



ELSEVIER



www.elsevierhealth.com/journals/jinf

Standards of care for patients with invasive fungal infections within the United Kingdom: A national audit

S. Schelenz ^{a,*}, R.A. Barnes ^b, C.C. Kibbler ^c, B.L. Jones ^d, D.W. Denning ^e

^a Department of Microbiology, Norfolk and Norwich University Hospital, Bowthorpe Road, Norwich NR2 3TX, United Kingdom

^b Department of Medical Microbiology, School of Medicine, Cardiff University, Cardiff, United Kingdom

^c Department of Medical Microbiology, Royal Free Hospital, London, United Kingdom

^d Department of Clinical Microbiology, Royal Infirmary, Glasgow, United Kingdom

^e Regional Mycology Laboratory, Manchester Education and Research Centre, Wythenshawe Hospital, Manchester, United Kingdom

Accepted 19 December 2008

Available online 29 January 2009

KEYWORDS

Invasive fungal infections;
Standards;
Audit

Summary Objective: The objective of this study was to audit the compliance and implementation of the British Society for Medical Mycology standards of care for patients with invasive infections in UK hospitals.

Methods: A multidisciplinary audit questionnaire regarding the processing of microbiology and histopathology specimens, radiology imaging and clinical management of patients with invasive fungal infections was distributed to UK hospitals.

Results: The study has shown that speciation of *Candida* and *Aspergillus* isolates from sterile sites was performed in 42–98% of hospitals. Microscopy of bronchoscopy specimens was not undertaken in 13 of 62 (21%) laboratories. Cryptococcal culture and antigen were undertaken routinely in abnormal CSF in 40–75% and 31–83% of at-risk patients but only in 12% of abnormal CSFs in patients without risk factors. Detailed fungal morphology was provided by <50% of histopathology departments. Most hospitals provided a timely HRCT or MRI on patients suspected to have an invasive fungal infection, but early treatment failed to occur in 15% of hospitals. In patients presenting with candidaemia, central venous catheters (CVC) were not changed routinely within 48 h in 15%.

Conclusion: Improvement in microbiology and histopathology specimen processing as well as rapid interventions such as initiation of anti-fungal therapy or CVC line removal could improve diagnostic rates and clinical outcomes of invasive fungal infections.

© 2009 The British Infection Society. Published by Elsevier Ltd. All rights reserved.

* Corresponding author. Tel.: +44 (0)1603 611 816; fax: +44 (0)1603 620 190.
E-mail address: sschelenz@doctors.org.uk (S. Schelenz).

Introduction

Invasive fungal infections such as candidaemia and invasive aspergillosis remain a significant cause of morbidity and mortality.^{1–3} Recent surveillance data confirms the year-on-year increase of candidaemia cases with an incidence of 3.1 per 100,000 population in England, Wales and Northern Ireland and 4.8 per 100,000 population in Scotland (i.e. around 2000 cases annually, a 40% rise over 5 years).^{4,5} Although the development of new anti-fungal agents has improved treatment options, the outcome of such serious infections remains poor, especially for candidaemia (32–50% mortality)^{1,6,7} and invasive aspergillosis in non-haematology settings such as in ICU (>50%)⁸ and COPD patients (95%).⁹ Improvements in outcome will greatly depend on early diagnosis and appropriate multidisciplinary management.^{6,7,10–13}

In 2003 the British Society for Medical Mycology (BSMM) published a set of proposed standards of care for patients with invasive fungal infections that included best practice guidance for microbiology and histopathology laboratories, radiology and clinical specialists (Table 1).¹⁴ This national audit is the first multidisciplinary United Kingdom (UK) wide survey involving key specialties (microbiology, histopathology, radiology and specialist clinical units) to measure the quality of care provided for patients with invasive fungal infections. The aim was to assess the laboratory and clinical aspects of services provided to manage such infections and to identify problem areas.

