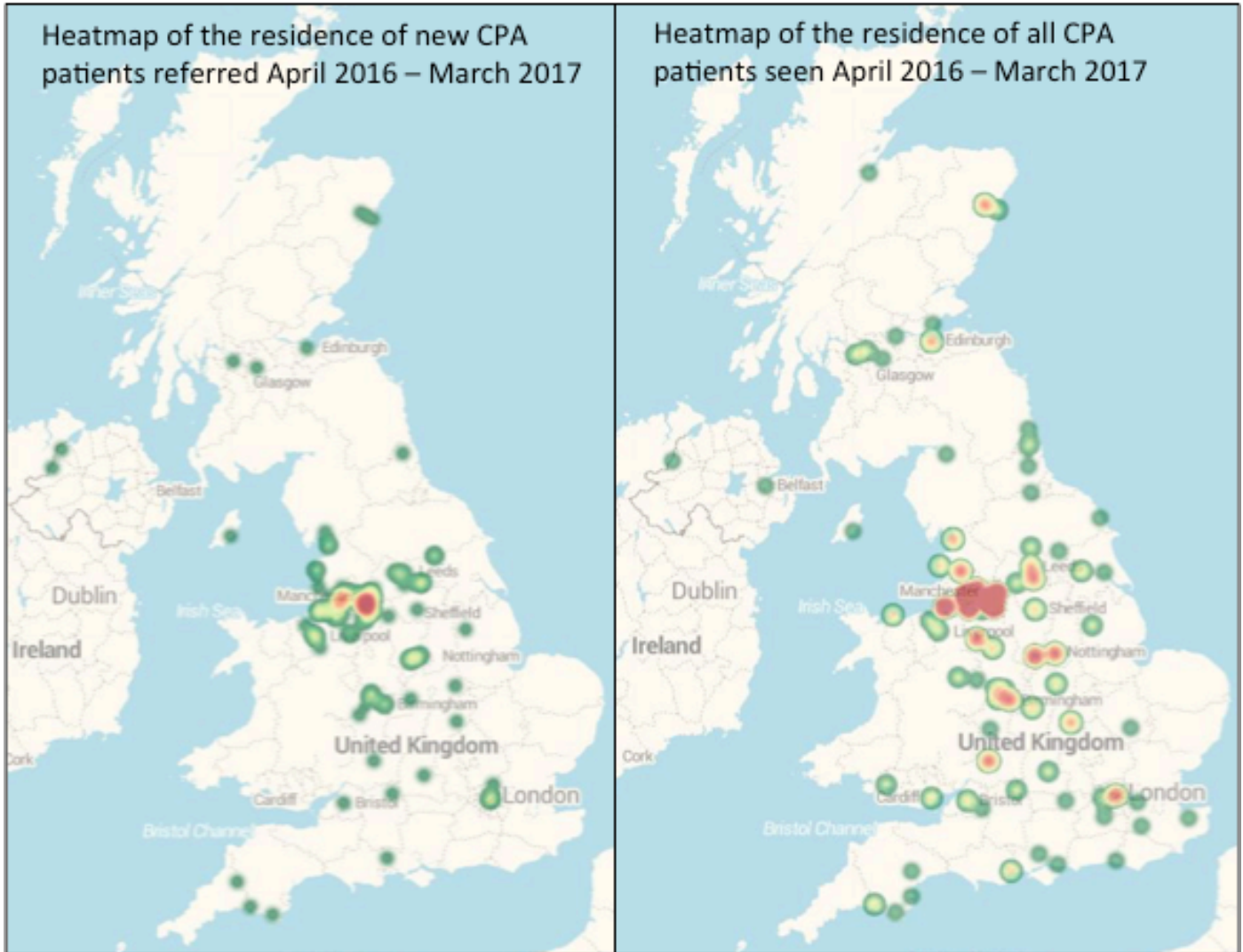
### **Referral to appointment time audit - April 2016 – March 2017**

\* The month seen is not always the month they are determined to have CPA, because of missing diagnostic data. Transition refers to new CPA diagnosis in a patient already under our care.

