Annual report 2017-2018





NHS National Commissioning Group - Highly Specialised Services

Chronic Pulmonary Aspergillosis National Service

The National Aspergillosis Centre

Annual Report 2017-2018





A European Centre of Excellence in Medical Mycology



European Confederation of Medical Mycology *Confédération Européenne de Mycologie Médicale*

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1 General Overview and highlights

This report covers the ninth full year of this National Aspergillosis Centre (NAC), commissioned as a Highly Specialised Service within the NHS. A total of 130 new patients with CPA (out of a total of 369 with some form of aspergillosis) were seen in the 12 months from April 2017 to March 2018. At the end of March 2018, 487 patients from England and Scotland were on service with an additional 16 patients from Wales, two from Northern Ireland and one from the Isle of Man. In the year fifty eight patients died and 26 were discharged from service. This represents a 15.3% growth (6.7% growth in prior year). Waiting times have increased for CPA patients from 7 to 9 weeks, and for other aspergillosis patients, partly because of a lack of clinic capacity and impact of RTT administrative procedures for non-CPA patients impacting on CPA waiting times. Not enough nursing support has impacted on basic data collection in clinic and between clinic follow up, affecting the total patient experience.

The overall drug expenditure has fallen substantially as voriconazole has come off patent. Admission days continue to fall as more patients receive IV micafungin (or AmBisome) therapy via home care (OPAT) services at the NAC and numerous other hospitals throughout the UK. Less AmBisome is used, because of the prior audit showing a 15% rate of persistent renal dysfunction. High levels of azole antifungal resistance, combined with drug intolerance or toxicity (notably peripheral neuropathy) continue to drive IV antifungal use. These patients have a relatively high frequency of subtle immunodeficiency, notably poor natural killer cell function, or low production of gamma interferon and/or interleukin 12 (required for gamma interferon production) necessitating increasing use of gamma interferon replacement therapy.

Posaconazole and isavuconazole was used in those intolerant or failing itraconazole and voriconazole as a trial of therapy. Posaconazole was successful in 17 of 39 (44%) but isavuconazole in only 1 of 14 (7%) trialled (p=0.02).

The NHS Mycology Reference Centre, which provides the high level diagnostic mycology service for the NAC, continues to grow and process more specimens and do more tests, year on year. Over 5 years the volume of internal work has more than doubled, notably mould identification and susceptibility testing, directly related to NAC activity. External work has also increased with a 3-fold increase in specimens submitted from 2013/14 to 2017/18.

There were 75 papers and 6 book chapters published in calendar year 2017, many of direct relevance to patients with CPA and pulmonary aspergillosis, including an estimate of the burden of serious fungal diseases in the UK (3,600 CPA cases), a detailed description of chronic fibrosing pulmonary aspergillosis, a summary of factors affecting survival in CPA (86%, 62% and 47% at 1, 5 and 10 years), a high frequency of immune defects of low antibody producing and natural killer cells, the poor diagnostic utility of galactomannan in sputum and the first description of echinocandin (micafungin) resistance in *Aspergillus* which arose in a CPA patient. Many audits were undertaken including the finding that *Aspergillus* IgG falls with resection surgery, but not usually to normal; a higher number of adverse reactions to posaconazole tablets compared to suspension, probably reflecting higher drug exposure; that bilateral disease is a risk factor for relapse of CPA after treatment discontinuation; the value of high volume sputum cultures in increasing microbial yield for sputum and detection of resistance mutations through pyrosequencing.

Patient support and outreach activities were maintained with more engagement and a remarkable growth in website and social media use. The number of requests for Aspergillus Website data surged to over 9,000,000 per month, with the USA, UK and India the top three country users. The declaration of February 1st 2018 as the first World Aspergillosis Day focussed minds on the topic as it was announced at the Advances Against Aspergillosis conference in Lisbon where a patient meeting was also held. Seven press releases and 67 blogs were published, with regular tweets.

2 Activity

The total referrals, inpatient stays, procedures, death and caseload in 2017/18 (Table 1) 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	18	34	30	33	35	29	31	34	33	36	25	31	369
New Patients Testing	4	11	10	7	11	10	12	15	12	14	10	14	130
Outpatient - Follow-Up Attendances	120	134	145	137	133	153	128	144	143	140	146	124	1,647
Caseload - Band 1	167	163	160	162	161	156	151	147	155	153	153	149	149
Caseload - Band 2	244	251	253	252	254	259	266	272	274	284	294	301	301
Caseload - Band 3	18	18	18	18	19	19	17	21	21	20	21	23	23
Occupied Bed Days	53	42	77	43	83	56	138	78	73	27	45	49	764
Inpatient Discharges	4	7	4	4	7	5	7	5	6	1	3	4	57
IV Homecare (OPAT)	27	20	0	20	84	116	15	23	31	15	13	126	490
Surgical Resection	1	1	2	1	0	0	1	0	0	0	0	0	6
Embolisations	1	3	0	2	0	3	1	0	1	0	0	0	11
Patient Death	6	1	6	6	5	6	6	5	4	3	4	6	58
Discharge from Service	0	1	7	3	2	4	4	1	0	3	0	1	26

* The NCG fund patients from England and Scotland only

Appendix 1 shows the Banding criteria used

Of the 369 new aspergillosis referrals from England and Scotland during the year 2017/18, 130 (35.2%) had CPA, a slightly increased proportion compared with prior years. Among the outpatient referrals, the mean time from referral to being seen was 9 weeks (Appendix 2), including 4 patients who rescheduled their appointments or were too unwell to attend which is reflected in their the long wait times of 4-6 months. Part of the reason for the longer waits compared to the previous years was displacement of CPA new patients by 18 week RTT pathway referrals. This reflects the lack of clinic capacity generally, but in particular clinic space. There were 6 transitions from another form of aspergillosis into CPA, 7 patients whose diagnosis took weeks to confirm and 6 from the TB service. A total of 19 patients under our care with another form of aspergillosis and transformed their disease into CPA.



Figure 1. New aspergillosis and CPA referrals (2016-2018) and CPA patients on service at the end of each year from 2009/10 to 2017/18. Patient discharges and deaths per year are also shown.

Appendix 2 shows the area of residence, date of referral and date of appointment. These numbers include 1 referral from Northern Ireland, 3 from Scotland, 1 from Wales, 1 from Portugal and 1 from Greece. There were five direct admissions and one ward referral at Wythenshawe Hospital from another team who died during that admission. Overall 11 of 130 (8.5%) referred patients died within the year. The locations of the referrals and all patients seen are shown in the maps, and displayed as heatmaps in Appendix 3.

The number of new patients with aspergillosis who do not have CPA but are seen by the same medical and nursing team is shown in Figure 1. These other forms of aspergillosis include allergic bronchopulmonary aspergillosis (ABPA), severe asthma with fungal sensitisation (SAFS), invasive aspergillosis, *Aspergillus* bronchitis, Aspergillus nodules and fungal rhinosinusitis, otitis, onychomycosis, building sickness syndrome and primary community acquired *Aspergillus* pneumonia.

There has a significant fall in Band 1 numbers from 180 to 149 patients and a corresponding rise in Band 2 patient numbers from 230 to 301, with Band 3 stable at 23 patients (see banding at Appendix 1). The principal reasons for these shifts are: substantial problems with antifungal resistance, especially with itraconazole, concern about a high rate of resistance with itraconazole, so more usage of voriconazole first line in those with aspergillomas and extensive disease, and the short-lived response seen with itraconazole. These shifts include 58 deaths (60 the previous year and 67 the year before that) and 26 discharges from service (29 the previous year). At the end of March 2018, 487 patients from England and Scotland were on service with an additional 16 patients from Wales, two from Northern Ireland and one from the Isle of Man. This represents a 15.3% growth (6.7% growth in prior year). Six patients were presumptively cured with surgery and 11 underwent bronchial artery embolization (20 last year), some because of poorly controlled disease attributable to azole resistance.



Figure 2. Number of admissions, bed days and OPAT days at Wythenshawe by year.

Admission days were lower than the prior year at 764 (906) the prior year), but with a major increase in home IV therapy (OPAT) - 73 IV days to 490. OPAT at other hospitals closer to home is not included in the figures.

3 Clinical service developments and personnel (Director Prof David Denning)

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

3.1. 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 Chris Kosmidis, Consultant in Infectious Diseases (5 PAs) Dr Paschalis Vergidis, Consultant in Infectious Diseases (5 PAs) Dr Rohit Bazaz, Consultant in Infectious Diseases (5 PAs) (from September 2017) Dr Ibrahim Hassan, Consultant in Microbiology (1 PA) Dr Riina Richardson, Consultant in Oral Microbiology & Infectious Diseases (4 PAs) Mrs Christine Harris, NAC manager (100%) Dr Alanah Proctor, 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%) (until December 2017) Mrs Hannah Olejnik-Foulger, Specialist Nurse (50%) (January 2018 – April 2018) Mrs Pauline Wright, Band 2 Nursing assistant (100%) Mr Philip Langridge, Senior Specialist Physiotherapist (50%) Miss Reyenna Sheehan, Specialist Physiotherapist (20%) Dr Isabel Rodriguez Goncer, Clinical Fellow (100%) Dr Firas Maghrabi, Clinical Research Fellow (100%) Dr Akan Otu, Clinical Fellow (100%) (from December 2017) Dr Ed Monk, Clinical Fellow (100%) (from February 2018) Dr Andrew Wright-Taylor, CT2 in Infectious Diseases (50%) Dr Graham Atherton, Senior Clinical Information Architect (Patient engagement) 40% Dr Rachel Orritt (Website for Patients) (40%) Dr Beth Bradshaw (Medical Writer and Web Manager) 100% Mr Azad Aziz, New antifungals Clinical Trials Manager (100%, 20% from January 2018) Mr Marcin Walczak, EPR and Clinical Database Manager (100%) Miss Alison Smith (50%) Ms Marian Webster (50%) Medical Secretary (50%) - vacant Mrs Megan Hildrop Clerical Assistant (25%)

3.2 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.

<u>NCG/ID MDT</u> – 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.

<u>Surgical MDT</u> – 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.

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

 $\label{eq:main-constraint} \frac{\text{Radiology MDT}}{\text{MDT}} - \text{Every Thursday with consultant radiologists to discuss difficult CTs}, embolisation etc.$

3.3. External opinions

There has been a substantial increase in requests for opinions, without referral. This reflects several factors, including travel distance, fragile patients, concern about RTT breaches, a focussed question only (such as duration of therapy). These require registration of the patient at MFT to import images and a detailed clinical response, usually without any additional laboratory data, but a suggestion to request it.