Methods

In April 2007 the BSMM, jointly with the Royal College of Pathologists (RCPATH), invited members to participate in a national audit to assess the compliance with the published standards of care for patients with invasive fungal infections.¹⁴ A questionnaire based on the four main specialty standards was piloted in hospitals in East Anglia. The questionnaire (Fig. 1) was subsequently published in the RCPATH Bulletin, the RCPATH website (www.rcpath.org/index.asp?PageID=1321) and, in addition, an invitation was sent via e-mail to UK RCPATH members and regional RCPATH chairmen including 200 registered microbiology laboratories.¹⁵

The questionnaire requested basic information on the type of hospital, presence of specialist units (HIV/infectious disease unit (ID), intensive care unit (ICU), special care baby unit (SCBU), burns unit, bone marrow (BMT)/stem cell (SCT) or solid organ transplant unit (SOT)) and awareness of the published standards. The core of the audit form contained standards of care questions for the four main areas namely microbiology, histopathology, radiology and clinical medicine requiring a yes or no answer. An option for free text feedback was also provided. In brief, the microbiology section required information on microscopy, culture and fungal speciation from a number of different specimens (blood, intra-vascular (IV) line tips, continuous ambulatory peritoneal dialysis (CAPD) fluid, bronchoscopy specimens, urine and cerebrospinal fluid (CSF)) as well as information on

Table 1 Summary of BSMM 2003 standards recommendations.

Microbiology standards

- Yeasts and moulds from sterile sites and line tips should be identified to species level
- Fungi from urine of patients in ITU, SCBU, burns unit and transplant patients should be speciated
- Bronchoscopy fluids from patients suspected of infection should have microscopy to look for hyphae and be cultured on specialized media
- Clinical isolates of *Aspergillus* should be speciated
- CSF from immunocompromised, HIV, transplant and sarcoidosis patients or those with abnormal CSF glucose, protein or lymphocytes should be tested for cryptococcal antigen and cultured for *Cryptococcus* (30 °C for 21 days), and bacteria (5 days).

Histopathology standards

- Tissues from immunocompromised patients with suspected infection should have fungal stains and positive results telephoned immediately
- A report should describe fungal presence/absence and morphology (fungal structures, presence of septae, melanin, relative size, cellular location)

Radiology standards

- Profound neutropenic haematology patients with new cough, chest pain, haemoptysis, abnormal chest X-ray, new mould culture, hyphae seen in sterile specimens or unresolved fever should receive a high resolution CT within 48 h
- Transplant patients with new mould culture should receive CT within 48 h
- Immunocompromised patients with new neurological features (including signs of meningitis) should have a CT or MRI scan of the brain

Clinical standards

- Request cards should state whether patient is immunocompromised
- Patients with candidaemia should have their central line removed within 48 h of diagnosis and be treated systemically with an anti-fungal agent at an appropriate dose
- Transplant or profoundly neutropenic patients with new mould culture, pulmonary or cerebral abnormalities consistent with fungal infection should receive a systemic anti-fungal agent active against moulds within 6 h of diagnosis/culture
- Cryptococcal meningitis should be treated with conventional amphotericin B (>0.7 mg/kg/d) or lipid based formulation (≥4 mg/kg/d) plus flucytosine (75–100 mg/kg/d)

(N/A if not applicable)