See separate data file

Appendix 3

Heat maps showing the geographical distribution of new and existing CPA patients March 2017



**Appendix 4**

**Quality of life (SGRQ), weights and MRC dyspnoea scores for new referrals 2016/17**

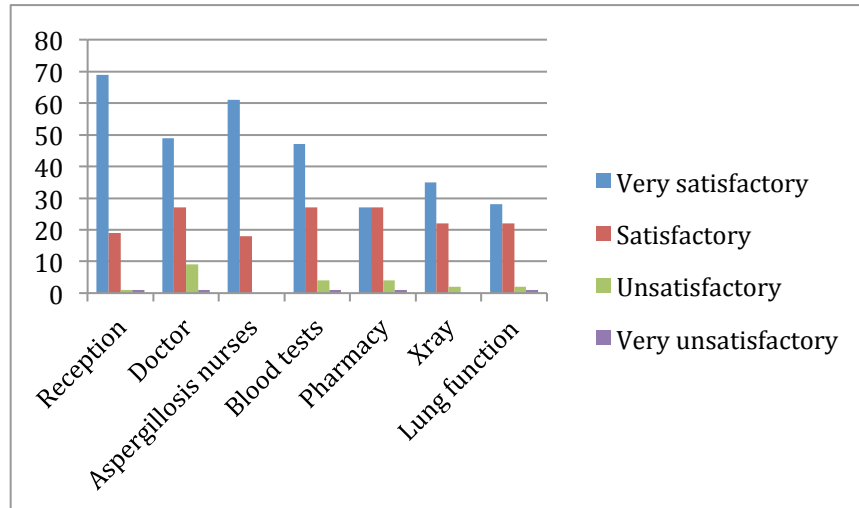
See separate data file

## Appendix 5

### NAC Patient Survey 2017 – Summary

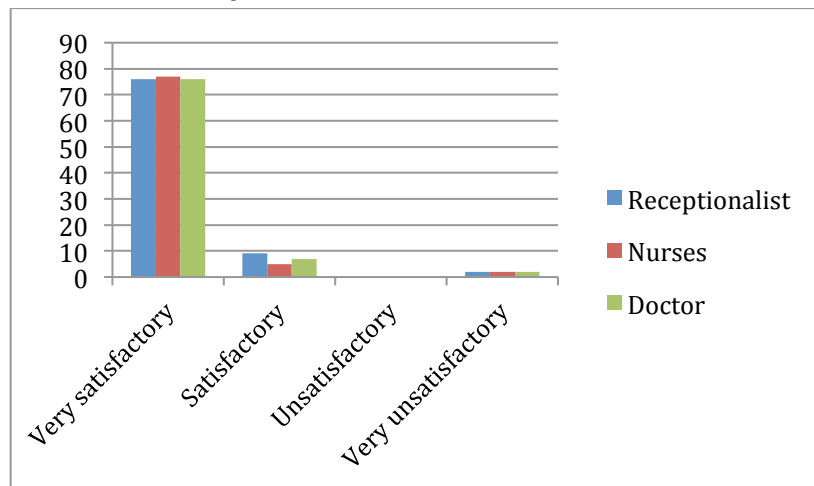
The survey was completed by 90 patients during February 2017, 3 (3%) of whom were attending clinic for the first time. Not all answered all of the questions.

#### **1. Waiting times**



10 (12%) patients found waiting time for doctors unsatisfactory or very unsatisfactory, 9% and 6% were unsatisfied or worse for waiting times for pharmacy and blood tests respectively.

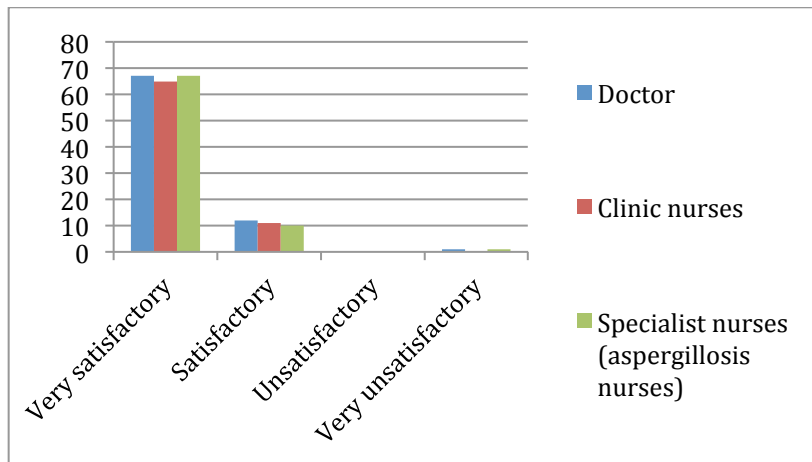
#### **2. Courtesy**



2 (2%) patients were very unsatisfied with the courtesy shown by all three staff groups, but over 76% found all three groups very satisfactory.