3.4 Antifungal therapy at a distance

Healthcare at Home continue to deliver high cost antifungal medicine and voriconazole 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.

3.5 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.

3.6 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 2017/18 data is presented in Appendix 4. The lack of nursing staff in Q1 2018 resulted in several missed baseline SGRQs being collected.

3.7 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 accepted for publication. We have also adopted this style of n-of-1 trials for isavuconazole. In the year April 2017 to March 2018, 39 patients were trialled on posaconazole (52 in 2016-17) and 14 on isavuconazole (21 in 2016-17). The outcomes are shown in the table below. Posaconazole success was superior to isavuconazole success (p=0.02).

Outcomes	Posaco	onazole	Isavuco	Isavuconazole		
		%		%		
Success	17	43.6	1	7.1		
Failure	17	43.6	9	64.3		
Death	5	12.8	4	28.6		
Total	39	100.0	14	100.0		
Pending	11		7			

Table 2. Trial of posaconazole or isavuconazole outcomes.

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

4.1 Background to the Mycology Reference Centre

The NHS Mycology Reference Centre provides a specialist medical mycology reference service to patients attending the National Aspergillosis Centre (NAC) clinics, patients of Wythenshawe Hospital, Manchester University Foundation Trust (MFT), and other hospitals throughout the UK and specialist clinics in Europe. The total workload is approximately 11,000 specimens per annum, resulting in approximately 25,000 tests per year.

Figure 3. The number of tests done supporting the NAC and associated departments at Wythenshawe Hospital split by different test types. The large increase of fungal culture and mould susceptibility test requests is mainly driven by the NAC. These data exclude pyrosequencing tests.



There has been a striking increase in the number of fungal culture, fungal identification and mould susceptibility tests done for the NAC and other departments at Wythenshawe Hospital, and a slight increase in Aspergillus PCR requests. There has been a fall in Aspergillus precipitins tests as the UK commercial test is insensitive. Over 5 years the volume of internal work has more than doubled. External work has also increased with a 3-fold increase in specimens submitted from 1377 in 2013/14 to 4154 in 2017/18.



Figure 4. The total number of tests done by the MRCM, split by internal and external.

The MRCM acts as a focus for training and research in Medical Mycology in the UK, and is an integral part of the UK Clinical Mycology Network. Furthermore, the MRCM provides undergraduate (University of Manchester Medical School) and post-graduate (PhD programmes in Medical Mycology) level education for the University of Manchester. The service is provided by MRCM within the MFT. The MRCM is an integral component of the Manchester Fungal Infection Network which includes the National Aspergillosis Centre and the Manchester Fungal Infection Group.

The objective of the MRCM is to provide a mycology reference service embracing all aspects of medical and public health mycology for the UK and beyond.

4.2 Role and Functions

The key aims and objectives of the MRCM are to provide and maintain:

- An exemplary NHS reference mycology service for the UK and beyond,
- International, national and local leadership in medical mycology diagnostic services, and training,

- A service, which is comprehensive, interpretative, accredited and appropriate to user needs,
- Education and training for all staff, including participation on national and international courses, that is appropriate and relevant to the departmental goals,
- A safe, appropriate and comfortable working environment which is inspirational and motivating that empowers a team environment,
- To maintain UKAS ISO 15189 Accreditation,
- Maintain a research programme in-house at the MRCM in collaboration with the NAC and support others undertaking mycology research within the Manchester Fungal Infection Network, within industry, and playing an integral part in clinical trials,
- To maintain an excellent and close working relationship with Wythenshawe Hospital Infectious Diseases and the National Aspergillosis Centre. Good working relationships within microbiology, pathology and with other departments within the Trust, and colleagues in other hospitals and Universities.

4.3 Service strategy

- The MRCM aims to provide a complete, comprehensive mycology service and clinical advice centre. This has been achieved by the appointment of a Consultant Clinical Scientist in Medical Mycology (2009), and a Consultant in Medical Mycology (2012), and additional clinical, scientific and technical help, and secretarial support.
- This expansion has allowed all aspects of mycological diagnostics, with an emphasis on molecular tools and serology. The educational remit of the MRCM has also grown by running CPD courses on site, in collaboration with the University of Manchester. Growth of the MRCM has provided much needed support for NHS research, including clinical trials of new antifungal agents.
- A major innovation and income stream has been the establishment of the Mould Surveillance Service: mouldy houses, hospital environments and work-places.

4.4 Research and Development

- Provision of undergraduate and post-graduate research training and supervision in many areas of medical mycology: BSc. research projects, Masters projects, MD and PhD programmes.
- Supporting clinical trials and Infectious Diseases research and development projects
- Development and evaluation of new diagnostic kits and platforms:
 - Pyrosequencing for mutations in *Aspergillus fumigatus* that confer resistance to azole antifungal drugs (audited)
 - o Development of a lateral flow device for Aspergillus fumigatus IgG

4.41 Audit presented at ID Week in San Diego, October 2017.

High-volume Sputum Culture for the Diagnosis of Pulmonary Aspergillosis

Pascalis Vergidis, Caroline Moore, Riina Rautemaa-Richardson, Malcolm Richardson.

Standard culture has a low sensitivity and can be slow whereas quantitative real-time polymerase chain reaction offers the opportunity for faster return of results. Very few comparative studies of diagnostic yield of fungi from respiratory samples have been done to date.

Methods

Specimens were collected from January 2015 through February 2017

Conventional culture: Sputum was homogenized by mixing with an equal volume of 0.1% dithiothreitol solution and diluted 500-fold in sterile water. Ten μ L of the diluted specimen was cultured on SA (2 plates) and incubated at 37°C and 45°C for up to 5 days. For HVC, the entire undiluted specimen (up to 1 mL) was cultured on SA (up to 2 plates) and incubated at 30°C for up to 14 days.

Results

We studied 306 paired specimens that were collected for both conventional culture and HVC on the same day. A total of 139 patients with positive cultures had the following conditions: chronic pulmonary aspergillosis (58%), allergic bronchopulmonary aspergillosis/severe asthma with fungal sensitization (27%), *Aspergillus* bronchitis (9%), cystic fibrosis/bronchiectasis (6%).

Aspergillus was recovered by HVC in 114 specimens that had no mold growth by conventional culture. The same *Aspergillus* species was recovered by both HVC and conventional culture in 50 paired specimens. For 142 specimens there was no *Aspergillus* growth by HVC (*Penicillium* spp. grew in 4). For two of the negative HVC specimens *A. fumigatus* grew by conventional culture. The following species were recovered by HVC: *A. fumigatus* (80%), *A. niger* (10%), *A. flavus* (3%), other (7%). Susceptibility testing (EUCAST standard) was performed for 127 isolates of *A. fumigatus*. Rates of antifungal resistance were as follows: itraconazole 28%, voriconazole 19%, posaconazole 28%, isavuconazole 32%, amphotericin B 8%. Panazole resistance was detected in 17%. If HVCs were not performed, resistance to at least one of the antifungals would have been missed in 18/37 (49%) of cases.

Conclusion

The recovery rate of *Aspergillus* spp. is significantly higher for HVCs compared with conventional cultures and this can impact patient care. HVCs can be performed in any microbiology laboratory without the need for additional tools.

4.42 Audit presented at the International Society for Human and Animal Mycology, Amsterdam, June 2018 (and a prior version at the Advances Against Aspergillosis meeting in Lisbon, February 2018

Pyrosequencing of *Aspergillus fumigatus* cyp51A reveals triazole resistance when susceptibility testing cannot

LilyAnn Novak Frazer, Darin Hassan, <u>Samuel Hill</u>, Rikesh Masania, David W Denning, Caroline B Moore, Riina Rautemaa-Richardson, Malcolm D Richardson

Objectives: Chronic pulmonary aspergillosis (CPA) and allergic bronchopulmonary aspergillosis (ABPA) are progressive, chronic pulmonary diseases causing significant morbidity and mortality in the UK. Many CPA and ABPA patients harbour *Aspergillus fumigatus* as a result of inhaling the abundant airborne conidia produced by this opportunistic fungus. Our high volume culture (HVC) procedure improves culture positivity, allowing identification and EUCAST susceptibility testing; moreover, *Aspergillus*-specific qPCR allows detection when culture fails, 25-49% of the time. Consequently, long-term antifungal treatment is complicated by lack of susceptibility data and the rising frequency of triazole resistance in *A. fumigatus* isolated in patients at the National Aspergillosis Centre (NAC) in Manchester. As a result of the limited coverage of polymorphisms in the target site, cyp51A, by commercial qPCR kits and the insensitivity conferred by Sanger sequencing, we developed a pyrosequencing assay to elucidate whether we could detect polymorphisms earlier in the treatment of CPA and ABPA patients. Methods: Patients were

perceived as potentially failing therapy and as candidates for pyrosequencing analysis if they maintained therapeutic antifungal drug levels but produced respiratory samples positive for Aspergillus spp. by qPCR but negative by HVC. Their sputum or bronchopulmonary lavage (BAL) extracts underwent PCR amplification of cyp51A to yield biotinylated products for pyrosequencing using the Qiagen Advanced PyroMark system. Positions G54, L98, Y121, M220 and T289 within cyp51A were assayed as well as possible insertions in the promoter region and results were confirmed by Sanger sequencing. Results: Ninety-one patient samples were analysed from March-November 2017: 40 (44.0%) had no polymorphisms, 23 (25.3%) had cyp51A polymorphisms, 15 (16.5%) were processed by Sanger sequencing only and 13 (14.3%) failed to be amplified. We detected only four samples with TR34 and/or L98H, potentially conferring panazole resistance; 5 with G54 (E, R or V), potentially conferring itraconazole and posaconazole resistance, and 14 with Y121F/T289A polymorphisms, potentially conferring voriconazole resistance, although the accompanying TR46 insertion was not found. Pyrosequencing results agreed with susceptibilities derived by HVC only half the time, possibly due to amplification insensitivity or PCR inhibition and definitively when species other than A. fumigatus were cultured or resistance was due to non-cyp51A polymorphisms, confirmed by Sanger sequencing. Conclusion: Pyrosequencing, although technically challenging for some patient samples, identified A. fumigatus cyp51A polymorphisms when culture failed and susceptibility testing was not possible and Aspergillus qPCR indicated escalation. Moreover, clearly discernible mixed wild type and polymorphic A. fumigatus cyp51A templates were used as an early indicator of infection with resistant isolates. The impact of resistance profiling by pyrosequencing on therapeutic management incorporating analysis of patient benefit, effect on antifungal drug stewardship and antifungal drug cost-effectiveness is being investigated.

4.5 Key achievements - summary

1. Sustained development of a rapid-access clinical advice and support service

2. Chosen as a UK development and evaluation centre as part of a European-wide fungal PCR initiative

3. Introduction of new assays:

- Nationwide provision of β-1-3-*D*-glucan pan-fungal ELISA (Fungitell, Associates of Cape Cod)
- Centralisation of Aspergillus galactomannan testing within Greater Manchester
- Expansion of DNA-sequence identification of unknown mould and yeasts nationwide
- Pyrosequencing for mutations in *Aspergillus fumigatus* that confer resistance in clinical samples directly in clinical samples

Key achievements - The Detail

The MRCM has completed its eighth year of operations and has expanded in step with the evolution and continued growth of the National Aspergillosis Centre. 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 PhD programmes in Medical Mycology. In 2018 the laboratory became a member of the Manchester University NHS Foundation Trust Division of Laboratory Medicine.

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 second time hosting University of Manchester work placement students highly successful placement year for both students.
- 4. Marked increase (87%) in requests for Aspergillus PCR tests on NAC patients. The overall increase in workload since 2009 is approximately 400%.
- 5. Active participation in weekly Infectious Diseases MDTs presentation of new clinical diagnostic findings and discussion of complex patients
- 6. Membership of the Wythenshawe Hospital's Antimicrobial Committee and Lead role for Antifungal Stewardship.
- 7. Clinical and laboratory audits ---
 - Comparison of Aspergillus galactomannan index with PCR signal in sputum from patients with CPA (see above)
 - Posaconazole formulations influence antifungal drug levels in CPA patients
 - Fungal glucan guided antifungal stewardship
 - High-volume sputum culture for the diagnosis of pulmonary aspergillosis (see above)
- 8. Participation in weekly programme of educational meetings, alternating between invited speaker, research, clinical and audit meetings.
- 9. Income: internal and external: increase of 20% compared to 2016-2017.
- 10. Income: environmental monitoring business unit: income in excess of £20,000
- 11. Fifth year of a Mould Surveillance Service for assessing the homes of NAC and Respiratory Medicine patients, Wythenshawe Hospital
- 12. Other services for non-CPA patients:
 - Sustained demand for the β-1,3-D-glucan ELISA test (Fungitell): a pan fungal assay for fungal cell wall glucan, including *Aspergillus* and *Candida*, offered nationwide (infographic: <u>https://vimeo.com/261490574</u>).
 - Environmental monitoring (air sampling and dust analysis) of the homes of patients with sarcoidosis and extrinsic allergic alveolitis (hypersensitivity pneumonitis) and interstitial lung disease.

B) Representation on national and international committees:

- UK Clinical Mycology Network
- RCPath Microbiology SAC (Dr Riina Richardson)
- WHO Committee for 'Damp Indoor Spaces and Mould' (Prof Malcolm Richardson)
- European Food Safety Authority: Biohazard and FEEDAP Scientific Committees (Prof Malcolm Richardson)
- External Examiner, Royal College of Pathologists (Prof Malcolm Richardson)
- ISHAM: Professor Malcolm Richardson as immediate Past-President
- UK Institute of Buildings and Health: Malcolm Richardson as President
- PHE/NHS: Standards Unit. Microbiology Services (Dr Riina Richardson)
- EUCAST: European Union Committee for Antimicrobial Susceptibility Tests (Dr Caroline Moore)

- UK NEQAS: Testing laboratory for microbiology/mycology identification and susceptibility schemes (Dr Caroline Moore)
- EUCAST: UK participating laboratory: Antifungal Fungal Susuceptibility Testing (Dr Caroline Moore)
- British Society for Antimicrobial Chemotherapy grants committee (Dr Riina Richardson)
- European Fungal PCR Initiative (FPCRI): UK test centre for *Aspergillus*, *Candida*, *Pneumocystis*, Mucorales and tissue (MRCM represented by Dr Riina Richardson)
- ESPAUR: Public Health England surveillance programme for antimicrobial utilisation and resistance (Dr Caroline Moore, Prof Malcolm Richardson, Dr Riina Richardson)
- BSMM: British Society for Medical Mycology Executive Committee (Dr Caroline Moore)
- ESCMID: European Society for Clinical Microbiology and Infectious Diseases (Prof Richardson as co-author of *Aspergillus, Candida* Mucorales guidelines); and Rare Fungi, and Candidosis diagnostic and treatment guidelines (Dr Riina Richardson)
- BASHH: British Society for Sexual Health: Candida vaginitis guidelines writing group (Dr Riina Richardson)
- Royal College of Paediatrics and Child Health (RCPCH): Working Group: Effects of Indoor Air Quality on Children and Young People's Health (Prof Malcolm Richarson as Member)

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 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 and workplaces for *Aspergillus*
- Provision of mycology services to national and international pharmaceutical companies who are developing new antifungal drugs.

D) Publishing activities 2017/2018: contributions to National Aspergillosis Centre and the Manchester Fungal Infection Group publication output (see Appendix 6)

E) Training:

- UCL/BSMM distance learning Masters in Medical Mycology: one staff member enrolled, to graduate in September 2018.
- 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 (<u>www.LIFE-Worldwide.org</u> - 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

F) Presentations, global outreach and social media:

- Society for Indian Human and Animal Mycologists meeting (SIHAM)
- 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)
- Royal College of Pathologists National Pathology Week Event in Manchester
- Advances Against Aspergillosis, 2018 (Lisbon)
- 28th ECCMID, 2018, 13 presentations/posters (Madrid)
- Twitter: @MycologyRefManc

G) Challenges:

- Increased workload in relation to part-time staff
- Provision of financial resources to equip the laboratory with new molecular platforms (MALDI-TOF)
- Provision of financial resources to employ dedicated staff within dedicated quality roles
- Space
- Succession planning

5 Clinical audits

5.1 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 the first time and overall 57 patients died on service, down on 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.

5.2 Mortality audits

In 2017 the NAC instituted a monthly mortality review to carefully review the cause of death of patients not expected to die when they did. One of the consultants carefully reviews the notes to ascertain all the key facts and events leading up to the patient's death and this, together with a brief literature summary of the particular problem, is presented to the whole team for discussion and learning. All these mortality events are minuted.

5.3 Clinical audits

The following audits were undertaken in 2017/18:

Self-assessment and symptom domains of St George's Quality of Life questionnaire predicts clinical failure in chronic pulmonary aspergillosis F Bongomin, C Harris, P Foden, AJ Simpson, C Kosmidis, DW Denning

Purpose: St George's Respiratory Quality of Life (QoL) Questionnaire is routinely used for monitoring progress of patients on long-term antifungals for the management of chronic pulmonary aspergillosis (CPA). The objective of this study was to assess the relationship between QoL scores and clinical failure in patients with CPA. **Methods:** We retrospectively analysed consecutive CPA patients diagnosed with clinical failure following discontinuation of antifungal treatment between June 2014 and May 2017. Forty-four CPA patients who were off therapy for 12 months and did not develop clinical failure were used as controls. Wilcoxon matched-pairs signed rank test was used to compare QoL scores obtained at the time of discontinuation of St George's QoL questionnaire. McNemar-Bowker test was used to compare the change in patients' self-assessment scores. QoL changes in controls were from baseline to 12 months.

Results: Thirty-three CPA patients were eligible (22 men, average age of 61). The median in the symptom domain of QoL changed from 78.4 at the time of discontinuation of therapy to 83.1 units at the time of diagnosis of clinical failure (p=0.043), whereas that of impact and activity domains changed from 62.7 to 59.1 units (p=0.387) and 85.0 to 85.9 units (p=0.153) respectively. The median difference in the total score changed from 71.3 to 72.9 units (p=0.133) (Fig.1). Controls (n=44) were stable at 3 months and saw an improvement in symptoms domain by 12 months (medians, 74.3, 77.3, and 68.0 units respectively). The change in the controls compared to clinical failure was statistically significant (p=0.009). The AUC for change in symptoms between controls and clinical failure was 0.675 (95%CI: 0.555 -(0.795). With an improvement of < 8 units used to define clinical failure we have sensitivity of 90.9%, specificity of 45.5%, PPV of 56% and NPV of 87% (Fig.2). There was a significant difference in the patients' self-assessment of their conditions (p=0.046). The proportion of patients who classified themselves as very poor increased from 9.1% at the time of discontinuation of therapy to 33.3% at the time of diagnosis of clinical failure.

Conclusion: Our data suggest that a deteriorating symptoms domain of the St George's QoL questionnaire and a worsening of patients' self-assessment are associated with clinical failure.

The role of Aspergillus immunoglobulin G level monitoring in chronic pulmonary aspergillosis patients with surgery as treatment option FS Sudradjat, RR Richardson, DW Denning.

Purpose: Surgery is one of the treatment options for chronic pulmonary aspergillosis (CPA) especially single aspergilloma, those with recurrent haemoptysis despite bronchial artery embolisation and unilateral azole-resistant disease. This study aims to evaluate the outcomes of surgery and the correlation between Aspergillus Immunoglobulin G (IgG) titre and clinical condition of the patients.

Methods: Retrospective study of patients who underwent surgery for CPA between 2007 and 2017, with Aspergillus IgG antibodies (Thermo Fisher/Phadia) correlated with surgical success and recurrence.

Results: 29 patients with CPA underwent surgery with most of them showed histopathology evidence of Aspergillus in lung tissue (n=25, 86%). The mean age was 52 years (20-77). The most common presenting symptoms were haemoptysis (n=16, 55%), cough (n=12, 41%) and shortness of breath (n=8, 28%) before surgery. Recurrent haemoptysis (n=16, 55%) was the most common indication for surgery. Assessed 2-5 months after surgery, 13 patients were asymptomatic (45%) and 7 experienced cough (24%). Twenty-two patients (76%) had single aspergilloma, 3 patients (10%) showed chronic cavitary pulmonary aspergillosis (CCPA) while 4 patients (14%) with Aspergillus nodules. Most of the patients had underlying lung disease; tuberculosis (n=5, 17%), bronchiectasis (n=5, 17%), chronic obstructive pulmonary disease (n=5, 17%), asthma (n=4, 14%) and sarcoidosis (n=2, 7%). The procedures included lobectomy (n=23, 79%), wedge resection (n=4, 14%), decortication (n=1, 3%), video-assisted thoracoscopic surgery (n=2, 7%) and myoplasty (n=1, 3%). Main complications were pneumothorax (n=6, 21%) and subcutaneous emphysema (n=3, 10%). The mean Aspergillus IgG level before surgery was 217.3 mg/L and 2-5 months after surgery 163.1mg/L. Recurrence of CPA was noted in 14 patients (48%). In this recurrent group, the mean Aspergillus IgG level when patients relapsed was 340.2 mg/L and decreased to 144.6 mg/L along with the clinical improvement of patients measured 6 months after antifungal therapy.