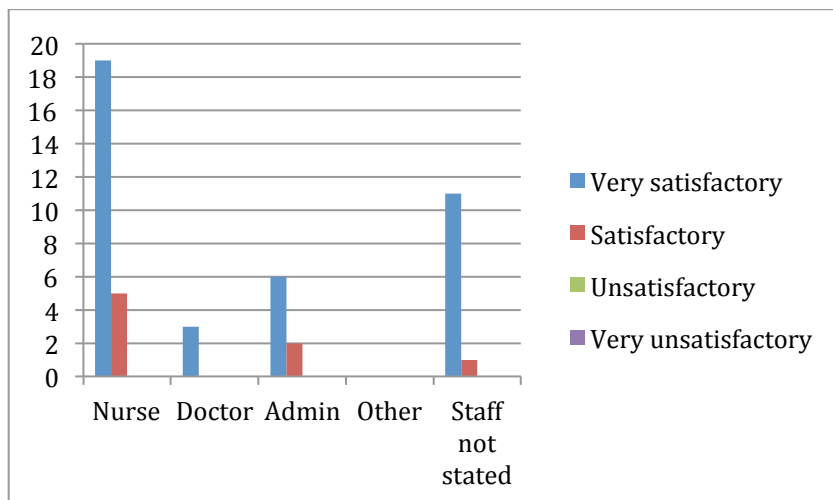
### 3. Quality of care



Quality of care from doctors and specialist nurses was rated satisfactory or better by 99% of all patients, 100% rated clinic nurses satisfactory or better.

### 4. Support outside of clinics

50% of all patients who replied to this question (83 patients) had been contacted by staff members after or in-between clinics.



All those who replied to this question were satisfied or better at the support offered outside of clinic. Comments were extremely positive with special mentions for Debbie Kennedy from two patients:

*This has been very good; both of the above very helpful & understanding; great service from this team. They actually go out of their way and care; Very helpful support; It was over a year ago, Think it was Deborah; Brilliant support shown by nurse Deborah Kennedy; Nurse wants to arrange home delivery of meds but that service needs to improve first.*

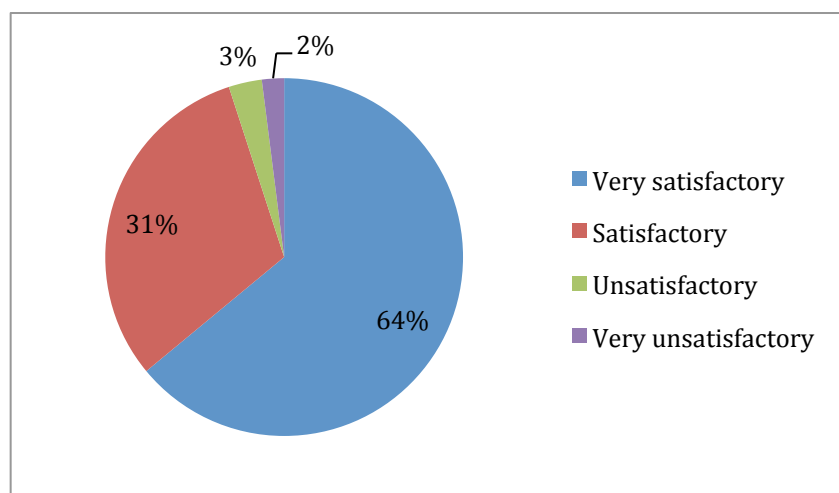
### 5. Specialist physiotherapy

22 patients (26%) had received care from our specialist physiotherapy team with 100% satisfied or better (86% very satisfied). Comments were very positive: *Very helpful, patient & courteous; Phil is very caring & helpful; due for physio today.*

## 6. Written information

67% (55 patients) had received written information about their condition which might be a little low considering that all patients have access and most should have received at least one leaflet albeit some time ago.

Comments are varied: *Would like more direction, e.g. what are we going to do about this?; All questions answered 10/10; A lot of info all at once but very good info; But not recently\*No clinic letters for last 2 appointments; No; No; Very useful, especially at diagnosis; Can't remember;*



95% (58 patients) considered the written information given to be satisfactory or better.

## 7. Information about potential symptoms

80% (61 patients) had received information about potential symptoms they may experience at home due to their illness or medication.