Conclusion: Surgery in these selected CPA patients resulted in favourable outcomes with the decrease in clinical symptoms and the Aspergillus IgG level of patients after 2-5 months post-surgery. These findings suggest that in general, Aspergillus IgG test is a potential tool for evaluating therapy and predict recurrences of CPA. Further work is required to establish this.

Posaconazole tablet therapeutic drug monitoring in patients with chronic pulmonary aspergillosis

Isabel Rodriguez-Goncer; Chris Kosmidis; Riina Richardson; Caroline B Moore; Malcolm D Richardson; David W Denning

Posaconazole tablet therapeutic drug monitoring in patients with chronic pulmonary aspergillosis I. Rodriguez-Goncer, C. Kosmidis, R. Richardson, C.B Moore, M.D Richardson, D.W Denning

Objectives: Posaconazole tablet offers better bioavailability than liquid suspension and a favourable side effect profile. Most posaconazole pharmacological data are derived from immunocompromised populations, with little experience in immunocompetent hosts such as those with chronic pulmonary aspergillosis (CPA). Due to variable absorption, therapeutic drug monitoring (TDM) is recommended for the posaconazole suspension. However, it is not clear what the role of TDM is when using posaconazole tablets. Our aim was to explore pharmacokinetics and side effect profile of posaconazole tablets in a cohort of patients with CPA. Methods: Medical records for patients with CPA who started on posaconazole tablet between February 2014 and October 2015 were analyzed retrospectively. Recorded data included patient demographics, posaconazole blood levels, prescribed dose, adverse events (AE) attributed to posaconazole and AE grade according to the common terminology criteria for AE. The correlation of posaconazole levels with demographics, prescribed dose and frequency and severity of AE was analyzed. TDM was performed by bioassay; a random level of >1 mg/L was considered therapeutic. Results: Seventy-two patients received posaconazole tablets. All patients had previously received other azoles but none were on concomitant antifungal therapy. Fifty (69%) were male and mean age was 48.5±12. Sixty-one were started on 300mg daily and 11 were started on 200mg daily. Dose adjustments were made in 31 (43%) patients; 29 (93%) needed a dose reduction. Forty-nine (68%) patients developed attributable side effects: 9 (18%) grade 1, 22 (44%) grade 2, 17 (34%) grade 3 and 1 (<0.1%) grade 4. Seven (9%) patients had liver function test (LFT) abnormalities; 5 (71%) grade 1 and 2 (29%) grade 2. Most frequent attributable side effects were fatigue (37%), breathlessness (18%), nausea (12%), headache (8%), peripheral neuropathy (8%), diarrhoea (6%), chest pain (6%), dizziness (5%), arthralgia (5%), dry skin (4%), hyponatremia (4%) and hair loss (2%). Side effects were present in 115/196 (58.7%) occasions in patients on 300mg and 45/115 (39.1%) in patients on 200mg a day, (p, <0.01). 58 (80%) patients had TDM performed, whereas in 14 (19%) patients posaconazole was stopped due to side effects before a TDM could be sent. A total of 383 measurements (mean of 5.3 per patient, range 0-15) were recorded. The mean posaconazole level was 1.94, (range 0.1-6.4). For patients on 300mg, mean level was 2.13±1.13, for patients on 200mg, mean was 1.95±0.84 and for patients on 100mg, mean level was 1.08±0.32. The proportion of samples with a sub-therapeutic level were 19/189 (10%), 11/114 (10%) and 15/43 (34.9%) for patients on 300mg, 200mg and 100mg, respectively. Mean level was 1.81±0.96 for patients reporting no side effects, and 1.90±1.11 for those reporting side effects (p=NS). The mean levels in patients with LFT elevation were 2.48±3.9. Conclusion: A daily dose of 200mg achieved therapeutic serum posaconazole levels and was better tolerated than the 300mg daily dose in patients with CPA. Sixty-eight percent of patients developed side effects but they were not significantly associated with out of range posaconazole levels.

Risk factors for relapse of chronic pulmonary aspergillosis after discontinuation of antifungal therapy

Felix Bongomin, Chris Harris, Philip Foden, Chris Kosmidis, David W. Denning.

Relapse is problematic in chronic pulmonary aspergillosis (CPA) following discontinuation of triazole maintenance therapy; however, very few studies have investigated this. The aim of this study was to identify the frequency and risk factors for disease relapse following cessation of antifungal therapy in CPA.

This retrospective audit at the National Aspergillosis Centre (NAC), Manchester, UK assessed outcomes for patients with CPA who had received antifungal treatment and for whom therapy was discontinued for at least one month between August 2009 and May 2017. We defined relapse as a deterioration in two of the following parameters: clinical, radiological, serological or sputum microbiological markers of CPA activity. Therapy was discontinued in 102 patients during the audit period. Age distribution of 63.7 ± 11.5 years. Therapy was recommenced in 43 (42%) patients of whom 21 met our definition of relapse - 31% of those with bilateral and 11% of those with unilateral disease. Patients with bilateral disease and patients with one or more aspergillomas were more likely to relapse on univariate analysis. Age, sex, underlying pulmonary disorder, duration of previous triazole antifungal therapy, reasons for discontinuation of therapy and presence of a single or multiple aspergilloma were not associated with relapse. In a multivariable logistic regression analysis bilateral CPA disease was the only independent risk factor for relapse (Odds ratio (OR): 3.0; 95% confidence interval (CI): 1.0-8.8; p=0.044).

In conclusion, bilateral CPA is a risk factor for relapse after treatment discontinuation. A longer duration of treatment, e.g. 24 months, may be associated with a lower rate of relapse in extensive CPA, whereas more limited disease may respond to shorter courses.

Micafungin may be safely administered as outpatient parenteral antimicrobial therapy for chronic pulmonary aspergillosis

Akaninyene A. Otu, Felix Bongomin, Rohit Bazaz, Chris Harris, David W. Denning, Chris Kosmidis.

Background

Intravenous micafungin is a treatment option for patients with chronic pulmonary aspergillosis (CPA) where oral triazole therapy is unfeasible.

Objectives

We evaluated the safety and efficacy of micafungin administered via the outpatient parenteral antimicrobial therapy (OPAT) service for the treatment of CPA Methods

We included all CPA patients who received micafungin via OPAT. Data on adverse events and line-related complications, and Quality of Life (QoL) scores at the start of micafungin course and 3 months later were extracted. Results

There were 21 OPAT episodes involving 19 patients with a median duration of micafungin therapy of 21 days. Improvement or stability in the symptoms, activity, impact and total score was seen in 14(78%), 12(67%), 9(50%) and 9(50%) of the patients respectively. However, half of the patients reported deterioration in the impact domain and total scores. By self-assessment, patients who categorized themselves as "poor" were comparable at the start of OPAT and at 3 months (43% vs. 50%, McNemar's p=0.7). Adverse events attributable to micafungin were recorded in 3(14.3%) episodes.

Conclusions

Micafungin may be safely administered via an OPAT service. Micafungin therapy was associated with an improvement/stability in QoL scores in at least 50% of the patients across the 4 domains.

6 Patient and public engagement

6.1. The first World Aspergillosis Awareness Day and website

In February 2018, the monthly patients and family/carers meeting was held in Lisbon, Portugal, as part of the <u>8th Advances Against Aspergillosis Meeting</u>. The first World Aspergillosis Awareness Day (<u>www.aspergillosisday.org</u>) was launched at this meeting.

The aims of this day reflect the very wide need for increased awareness throughout the world and complements the US-CDC- summertime initiative 'Fungal Disease Awareness Week' <u>www.cdc.gov/fungal/awareness-week.html</u>.

- Clinicians need better awareness to be able to 'think fungus' when repeated attempts to treat infections fail. Serious fungal infections are underdiagnosed worldwide
- People with one of the <u>multiple forms of aspergillosis</u> need <u>much</u> <u>better support and information</u> as aspergillosis is a rare infection that isolates people.
- People who live with and care for people with aspergillosis often need to better understand what the patient is going through and themselves need <u>understanding & support</u>
- Last but certainly not least those who fund our health services need to be <u>more</u> <u>aware and to better provide</u> diagnostics and treatments worldwide.

Figure 5 Poster presented at the AAA meeting in Lisbon explaining the key interactions between the NAC and patient and their carers.

MANCHESTER

Patient Communications and Support – A Two Way Street

The University of Mancheste

R Orritt^{*1,2}, B Bradshaw², GT Atherton^{1,2}, C Harris^{1,2},

DW Denning^{1,2}

¹Division of Infection, Immunity and Respiratory Medicine, University of Manchester, UK; ²Science and Medical Communications Team, National Aspergillosis Centre, UK

Overview

At the National Aspergillosis Centre (NAC) in Manchester, UK, additional patient support is facilitated by the Science and Medical Communications Team:

Patient support meetings NAC patients are invited to our monthly support meetings at the centre.

meetings are live streamed and recorded for viewing online

Facebook groups

These groups total over 1500 members (16.01.18) from 63 countries. Members can choose to join a group local to them, the main discussion group, or a private discussion group. There is also a group for friends, family and carers.

Patient website

The patients' website (nacpatients.org.uk) is an online resource on aspergillosis, including information on diagnosis, treatment and wellbeing.

Skype meetings

Up to 24 patients can join the weekly national or international Skype group, nd discussion is inform nal and led by the patients themselves

cribe a model of patient-clinician-researcher communication that could be adopted by other centres, with the aim of addressing patients' non-clinical needs. Quotes used were collected in Jan 2018, from members of our Facebook groups.



'How have the online communities and resources run by the National Aspergillosis Centre affected you? (this could include the Facebook group, the skype groups, our blog items, or our monthly patient meetings at the centre etc.)'

Larger fonts represent words that were more commonly used in responses.

Communication to Patients

Evidence-based

To help patients navigate their disease, and particularly treatment, we have a responsibility to base our advice on scientific evidence. This also helps to dire combat some of the pseudo-treatments that occasionally surfaces in discussion discussion of the pseudo-treatments that occasionally surfaces in discussion discussion discussion and the second discussion of ectly

Accessible

On each of our communication channels, care is taken to ensure information and discussions are open to everyone. This involves

- · Using language and tone appropriate for the audience
- Using different media to present the same information (writing, video, images)
- · Optimising content for screen readers

Consistent and Responsive

To maintain levels of trust and perceived support, the science and communications team are consistent with content uploads over time. From newsletters to blog posts, reliable and timely content can become a source of stability as well as support in a stability as well as support in a patient's journ

It's also imperative that members of the team are responsive to patients' queries directing them towards reliable information or addressing their concerns as needed

"The resources provided on the Aspergillus and Aspergillosis Website "As a deaf patient I find the fact that so and the NAC website meant that we received accurate information that was much information is available on line nowhere near as terrifying as that via the web site is revealed by Dr Google' wonderful"

Faculty of Biology, Medicine and Health

'The Facebook group was immenselv life changing for me. Up until I joined I felt extremely

"I feel I am in a community where no question is classed as silly or unwarranted and I'm learning about it the more I go

Communication from Patients

We have found that maintaining multiple, informal channels for communication removes barriers that might otherwise prevent patients from offering feedback and constructive criticism

ome examples of helpful input from patients been particularly helpful are listed

Improving clinical practice

Patients from the centre have provided feedback on various aspects of clinical practice, by coming to the monthly patient meetings held at the NAC. Some of the feedback received in recent months has included: improvements to packaging for sputum samples, nurse etiquette and blog article topics.

Refining online content

In various for a, patients suggest topics for blog articles and webpages, helping the Science and Medical Communications Team with the necessary knowledge to provide non-clinical support.

However, it is important to consider the limitations of our current communication Channels, so that we can be avaie of groups that we not renor tommandature channels, so that we can be avaie of groups that we not reaching and take appropriate action. Often the most involved patients are the least isolated and most well informed. We have also noticed that there is a particular demographic that is over represented (white, middle class females) in terms of involvement.

Communication between Patients

The value of peer-peer support in illness can not be overstated. Patients learn from other patients and carers, particularly those who have been affected by aspergillosis for a long time. But the biggest benefit seems to be the communities and friendships that develop between patients, who understand each others conditions. This helps to combat feelings of loneliness, isolation and depression, and can have a real affect on outcomes

The Science and Medical Communications Team helps to facilitate this mutual support, keeping discussions friendly, inclusive and on topic, by: • Moderating Facebook groups including managing membership

- · Charing meetings in person and online
- Quickly responding to notifications of spam content

'The support is remendous and this horrible disease can bring you down so quickly. Talking to people that understand helps me get through.

'I feel more sane since I've met the people in the Skype group, before that I felt all on my own, I didn't understand what was happening to me. I felt that no one believed what I was going through.

Summary

The Science and Medical Communications Team at the National Aspergillosis Centre ct of patiei nols tc The science and medical communications ream at the validhar Aspergimosis co-in Manchester provide valuable non-clinical support to patients, an aspect of pati-care that is often neglected. Through opening informal communication channels i and between patients, a supportive community has formed that benefits patients, carers, researchers and clinicians in different ways.

In the future we hope to continue to grow our capacity to support patients and the wider aspergillosis community by redesigning our patient website based on user feedback and evolving as other social media platforms become more widely used by our target audience

www.bmh.manchester.ac.uk

World Aspergillosis Day 2018 was themed around highlighting the support that people who provide day-to-day care for aspergillosis patients need. The theme was entitled 'Caring for Carers' and we featured a short video together with several stories written by carers on a purpose-made website at

https://www.aspergillosisday.org/world-aspergillosis-day-feb-1st/care-for-a-carer/.

The meeting was attended by local patients who were able to keep in touch through the ALGSPortugal Facebook group

(https://www.facebook.com/groups/ALSGPortugal/). Each member of our team presented a short talk, followed by two longer research talks. A video of this meeting can be viewed on the NAC Patients website (https://www.nacpatients.org.uk/content/patients-meeting-8th-aaa-lisbon-february-2018).

- Chris Harris The history of the National Aspergillosis Centre
- Graham Atherton resources for patients
- Beth Bradshaw online support: a double-edged sword
- Rachel Orritt World Aspergillosis Day 2018

These resources were widely disseminated via our Aspergillus Website newsletter & blogs, Twitter, patients groups reaching over 30,000 subscribers and via PR company Goodwork.

We have provided a support group in Facebook

(<u>www.facebook.com/groups/aspergillosis.carers/</u>) and our primary measured outcome was to encourage carers to join the group. After all of our publicity the group currently has 117 members (August 2018).

6.2 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, facemasks, coping with stress, pharmaceutical advice details and seasonal advice e.g. allergies. It also provides contact numbers or website addresses for groups that offer social support.

6.3 The Aspergillus Website @ <u>www.aspergillus.org.uk</u> and

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 12,500 scientific articles (including a unique collection of 828 historical articles) and well over 15,560 conference abstracts from 1974 onwards. A separate linked website for patients and carers (nacpatients.org.uk) provides answers to multiple questions in lay language.

The Aspergillus Website is listed at number 1, 1, 2 and 3 in Google.co.uk, number 1, 1, 2 and 3 in Google.com, number 2(2), 2(2), 4(5), 4(4) in Bing and (Yahoo!) for 'aspergillus', 'ABPA' 'aspergillosis' and 'aspergilloma' respectively. If 'aspergillus' is searched in Google, there are over 6.5 million results. The Aspergillus Website

(AW) had >100,000 unique visitors in a typical month and the Website for Patients (WfP) 17,000 visits. 65% of visitors to the WfP are using smaller devices, corresponding to 45% of visitors to AW. USA is 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 9,000,000 per month. [NOTE changes are currently taking place with our web hosts such that we will be collecting usage statistics in a very different way from now onwards. This is a more secure way of running each website. Our current figures are based on the 'pure' figures for total numbers of visitors. Future figures will be much more sophisticated and will contain a lot more information but will be based on heavily cached numbers, markedly reducing apparent total numbers. This is an artefact of the way the figures will be collected and not a reflection of falling numbers of users or falling activity.]

Monthly newsletters from the Aspergillus Website were sent out to over 27,000 (free) subscribers. This figure is driven by newly registered members seeking to access our secure 'articles' that opt in to receive our newsletter.

There are now 6,192 people active & registered on The Aspergillus Website (3% doctors, 12% other clinicians, 12% researchers, 9% vets, 10% patients and 10% other members of the public).



Figure 6. Usage of the Aspergillus Website for June 2017



Figure 7. Usage by country is depicted here (1st May – June 30 2018):

6.4 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 <u>www.nacpatients.org.uk/monthly_meeting</u> and include

- Dr Paul Bowyer feeding back on winning funding for the genomic investigation of aspergillosis by setting up a reference library of clones of Aspergillus fumigatus. Patients played a major role in supporting this grant application.
- Getting patients opinions on how we need to change sputum sample postal packaging
- Live broadcast from the patients meeting held at the 8th Advances Against Aspergillosis conference in Lisbon, Portugal.
- Gardening, exercise & myth-busting
- New clinical drug trial to treat ABPA & SAFS

6.5 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 >3,000 participants
- The NHS Choices online community for Aspergillosis has 1,488 participants
- <u>www.nacpatients.org.uk</u> website (averaging 11,000 visitors per month)
- Local online Facebook groups (18 groups, 9 in the UK serving 313 people)
- Facebook group specifically for carers (116 members)
- The Professional LinkedIn members group (Aspergillus and Aspergillosis Group) has over 520 members.
- Monthly meeting viewed live & by recordings (250-450 viewings per month in 2018)

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.
- Weekly meeting via Zoom conferencing software attended by 4 10 people.
- 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)

6.6 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/carer volunteers who report steady interest.

7 Research and key publication findings

7.1 Papers and book chapters

Amongst the 81 papers and book chapters published in calendar year 2017 (see Appendix 5) (45 were published in 2016), there were several areas of direct relevance to patients with CPA and pulmonary aspergillosis. These were:

- 1. Pegorie M, Denning DW, Welfare W. Estimating the burden of invasive and serious fungal disease in the UK. J Infect 2017; 74: 60-71.
- 2. Denning DW, Perlin DS, Muldoon EG, Colombo AL, Chakrabarti A, Richardson MD, Sorrell TC. Delivering on the antimicrobial resistance agenda not possible without improving fungal diagnostic capabilities. Emerg Infect Dis 2017; 23:177-183.
- 3. 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.
- 4. Lowes D, Al-Shair K, Newton PJ, Morris J, Harris C, Rautemaa-Richardson R, Denning DW. Baseline parameters of survival in chronic pulmonary aspergillosis. Eur Resp J 2017; 49: 1601062.
- 5. 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.
- 6. Denning DW. Sarcoidosis and aspergillosis: a tough combination. Eur Resp J 2017 49:17E4906.
- 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.
- 8. Denning DW, Chakrabarti A. Pulmonary and sinus fungal diseases in nonimmunocompromised patients. Lancet Infect Dis 2017; 17:e357-66.
- 9. Oladele RO, Irurhe NK, Foden P, Akanmu AS, Gbaja-Biamila T, Nwosu A, Ekundayo HA, Ogunsola FT, Richardson MD, Denning DW. Chronic pulmonary aspergillosis as a cause of smear-negative TB and/or TB treatment failure in Nigerians. Int J Tuberc Lung Dis 2017; 21:1056-1061.
- Maghrabi F, Denning DW. The management of chronic pulmonary aspergillosis: The UK National Aspergillosis Centre approach. Curr Fungal Infect Rep 2017; 11:242-251.
- 11. Jiménez-Ortigosa C, Moore C, Denning DW, Perlin DS. Emergence of echinocandin resistance due to a point mutation in the fks1 gene of *Aspergillus fumigatus* in a patient with chronic pulmonary aspergillosis. Antimicrob Agents Chemother 2017; 61:e01277-17.
- 12. Perlin DS, Rautemaa-Richardson R, Alastruey-Izquierdo A. The global problem of antifungal resistance: prevalence, mechanisms, and management. Lancet Infect Dis 2017; 17:e383-e392.
- 13. Richardson M, Page I. A*spergillus* serology have we arrived yet? Med Mycol. 2017; 55:48-55.

7.2 Key book chapters related to CPA:

- 1. Overton N, Gago S, Bowyer P. Immunogenetics of chronic and allergic aspergillosis. In Carvalho A, editor, Immunogenetics of Fungal Diseaes. Springer. 2017. p. 153-171.
- 2. <u>http://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-</u> <u>chronic-pulmonary-aspergillosis (2011-)</u>
- 3. <u>http://www.uptodate.com/contents/treatment-of-chronic-pulmonary-aspergillosis</u> (2011-)

4. Denning DW. Aspergillosis. Eds Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Muldoon EG, Denning DW, Kosmidis C. Cystic fibrosis and chronic respiratory diseases. Eds Kibbler CC, Barton R, Gow G, Howell S, MacCallum D, Manuel R. 2017 Oxford textbook of Medical Mycology. Oxford University Press, 2017.