Comments suggest some service inconsistencies: *Not on meds at the moment; Information on the medication; Provided a level of reassurance; I've been told different things by different doctors so it's confusing; Details outlined in medication leaflet.*

## 8. Asking doctor questions

97% (74 patients) were happy that they had understood replies given by doctors when they (i.e. the patient) had asked for important information.

Comments are varied in approval and constructive: *I don't seem to get any direction; Very clear and patients responses; No; Sometimes; Very helpful (Dr Isobel Rodrigues); Has not been helped by seeing a different doctor on each visit to the clinic. I feel that this leads to a bit of inconsistency;*

## 9. Have you ever had an in-patients stay?

41% (33 patients) had been an in-patient at UHSM, of these 97% (32 patients) felt that they had been treated with respect and dignity while in hospital.

Comments are very positive: *Excellent care by all staff; Mostly; Was a good stay, thanks to the staff; Good; Very well cared for;*

### **10. Recommend UHSM to family and friends?**

97% (75 patients) would recommend UHSM to family & friends.

*Why?: Not had any problems at all - all staff very nice & efficient; Have always been extremely satisfied with treatment & friendliness of everyone; Effective; Service has been excellent overall; A caring hospital; Very friendly & helpful; Great staff, specialist care; Very friendly; Because you get very good service from all; Great service; Very thorough; Efficient care; Friendly, efficient; Excellent service; Treated with respect, dignity and staff always courteous very good service provider; Feel I get first class, professional advice & treatment; I have always had good care; Seems very thorough; Excellent dedicated staff; Treated well; It is a fantastic centre, Care & information is second to none; I receive the best treatment here; Good care, best place to be;*

### **11. Postal service for drug levels and sputum samples**

Comments are generally positive with some constructive suggestions: *Was fine for me; None; Yes; How to get more packs; Worked OK. Need better packaging won't fit in the letter box; The sample pot did not fit in the plastic container; So far so good, system seems to work; None; Excellent service; Remember to enclose returns labels; None; A brilliant service; No; It worked well; No it works extremely well; No; Samples taken by GP's but a bit of confusion as to the forms to use. Perhaps provision of all necessary forms to avoid such circumstances; Yes very satisfied; Satisfactory service; No problems. Found this service easy to use; More information with request for phlebotomists; Great service, saves on driving from Warrington to Manchester; No; Delivery slot options poor; No; Worked well;*

### **12. Delivery of antifungal drugs to patients homes**

Comments are generally very positive with one or two constructive suggestions: *Very good; Unreliable; Very good service; Very good; Always on time; Good service; A very good service; Would like information; delivered by homecare; No good service; Has a couple of issues but generally a great service; Not used; Service first class; Very good efficient & helpful company; No; Very good service, they phone me to arrange delivery; No; Very good; Excellent service; Was a very good service; Satisfactory service; First class services, very helpful; Great service, saves on driving from Warrington to Manchester; Delivery slot options poor; No;*

### **13. Patients website ([nacpatients.org.uk](http://nacpatients.org.uk))**

46% (37 patients) of patients had visited the Patients Website. This equates quite closely to the use recorded for the Aspergillus website in previous patient's surveys. We had introduced changes to our websites to allow them to be better viewed on a range of portable devices in the hope that this figure would rise further and this may have helped boost viewing figures as we have recorded 66% of the users of this website do so on portable devices. 100% of patients who visited the website found it to be satisfactory or better.

Of those who had not visited the website we have the following comments revealing that most have no access (5 patients (33%)) or feel no need to visit the website (4 patients (26%)), only 2 patients (13%) were not aware of it.

Comments: *No computer; Not online; No computer; I am not aware of website; Find booklets helpful; No access; No reason; Don't know; No; Did not know; Have enough*

*information from Doctors & nurses; No computer; Not sure, will visit site now I have been reminded;*