7.3 New antifungals

There are 7 new antifungal agents for systemic use and 2 for inhaled use in clinical development (Rezafungin (once weekly echinocandin), SCY078 (oral glucan synthase inhibitor (similar to an echinocandin)), olorofim (an orotomide, oral and IV, novel structure and mode of action), APX001 (novel structure and mode of action, oral and IV), VT-1161 (oral broad spectrum antifungal), MAT2203 (an oral formulation of amphotericin B), VL-2397 (novel structure and mode of action, IV and focussed on invasive aspergillosis). PUR1900 (inhaled itraconazole) and PC945 (inhaled broad spectrum antifungal). 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). A briefing meeting was hosted with the FDA and PMDA at the Advances Against Aspergillosis meeting in Lisbon in 2018 to address clinical study design and endpoints.

7.4 Global health and CPA

In 2017, the burden of fungal diseases, including CPA, has been estimated and published for the following countries in: Algeria, Bangladesh, Canada, Chile, Ecuador, Egypt, Guatemala, Pakistan, Peru, South Korea, the Philippines, Portugal, Thailand, United Kingdom and Uzbekistan. In early 2017, fungal burden estimates were published in the Journal of Fungi for Colombia, Uruguay, Argentina, Burkina Faso, Cameroon, Mozambique, Malawi, Jordan, Romania, Serbia, Norway, Kazakhstan and Malaysia. This takes the mapping and estimation by country of serious fungal diseases to > 75 countries, of which 58 are published.

8. Public awareness and educational outreach

8.1 Awareness among the public

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 a public relations company 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.

Appendix 7 shows all Aspergillus blogs and press releases issued by the NAC. Seven press releases and 67 blogs were published in 2017-18, with regular tweets.

8.2 National pathology week

The MRCM played an important role in National Pathology Week (6 to 12 November, 2017) and hosted a display at the hospital for high school students and their parents.

Figure 8. School students learning about mycology at Wythenshawe Hospital during National Pathology Week.



8.3 Educational resources and outreach

The NAC has lead several important educational initiatives for health professionals including the Aspergillus Website (section 6.3) (www.aspergillus.org.uk) in its 20th year in 2018; Leading International Fungal Education (LIFE) (www.LIFE-Worldwide.org) (launched in 2012 and in English and Spanish); the global advocacy foundation the Global Action Fund for Fungal Infections (GAFFI) (www.GAFFI.org), founded in 2013; a database and apps for antifungal drug interactions (www.aspergillus.org.uk/content/antifungal-drug-interactions) from 2013. In addition, 56 news items were published on LIFE for healthcare professionals. Figure 9 Poster presented at AAA in February 2018 with all the online resources that the NAC offers.



Microfungi, the world's first online microscopy and histology course for fungal disease (<u>www.microfungi.net</u>) launched in 2016, and now translated into Spanish, French and Portuguese. Collectively these online resources provide a substantial proportion of the world's high quality educational and advocacy materials for the world in fungal diseases.

At the AAA meeting in Lisbon Beth Bradshaw and Rachel Orritt also presented posters and a leaflet stall to inform the conference delegates about the electronic resources available for clinicians, scientists and patients through the National Aspergillosis Centre, including Microfungi.net (free online microscopy training), Drug Interactions Pro as described above. Many opportunities are taken at numerous conferences to distribute leaflets about these resources.

9 Statutory reports

9.1 MRSA

No cases of MRSA were reported.

9.2 C. difficile and CPE infections

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

9.3 Serious Untoward Incidents (SUIs)

No SUI's were reported.

9.4 Complaints

No complaints were made in 2017-18.

9.5 Hospital Incident Reporting System (HIRS) alerts

3 HIRS were submitted.

- 1- Related to posaconazole results that were not acted upon appropriately
- 2- Incorrect dosing of gamma interferon given
- 3- Email communication not followed up

10 Future developments and direction

11.1 The developments planned for **2017/18** were (outcomes):

- Implementation of year 1 of the NIHR BRC research plan in infection. Achieved – increased volume and delivery of pyrosequencing results with the MCRM, genetics of CPA nearly finalised.
- Implementation of direct detection of azole resistance by pyrosequencing into routine clinical service. Achieved
- 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. Achieved.
- Eighth Advances Against Aspergillosis Meeting to be held in Lisbon (February 1-3rd, 2018), and a Portuguese patient's meeting is planned. Achieved – and a very successful meeting, including an evening dialogue with the FDA and Japan's PMDA on clinical trial designs required for registering new antifungals for chronic and allergic aspergillosis.
- A primary therapy study of isavuconazole for CPA funded by industry. Other new antifungal developments are in the planning phase. Study withdrawn by sponsor. Sale of isavuconazole from Basilea to Pfizer prevented this project from going forward.

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. Not achieved in 2016/17 but achieved in 2017/18.

11.2 The developments planned for 2018/19 are:

- Implementation of year 2 of the NIHR BRC research plan in infection, including mycobiome assessment of CPA patients, and publication of CPA genetic results.
- Re-introduction of Skype clinics for some consultation for distance patients.
- Increased clinic capacity required including evening clinics. Space is a challenge.
- Recruitment of 2 additional nurses, 1 NHS consultant, 50% of a senior physiotherapist and another administrator for the non-CPA patients with aspergillosis.
- Increased audit efforts to better understand how to more quickly assess progression of CPA, associations with the development of resistance and radiological interpretation and scoring approaches.
- Initiate a focussed program on assessment of therapeutic response that will satisfy regulatory authorities.
- Introduce an Aspergillus IgG serology test into the MCRM portfolio to replace Aspergillus precipitins assay, and assist in diagnosing 'sero-negative' cases.

Categorisation of complexity (Banding)

Stage 1

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

Stage 2

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

Stage 3

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

Referral to appointment time audit - April 2017 – March 2018

* 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

Heat maps showing the geographical distribution of new and existing CPA patients March 2018

Figure 11. NCG New patient referrals 2017-18





Figure 12 NCG Review patient referrals 2017-18

Appendix 4 Quality of life (SGRQ), weights and MRC dyspnoea scores for new referrals 2017/18

See separate data file

Appendix 5 NAC Patient Survey 2018 – Summary

154 patients attempted the patient survey this year. Comments on levels of satisfaction are invited from patients on the wide range of services offered at NAC clinics, clinical research and on much of the support work on information, awareness and social support.

The same questions have been asked year on year so we can compare performance, and this is helpful to identify any concerning trends as well as positive trends. This year we can see that there are a small number of issues of note/concern:

- In particular dissatisfaction about waiting times for doctors and pharmacy have risen to 26% (12% 2017) and 10% (9% 2017) respectively.
- We seem to be contacting patients less between clinics. This year 35% of patients report a contact between clinics, in 2017 this was 49%. A comment from a patient in response to this question was '*I* had one bad experience with one of the doctors who didn't explain my treatment properly' and 'staff shortages delay a return call'.
- Slight falls in satisfaction levels for
 - written information about their condition
 - o quality of the information they received
 - o information about potential symptoms
 - o in-patient stay
- Use of Patients website falling
- 20% had not received any information leaflet
- 10% would like information about end of life care from doctor, 10% from nurse. 80% did not want to discuss it
- A fall in happiness to participate in clinical trials(72% 2018, 86% 2017)

There are also numerous examples of the very high standard of care offered by NAC and most issues listed above are examples of change from a very high standard. We should keep an eye on any of these changes becoming trends over a longer term. The postal service for drug levels & sputum and antifungal drug delivery is working well and is well accepted. Lots of positive comments and useful feedback for the Patients website, leaflets, monthly meetings, quarterly booklets.

Members of staff mentioned by name for their excellent work are Debbie, Phil, Jenny.

Note on format: All % figures are given as a proportion of *those who responded to the question* and not the total number of people who attempted the survey. Everyone who attempted the survey did not answer all of the questions. We give each proportion as % with actual number of patients in brackets.

This year, 154 patients had attempted the patient survey, 5%(7) of which were attending the clinic for the first time. This is similar to last year, where only 3% of the patients who attempted the survey were attending the clinic for the first time. It should be noted that not all patients answered all of the questions.

Q2. Waiting times



Most patients were very satisfied with the time they had to wait for the receptionist in particular and generally either very satisfied or satisfied with the time they had to wait for the other sectors. However, 21% (25) of patients were unsatisfied with the time they had to wait for the doctor and 5%(8) were very unsatisfied. This is an increase from 2017, where 12% of patients had found waiting for the doctor unsatisfactory or worse. Furthermore, 8%(7) of patients were unsatisfied for the time they had to wait for pharmacy and 2%(2) were very unsatisfied. This is also a slight increase from last year, where 9% of patients were unsatisfied or worse with the time they had to wait for pharmacy. 2% of patients were unsatisfied with the time they had to wait for lung function.



Q3. Courtesy

Most patients were very satisfied with the courtesy shown to them by receptionists, nurses and doctors and some were satisfied. This is a similar result to last year. No patients were unsatisfied or worse, which is an improvement from 2017 where 2% of patients had found the courtesy shown to them by all 3 staff members very unsatisfactory.



Q4. Quality of care

Most patients were very satisfied with the quality of care received from all 3 sectors and some patients said they were satisfied. Only 1%(1) of patients said they were unsatisfied with the quality of care received by the doctor. This is a slight improvement from 2017, where 1% of patients were very unsatisfied with the quality of care received by the doctor and 1% was very unsatisfied with the quality of care received by specialist nurses.

Q5. Support outside of clinics

In 2017, almost half the patients who had completed the survey had been contacted by a member of the NAC team in between or after clinic visits. However, this year, this was the case for only 35%(45) of patients who had completed the survey.



Patients who had been contacted by a member of the NAC team were all at least satisfied with the support they received, particularly from the nurses.

Comments were generally very good: Jenny and Deborah are very good; solved all my problems; always great help and support; staff/nurse team are always excellent; very good service; very helpful and speed in reply.

Few were negative: *Staff shortages delay a return call; I had one bad experience with one of the doctors who didn't explain my treatment properly.*

Q6. Specialist physiotherapy

30% (39) of patients said they had received specialist physiotherapy from either Phil Langridge or Reyanna Sheehan and 100% were satisfied or better (86%(31) were very satisfied which is the same as for last year). Comments were very positive: *Very helpful; Phil is brilliant but overworked; Both Phil and Reyanna are brilliant; Very knowledgeable; helpful and understanding; Great guy; Phil was great; Phil was very good and gentle; 10/10.*

Q7. Written information

63% (85) of patients said they have received written information about their condition, which is less than for 2017 where 67% of patients had received written information about their condition. As mentioned last year, this may be a little low because all patients have access and most should have received one leaflet. Similarly to last year, comments are varied: *Concerned; would like a copy of doctor's letters; very helpful; always helpful and informative; in a letter years ago, have been a patient for 10 yrs ; a copy of consultant's letter would be good, showing results etc; very useful; have had to request clinic letters; interesting ; very useful*



Q8. 93% (88) of patients found the information they received either satisfactory or very satisfactory.

Q9. Information about potential symptoms

71% (93) of patients have received information about potential symptoms regarding their medication or illness to watch out for at home. This is a decrease from 80% in 2017.

Comments are varied: We even had prof. Malcolm Richardson come and do a personal home visit; doctors fully explained this to me; Not told about side effects; Was told long ago so have forgotten; was told initially but not lately; very helpful; partially but treatment may be subject to change- need advice; we never discussed this; very good, appreciate this input; generally not very helpful.

Q10. Asking Doctor Questions

The same as for last year, 97% (120) of patients got an answer they could understand when they asked a doctor an important question.

Comments were varied: *Explained in a very straightforward way; most helpful and in depth- thanks; satisfied with answers; always positive communication with prof Denning; Piper Newton is very good; not always; not always clear; I have never felt rushed in terms of the time taken to answer questions; last doctor was informative; could not always understand; good clear answers; very good; very clear.*

Q11. Have you thought about supportive care/ end of life care?

76% (98) of patients said they had not thought about this.

Comments: Fully aware of the issue; I don't want to die in a hospital- would like to be in a hospice; still fighting; don't feel this is an urgent consideration for me; Should we be worried about how long??; Tendency towards anxiety, positive messages help; Do my best to manage my condition following consultations; I'm not this badly affected yet; Well at the moment; Only 47

Q12. 10% (11) of patients said they would like the opportunity to discuss end of life care with doctors and 10% (12) of patients said they would like to discuss this with nurses. The rest of the patients said they would not like the opportunity to discuss end of life care.

Q13. Have you ever had an in-patients stay? 35% (47) of patients have had an inpatients stay at Wythenshawe hospital and 93% of these patients thought they were treated with respect and dignity whilst in hospital.

Comments were polarised: mad ward, no private room, felt like a prison; couldn't fault anyone. Brilliant staff; all staff were lovely.

Q14. Would you recommend Wythenshawe hospital to friends and family?

96% (112 patients) said they would recommend Wythenshawe hospital to friends and family.

Why?: Very helpful and understanding; very supportive and immediate care; out patients yes, inpatients no; they helped me understand my condition and gave me very professional support; my experience of all staff has been consistently positive for the past 2.5 years that I have been attending; very pleased with my treatment; the staff are very professional in their approach and friendly and welcoming with a smile; local hospital's much closer to home ; been treated very well by all staff; I was looked after 10/10; always had great care; very good at their specialism; the hospital (including its previous incarnation as Baguley) has given me a consistently high standard of treatment for 50 years!; I regularly do; it can help with medication; It's the best; well organised and thorough; excellent care; professional and sufficient; hospital so large it lacks personal empathy; very satisfied with all staff; supportive and caring staff; excellent service; dedicated staff: majority going the 'extra mile' in most challenging circumstances; 'long clinic waits but the rest of the care is great and staff happy and friendly; good service; no- there was dirty toilets on Doyle ward; they are all very good; perfect service; no complaints at all; excellent care by staff; very professional and excellent level of standards.

Q15. Postal service for drugs levels and sputum samples

Comments were generally excellent for this service although quite a few patients noted problems with the packaging: I find this service works extremely well for me; worked well posting etc. but not heard if you received it or the results; very good service; a good service; satisfied with service; always works well and efficiently; they worked; I found the service 100%; send recorded as quite a few have gone missing; system works; one blood sample from my GP never arrived; good service; I found the packaging for return difficult; very good; works well, no issue with this; satisfied; it was okay; it would be helpful to have specific labels for either Aspergillus or infection testing; was arranged but never happened, still waiting for medication; It's super; does not need to be improved; It works fine; One time showed incorrect address medicine drop; A quick text or email if satisfactory rather than 'we will let you know if there is a problem; Excellent; no problem; GPs not aware of required labelling (perhaps labels sent with samples requested); works well; good service; no problems; was unaware of this; very good; make the sample packs bigger as it's not easy to put the bottles in; works fine; works fine; a phone call with results; packaging of the sputum difficult to close; once it got lost and didn't arrive; good service;

Q16. Delivery of anti-fungal drugs to patients' homes

Overall, comments on this service were excellent with some constructive suggestions: *I live in Kent so probably wouldn't apply; very satisfied with company; very efficient; excellent service; good service; very satisfied with the service I have received; very prompt and convenient; excellent, no problems; shouldn't depend on where you live; it works well; always been very good; impossible to reach on phone; it is very useful and I have been contacted before the next supply; I have no problems with thismedications arranged and delivered on time; the service is excellent. I am always contacted beforehand to let me know of my delivery and the drivers are always polite; I did not know about this service- it would be useful as I live 180 miles away; good ; very good ; no problems; always within the 2 hour slot; first class service ; very good; much improved service now- still rather difficult to contact the supplier by telephone; very good; runs very well; they delivered to wrong house; excellent; works well; great idea; was unaware of this; very good; very good; service good; works fine; good service; very good; most times I have to remind them about my delivery; very keen to help; 10/10; excellent service; excellent service; driver very courteous,*

Q17. Patients' website (<u>www.nacpatients.org.uk</u>) Only 35% (48) of patients have visited the patient's website. This is a decrease from last year, where 46% of patients had visited the patient's website.

100% of patients who had visited the website said they were satisfied or very satisfied with the website.

The comments indicate a few main problems such as patients not having access to internet/ computers or being computer illiterate. Many patients were also not aware the website existed: Not on the internet; no internet; I received all the information I needed; was not aware; don't use computers; computer illiterate; not very aware of it; was not aware; I have booklets and information on my condition; unaware there was one; lack of time; not online; unaware of its existence; no computer; no computer; no

computer; no access; not tech literate; No laptop; no access; unaware it existed; no computer; don't use internet; no computer; no computer,

Q18. Patient information leaflets 77% (92) of patients found the information leaflets either useful or very useful; however 20%(24) of patients had not received a leaflet.

Ideas for booklets: Have I got Aspergillus or is it something else? Ongoing investigations; more info on treatments and drugs; guidelines about exercise and diet relating to improving symptoms; more info on bronchiectasis and depression; more info on diet and nutrition; it's good to understand the technical side of aspergillus- but in layman's terms; any informative information tailored to the person; Send copy of letters to GP- they don't always;

Q19: Monthly patients meetings 10% (13) of patients had attended a meeting, which is a big increase on 2017 which only had 4% (3 patients) that had attended a meeting

If yes any comments? : difficult to make them pertinent to all diagnoses, people's experiences are so varied; interesting; very good and supportive



Of those who did not attend a meeting the following responses were given

63% (68) did not attend as it was inconvenient to do so. This is very similar to 2017 (65%) and remains a difficult barrier to overcome for this meeting, though this is offset a little in Q21.

Comments: I live in Kent unfortunately, otherwise I would attend; not yet received a diagnosis; too far to attend unless it is part of clinic visit; inconvenient as I live in Rhyl; live too far away; too far away; live a long way from Manchester; I live 156 miles away; I live in London so it is too far; we live on north side of Manchester; I live 180 miles away; I live 60 miles away; I would like the opportunity to attend something like this; have not felt well enough to attend; I live far away; too far (3 hours away); with advanced notice, I would attend for sessions of particular interest; we live 100 miles away so travelling is difficult; Too far to travel; It's a strain for me to attend clinics and appointments and there are associated risks, so cannot see how they might assist me; Have CPA and almost all meetings seem to cover aspergillosis and mould allergies.

Q20 Regional patient-led support groups

46% (60) patients were aware of these groups but only 8% of these had made any contact with the group leader. 8% is significantly more that 2017 when only 4% made contact.

If no why not : I didn't know, however not very close to me; I work when they meet; not felt it necessary; too far; never crossed my mind; can be a bit frightening at times; wrong place/wasn't interested; do not feel the need to contact, always use Prof Denning for support; they meet too far from my home; too far to travel; too far away from home; time, man online forum; work commitments/bit too far; don't need a support group; not needed to; no reason to ; didn't feel the need to; nothing where I live; nothing near me; do not feel its appropriate; not local to me and do not feel the need; not interested; no need; too far away (many people have said this); have sufficient support available from specialist nursing/ doctor teams; don't feel the need; not applicable; too far away; do not think i would benefit from this;

Q21. Recordings of patient meetings

12% (15) of patients had accessed a recording of the monthly patients meeting which is a larger number than had attended in person.

If yes any comments?: good; Very interesting; very informative and supportive; very good website, interesting to hear how this condition effects people's lifestyles.

Q22. Viewing patients meeting live over the internet

6% (8) patients viewed a meeting live

Comments if yes: more information about these please, I watch the recordings; would do this if they could be accessed retrospectively; very good zoom website? Overall a total of 28%(36) of patients had viewed a patients meeting using one of the above routes out of a total possible 130 who responded to the question. This is encouraging and a marked increase on 17% (15) of patients who attended in 2017. NOTE this has been a year of transition for remote streaming of the patients meeting as our regular streaming service has been discontinued. Our latest meeting (July 2018) streamed the meeting directly onto our Facebook support group (whose members are made up of patients & carers worldwide) and was watched by over 350 people.

Q23. Hospital transport

7% (9) have used hospital transport and of those 7 found the service satisfactory or better with 1 finding it unsatisfactory. In 2017 no user found the service unsatisfactory (9 users in 2017).

Postcode (not hospital transport): M18, M33, WN2, CM, NN6, M23, WA3, CW2,M18, SN5, OL10, FY4, NN10, L527, OL10, SK6, S12, GL6, GL51, PR1, CF23, WA15, M33, M22, SK16, M34, BL8, BL1, BL3, LL29 Postcode (hospital transport): LL18, LL11

Q24. Clinical research

72% (88) were happy to participate in clinical research (86% 2017). Of these 98% were satisfied or better with the procedures and consent process



Q25. Patients Website redesign.

What are the 3 main things you would like to find on that website? What, When, Why, How and FAQs; up to date information; helpful hints for day to day living; self help, what patients can do; different treatments; news about new treatments/drugs; information about all of the diseases; patient experiences; where to go for help; advice from doctors and patients e.g. Q&A; Healthy eating advice; useful info for everyday life- Hol ins, life ins etc.; results of research; comments/inputs from other sufferers; new treatment; latest news; who's who!; thoughts on improving diet and exercise tailored to the disease; links to other resources eg. relating to bronchiectasis; info on face mask suppliers; possibly advice on what to do in certain situations eg. haemoptysis; how to manage day to day life; suggestions on how to improve condition; an emergency contact no. to help/ offer advice; latest research and breakthroughs; new medications; information on aspergillus; user friendly; updates on new treatments; more info on my condition; info on the condition; where to find help and support; exercise, diet, nutrition; success stories; options; myth busters (truth on what you can and can't do); accessible articles for non-medical professionals; progress; easy access; information explained well; up to date information; progress on medication;, interactions with other drugs; advances in medication for aspergillus; help for when chest is bad (relapse); new treatments in trial; specialist support/ teams I can access; tips on how to stay healthy and manage condition; general info regarding aspergillus; new treatments; contact info for help; treatment options; managing sideeffects esp. HX, information sheet for GPs; medication; new treatments or therapies; ways to connect with other local people with the condition; general information, questions and answers; contacts for more info; Lots of great suggestions here that we will use!