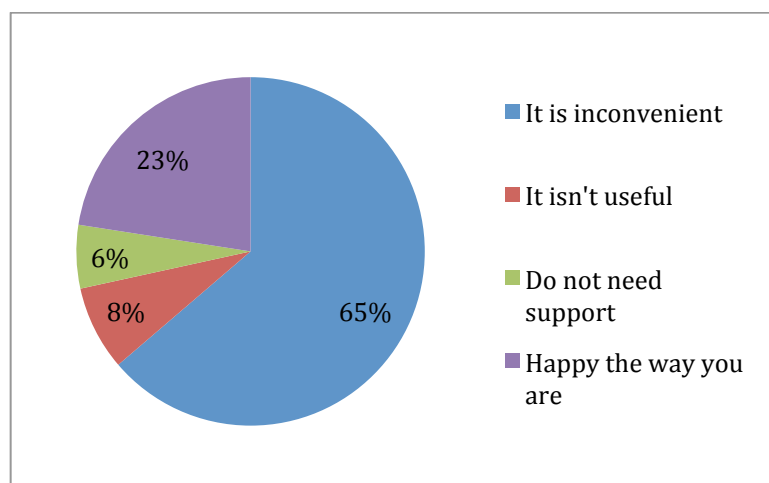
#### **14. Suggestions for more patient information leaflets.**

There were no suggestions, one person finding our quarterly booklets useful.

Comments: *No; Booklets are very useful; No; No; None; No; No; Currently OK; How do we solve this problem;*

#### **15. Monthly patients community meetings**

4% (3 patients) had attended a Patients Community Meeting in Manchester, one of who commented that it was very informative. The reasons why patients had not attended meetings are given in the pie chart below:



65% (34 patients) would seem to like to be able to attend but it was too difficult to do so and the comments bear this out. The remaining 35% (19 patients) gave reasons indicating that they did not think it would help them.

Comments: *Work full time - find hard to get to; Live too far & unwell; Didn't know about them; We travel from South Wales - even if clinic was in the same day it would delay our homeward journey too much; Very very busy lifestyle & too far away; I travel from West Wales a 6hr drive so unless the day of my appointment unable to attend;*

#### **16. Regional support groups**

Awareness of regional groups was quite good at 49% (36 patients) but of those only 4% (2 patients) had made contact with a group. Nobody (none of 24 patients) wanted information on setting a group up. Comments made on why patients had not made contact were mostly about travel difficulties or not interested, with only 4 (11%) not being aware of the groups.

Comments : *I am happy as I am; Too far to travel; Not aware; Didn't know they existed; Too far; On my agenda; I live in West Wales; Not required; Too far away and inconvenient; Distance; Not really needed; Not a good time; None near me & no transport; Dont feel well enough to attend; Not so comfortable in these matters; Too busy; Did not know; Transport difficulties; A little faraway plus concerned about feeling depressed seeing other patients; Didn't know about them; Not aware; Too far for me to get to; Because of time and distance; Cant do; I live in Bournemouth,*

*Dorset. Travelling not easy; Out of reach; Not in my area; Not necessary; I live in Hampshire; Nearest is UHSM; Out of area-Lancashire; Dont know; Not interested; Dont know about them; Cannot see any benefit; Ill;*

### **17. Manchester patients community meetings broadcast on Patients Website**

**Recorded meetings:** 12% (8 patients) reported watching at least one recorded session. Comments hint that some would like to watch but did not have access to a computer. If yes any comments?: *Very good; No computer; No; Not relevant; Not got the capacity to view;*

**Live broadcasts:** 5% (4 patients) had watched a meeting live. Comments if yes: *Hope to watch in future; NB we had noted a lack of people watching live and in 2017 have explored putting the live broadcasts onto our Facebook pages. In June 2017 the meeting got 291 views.*

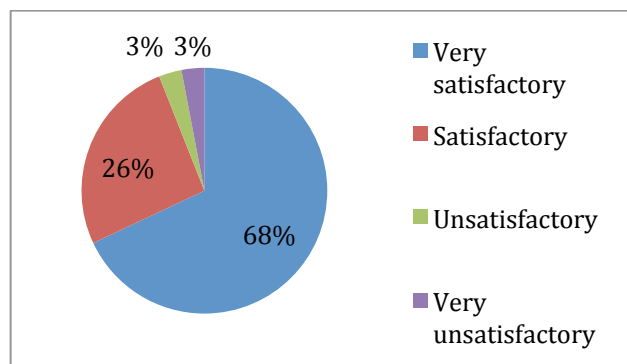
### **18. Hospital transport**

11% (9 patients) had travelled using hospital transport, 100% found the service very satisfactory.

### **19. Clinical research participation**

86% (69 patients) were generally happy to participate in clinical research. Of those the above table shows 94% (36 patients) were satisfied or better with the clinical trials procedures and consent process.

Comments: *Seems disorganised and not joined up with the clinic; No;*



### **20. General comments**

General comments identify that patients have experienced the following:

- An issue with waiting too long for clinic letters & a referral
- Arriving on time for appointment after 3 hour journey only to have to wait 2 hours to see doctor
- Limited communications with GP & other dietary specialist. One suggestion is for Skype MDT with GP team
- Lack of consideration given to comorbidities ie coeliac disease

*Comments: Very happy and grateful for the help I have received; Great support from the aspergillosis team; Best clinic in the North West; Still waiting for last two clinic letters and also waiting since inpatients stay OCT 16 for chest clinical appointment with sarcoidosis doctor; Always very helpful and supportive staff; Very happy with all aspects of treatment by every member of staff on the unit Many thanks; Invaluable service thank you; I was kept waiting for 2 hours despite arriving on time for my appointment & my notes got lost in the queue; Communication with GP and other specialists for coeliac is very limited. This seems to be causing difficulties with an overall consideration of patients health rather than just focussing on chest condition; Improve communication between Wythenshawe & GP practice locally. Need for MDT meetings (eg over internet); I find all staff in clinic very pleasant & approachable; Staff very nice;*

Appendix 6

**Publications from the Fungi@Manchester Group (2016)**

1. Denning DW, Cadranell 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.
2. Langridge P, Sheehan R, Denning DW. Microbial yield from physiotherapy assisted sputum production in respiratory outpatients. *BMC Pulm Med* 2016;16:23.
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4. Page ID, Richardson MD, Denning DW. Comparative diagnostic performance of six *Aspergillus*-specific IgG assays for the diagnosis of chronic pulmonary aspergillosis. *J Infect* 2016;72:240-9.
5. Al-shair K, Muldoon EG, Morris J, Atherton GT, Kosmidis C, Denning DW. Characterisation of fatigue and its substantial impact on health status in a large cohort of patients with chronic pulmonary aspergillosis (CPA). *Resp Med* 2016;114:117-22.
6. Jones N, Garcez T, Newman W, Denning D. Endogenous *Candida* endophthalmitis and osteomyelitis associated with *CARD9* deficiency. *BMJ Case Rep* 2016 Mar 3;2016. pii: bcr2015214117.
7. Oladele R, Akanmu S, Nwosu A, Ogunsola F, Richardson MD, Denning DW. Prevalence of cryptococcal antigenemia in antiretroviral naïve and antiretroviral experienced HIV infected patients with CD4+ count below 250 cells/mm<sup>3</sup> in Lagos, Nigeria. *Open Forum Infect Dis* 2016;3:ofw055.
8. Sintes M, De Moliner F, Caballero-Lima D, Denning DW, Read ND, Kielland N, Vendrell M, Lavilla R. Electrophilic, activation-free fluorogenic reagent for labelling bioactive amines. *Bioconjug Chem* 2016;27:1430-4.
9. Gamaletsou MN, Drogari-Apiranthitou M, Denning DW, Sipsas NV. An estimate of the burden of serious fungal diseases in Greece. *Eur J Clin Microbiol Infect Dis* 2016 35:1115-20.
10. Bromley M, Johns A, Davies E, Fraczek M, Mabey-Gilsenan J, Keays M, Kurbatova N, Kapushesky M, Gut M, Gut IG, Denning DW, Bowyer P. Mitochondrial complex I is a global regulator of secondary metabolism, virulence and azole sensitivity in fungi. *PLoS One* 2016;11:e0158724.
11. Guto JA, Bii C, Denning DW. Estimated burden of fungal infections in Kenya. *J Infect Dev Ctries* 2016;10:777-784.
12. Bartholomew J, Banfield S, Atherton GT, Denning DW. Antifungal therapy: adverse drug–drug interactions database and Smartphone APPs. *J Antimicrob Chemother* 2016 71:2062 (Letter).
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  15. Kneale M, Bartholomew JS, Davies E, Denning DW. Global access to antifungal therapy and its variable cost. J Antimicrob Chemother 2016; 71:359-606.
  16. Denning DW. Minimizing fungal disease deaths will allow the UNAIDS target of reducing annual AIDS deaths below 500 000 by 2020 to be realized. Phil Trans Roy Soc B 2016; 371: 20150468.
  17. Overton NLD, Bowyer P, Denning DW, Simpson A. Genetic susceptibility to allergic bronchopulmonary aspergillosis in asthma: A genetic association study. Allergy Asthma Clin Immunol 2016;12:47.
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