Q26. What is your biggest criticism of the patients website? There's a lot to navigate through- maybe something more streamlined with links?; looks rather cluttered; none; not very streamlined;

This is good because it confirms our feelings too!

Q27. Weekly online meeting for patients and carers on Thursday at 11:00am, currently using Skype.

3% (4) have attended the meeting, which has been running now for 18 months. We have switched to Zoom software which has great privacy.

Q28. Would you like to know more about the weekly Skype meeting?

11% (14) would like to know more about this meeting

NOTE: this means that we now have a small group of patients who are comfortable using an online video service and have all the requisite hardware and software. This bodes well for future contact from our more remote patients for example for research contact.

Q29. Quarterly booklet.

62% (88) patients have picked up and read the quarterly booklet. This fits well with our strategy to reach all of our patients with relevant information on aspergillosis, support for patients and carers, and other NAC notices. If 62% are reading the booklet and 36% use the Patients Website then there is a good chance that we are able to pass on information to most of our patients (and presumably carers) at least four times a year.

Suggestions for content: good general content; I found this interesting; interesting read; ideas for exercise and diet beneficial to sufferer; info re. suppliers of affordable face masks; advice on good breathing techniques; advice on chest clearance techniques; advice on use of chest clearance devices e.g. acapella; suggestions on how to manage day to day activity; contact details of clinic/nurses; advice to avoid contact with mould; benefits available to patients and carers; helpful tips; travel insurance; research; who people are/what they do; diet, nutrition, exercise; how to stay fit and active, engaging in sport; living a healthy life; new treatments; therapies; research findings

NOTE: lots of helpful food for thought there.

Any general comments about NAC?: I have been extremely happy with the service here at the clinic and very thankful to be seen; This place is the best in the UK!; the clinic is a constant help and support and a positive, professional group of doctors and nurses; the facebook page is useful; some information about assistance for long distance travel; I am pleased with the service that the hospital has offered me as my health has remained goo since the trials service; I appreciate the opportunity of making you aware of my views through this questionnaire; too far for me to travel to Wythenshawe hospital more regularly than required due to my health limitations; physio was particularly helpful and kind (Philip); happy with help and info received; would like a copy of clinic letters to be sent to patients following clinic appointment -I always have to ring and request; there used to be tea and coffee available in the waiting room - as I attend alone this was a useful service as I don't have anyone to get coffee for me; really appreciate all the resources and expertise the NAC has to offer; ready availability of water in the clinic would make my blood tests easier! I always seem to be dehydrated; Struggle to move around, wash, eat, go to bathroom, any suggestions on this to help; All good, excellent service from the professional and supporting staff; it would be helpful if people were requested not to wear perfumes/hairsprays when attending clinics (makes breathing difficult); had a big problem trying to book an appointment; so many patients (maybe an extra clinic should be warranted for aspergillus patients); treatment changes not always shared with GP/ Trafford community matron service; really happy with the service I've received; I understand that clinics are very busy and often overbooked, hence can run late. Thank you for your help, need more local support in the south west e.g. satellite hospital; I am not on the internet; all is ok with your team; a big thank you, very

happy with the care from all the team in clinic; I use the website/ facebook/ skype and run a local support group meeting; Well pleased, many thanks

Survey data collated by Emma Kington and Megan Bridgeland (students) Report part-written by Emma Kington Graham Atherton July 2018

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PR work – Raising awareness and supporting NAC and aspergillosis generally

Public relations are handled by the PR company <u>Goodwork</u>, in co-ordination with the University of Manchester communications team. The <u>Aspergillus blog</u> highlights one or two stories per week (titles listed below), featuring a mixture of relevant world news, new diagnostics and antifungals, and the latest research.

Mar	•	Predatory Journals?
2018	•	Severe fever with thrombocytopenia syndrome complicated by
		invasive aspergillosis
	٠	Therapeutic dilemma in fungal keratitis: administration of steroids for
		immune rejection early after keratoplasty.
	٠	Latest ESCMID-ECMM-ERS Clinical Guidelines for Aspergillosis
		Published
	•	Lessons to be learned from an invasive aspergillosis outbreak in a
		Japanese haematology ward
	٠	Accuracy of fungal disease prevalence estimates from LIFE
	•	Itraconazole and prednisolone are compared for ABPA-complicating
		asthma treatment
	•	Complete fungal microscopy e-course launched today
	٠	Three generic forms of caspofungin approved by the FDA
Feb	•	Fungal Contamination of Green Turtle Nests
2018	•	Patients' and Carers' meeting in Lisbon
	•	Single Aspergillus fumigatus inoculation induces aspergillosis in
		falcons
	•	Harmless strains of Aspergillus prevent maize crop loss, by competing
		out toxic strains
	•	8th Advances Against Aspergillosis Conference Round-Up
Jan 2018	•	Announcing the Launch of World Aspergillosis Day Feb 1st
	•	New Jersey residents became sensitized to moulds after flooding
		caused by Hurricanes Irene and Sandy
	•	Tokyo researchers confirm that the 'G-positive substance' of
		Aspergillus that causes horseshoe crab blood to coagulate is indeed β -
		<u>1,3-D-glucan</u>
	•	Patients Meeting at the 8th AAA, Lisbon 2018
	•	Fungal microbiome explored in patients with respiratory fungal disease
	•	UK research investment analysis shows HIV and TB are relatively
		well funded, but pneumonia is neglected
	•	Posaconazole Pharmacokinetics in Adults with Invasive Fungal
		Infections
	•	Invasive Aspergillosis in Heart Transplant Recipients
		<u>Press release</u> promoting World Aspergillosis Day on the theme of
		Caring for Carers, including a set of 5 aspirational targets for
	7	asperginosis to be achieved by 2030.
		<u>Press release</u> for a research paper published by in collaboration with

		scientists from the University of Manchester that described the high
		burden of Aspergillus in the lungs of asthma patients treated with
		steroids, and the benefits of treating such patients with antifungal
		drugs.
Dec	•	Could the antifungal terbinafine be working through a dual action?
2017	•	Antarctic birds' nests home to Amphotericin B resistant fungi
Nov	٠	New formulation SUBA-itraconazole prophylaxis – therapeutic levels,
2017		safety and tolerability
	•	First UK case reported of fungal lettuce wilt (Fusarium oxysporum
		<u>I.sp. lactucae)</u>
	•	Panfungal DNA sequencing assay for invasive fungal infections shows good sensitivity (97%) and specificity (98%)
	•	Evaluating CT guided lung biopsies for diagnosing fungal infection
	•	First CPAnet symposium identifies four key research areas for chronic
		pulmonary aspergillosis
	•	ImmunoPET: the future of lung scans in aspergillosis?
	•	Unravelling the pharmacokinetics of triazole antifungals in snakes
	•	First case of echinocandin resistance caused by fks1 mutation found in
		Aspergillus
	•	Vitamin D deficiency and aspergillosis
	•	A. terreus conidia use dendritic cells to their advantage
	\triangleright	Social media campaign for the new French translation of the online
		microscopy course Microfungi.net generated 2,342,284 verified
		impressions in the first two days.
Oct	•	Jekyll-and-Hyde yeast makes chocolate taste great but also causes
Oct 2017	•	<u>opportunistic infections</u>
2017	•	<u>Jekyll-and-Hyde yeast makes chocolate taste great but also causes</u> <u>opportunistic infections</u> <u>Could gamers help tackle aflatoxins?</u>
Oct 2017	•	<u>Jekyll-and-Hyde yeast makes chocolate taste great but also causes</u> <u>opportunistic infections</u> <u>Could gamers help tackle aflatoxins?</u> <u>Did Ötzi the Iceman have aspergillosis?</u>
Oct 2017	•	Jekyll-and-Hyde yeast makes chocolate taste great but also causes opportunistic infections Could gamers help tackle aflatoxins? Did Ötzi the Iceman have aspergillosis? Is the Arg1 protein key to preventing cryptococcal meningitis?
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Δμα	Making HSC Transplants a Thing of the Past
2017	
2017	• <u>First Global Research Centre on Killer Fungi</u>
	<u>Press release</u> for a series of public health paper on fungal infections
	published in the Lancet.
July	 Future of Fungal Taxonomy to be Decided by Mycologists
2017	<u>Asthma Breakthrough: Azithromycin Improves Quality of Life for</u>
	Asthma Patients
	Press conference at the House of Commons to call on the UK
	government to review the requirements for ventilation in building
	regulations, in order to reduce the number and severity of asthma
	cases. Also to restrict the use of antifungals in agriculture.
June	Mouldy Wallpaper and Mycotoxins
2017	• Pfizer Will Manufacture and Commercialise Isavuconazole in Europe,
	Russia, Turkey and Israel.
	Press release on the transfer of azole-resistant Aspergillus via tulip
	bulbs and cut flowers following agricultural use of azoles.
May	<u>National Collection of Pathogenic Fungi Launches Newsletter</u>
2017	• Patient Engagement Survey: How to Hardwire Engagement into Care
	Delivery Processes
	• Can I Eat Food That is a Bit Mouldy?
	Western Food Goes Mouldy and its Good!
	World Asthma Day 2017: Promoting Awareness and Improved Care
Apr	New Antifungal SCY-078 Showing Promise after Phase 2 Trials
2017	UK Contribution to Fight Fungal Diseases Overseas Increased
	• The battle for breath - the economic burden of lung disease
	A Step Forward for Treatment of Fungal Infection Worldwide
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Social media

Twitter is the main social media platform for promoting NAC activity, with separate accounts for LIFE Worldwide, Aspergillus&Aspergillosis and GAFFI. These are kept active with several tweets and retweets each week.

N7	Twitter handle	Followers	Tweets				
LIFE Worldwide	@LIFEworldwide	394	379				
Aspergillus &	@AspergillusWeb	1351	6764				
Aspergillosis							
GAFFI	@gaffi_org	1332	371				
Aspergillosis Trust	@aspertrust	41	154				
MRCM	@MycologyRefManc	96	36				
As of 8 th Aug 2018							