A		yes	no
Type of hospital (circle): DGH or University Hosp. or other (state): _____ Your Region: _____ Specialties served (tick): BMT/SCT <input type="checkbox"/> , Solid organ transplant <input type="checkbox"/> , Haematology/oncology <input type="checkbox"/> , ID/HIV <input type="checkbox"/> , ITU <input type="checkbox"/> , Burns <input type="checkbox"/> , SCBU <input type="checkbox"/>			
B Are you aware of the BSMM standards (<i>Lancet Infect Dis</i> 2003)?			
C MICROBIOLOGY STANDARDS OF CARE			
1	Do you routinely speciate all yeasts and moulds isolated from the following sites?:		
a	Blood cultures		
b	CAPD fluids		
c	IV line tips		
d	Bronchoscopy specimens (except for <i>Candida</i>)		
2	Do you speciate all fungi isolated from urines of the following patients?:		
a	Intensive care patients		
b	Special care babies		
c	Burns patients		
d	Transplant patients		
3	If any of the answers to question 2 is 'no' do you refer isolates to the reference lab for ID?		
4	Do you perform the following tests 'in house' in your laboratory?		
a	<i>Candida</i> speciation on clinically relevant isolates		
b	Speciation of clinically relevant moulds		
c	Serology - <i>Candida</i> antibodies		
d	Serology - Galactomannan		
e	Serology - <i>Aspergillus</i> precipitins		
f	Molecular tests for the detection of fungal infections		
g	Antifungal-sensitivity testing		
h	Antifungal serum levels (e.g. itraconazole, 5-FC)		
5	If any of the answers to question 4 is no, do you refer those tests to a reference laboratory? (if yes please specify a-h)		
6	Does your laboratory perform the following tests on bronchoscopy specimens from suspected infected patients:		
a	Microscopy for fungal elements		
b	Culture on specialised media (e.g. Sabouraud media)		
7	Do you routinely speciate <i>Aspergillus</i> from all clinical specimens?		
8	Do you test GRAM stain negative CSF for cryptococcal antigen in the following patients:		
a	HIV positive patients		
b	Transplant recipients		
c	Sarcoidosis patients		
d	Immunocompromised patients other than the above		
e	Any patient with abnormal CSF glucose, protein or leucocytes		
f	Is the cryptococcal antigen test done in your laboratory?		
9	Does your laboratory culture all CSFs for <i>Cryptococcus</i> in:		
a	Immunocompromised patients		
b	Sarcoidosis patients		
c	Any patient with abnormal CSF glucose, protein or leucocytes without an adequate explanation		
10	On CSF samples of patients in Q8 and 9, does your laboratory incubate:		
a	All bacterial plates for at least 5 days		
b	All fungal plates at 30°C for up to 21 days		
D HISTOPATHOLOGY STANDARDS IN SYSTEMIC FUNGAL DISEASE			
11	All tissues from immunocompromised patients with suspected infection:		
a	get a fungal stain (e.g. PAS, silver, fluorescent) in parallel with regular stains		
b	Positive results are phoned to treating clinician immediately		
12	Reports on specimens containing fungal elements always include the following:		
a	Presence or absence of yeast forms		
b	Presence or absence of hyphae and whether they are septate or not (if possible)		
c	Presence of melanin		
d	Relative size of fungi		
e	Cellular location of the fungi		
f	Any specialised structures or forms of the fungi		
E RADIOLOGICAL STANDARDS OF CARE			
13	Stem-cell transplant, leukaemic or neutropenic (<500 Neutr./ μ L) patients receive a high resolution (or spiral) CT of the chest if:		
a	New cough, chest pain or haemoptysis		
b	Abnormal chest radiograph		
c	New positive <i>Aspergillus</i> or other mould cultured from any site		
d	Hyphae seen on microscopy in any invasive sample		
e	Unresolved fever after 7 days antibiotics or anti-fungal agents		
f	CT is performed within 48hours (if not, please state average time it takes to get a CT)		
g	CT image is immediately reviewed by the relevant consultant		
14	All transplant patients with a positive <i>Aspergillus</i> or other mould culture receive a chest CT within 48h		
15	All immunocompromised patients with new neurological features (e.g. seizures, stroke, persistent headache) or signs of meningitis get a CT or MRI of the brain		
F CLINICAL STANDARDS OF CARE			
16	Most request cards for microbiology, histology and radiology state clearly whether the patient is immunocompromised		
17	Patients with candidaemia have their central venous catheter removed/changed within 48h of documented infection		
18	Candidaemia is treated with a systemic anti-fungal agent at an 'appropriate' dose		
19	All transplant or neutropenic patients receive a systemic anti-fungal agent active against moulds within 6 h if:		
a	A new <i>Aspergillus</i> or other mould is cultured		
b	A new pulmonary or cerebral abnormality consistent with fungal infection is noted		
20	Cryptococcal meningitis is initially treated with conventional amphotericin B >0.7 mg/kg/d or lipid based AmB >4mg/kg/d with flucytosine 75-100 mg/kg/d (adjusted for renal function)		

Thank you for your participation. Anonymised results will be available through the RCPATH and BSMM.
Please let us know any comments and also areas that you think should be included in a set of standards

Version 4; 15/02/07

Figure 1 Questionnaire on behalf of the BSMM and RCPATH: Survey on the British Society for Medical Mycology (BSMM) proposed standards of care for patients with invasive fungal infections. *Lancet Infect Dis* 2003;3:230–40.

the use of specific tests for the detection of fungal infection including cryptococcal antigen, galactomannan antigen and molecular assays. Many of the questions sought information on current practice that was not in the proposed 2003 standards, to inform a revision of those standards.

The histopathology section required information on the routine use of fungal stains, communication of positive results and reporting of fungal morphology.

The radiology section required information on the timely request of computer tomography (CT) and other imaging in high-risk patient groups and speed of scan review.

The clinical standards required information on the quality of patient information on request cards, management of candidaemia, treatment of suspected invasive fungal infection in the transplant or neutropenic patient and appropriate treatment of cryptococcal meningitis.

The questionnaire was completed by a senior scientist or consultant medical microbiologist, histopathologist or haematologist and returned to the RCPATH standards unit within two months. Replies were analyzed in Microsoft Excel and results are presented nationally for England, Wales, Scotland and Northern Ireland combined. Not all questions were answered by all participants. The results are presented as a percentage of the total responses received for each specific question or section.

Results and analysis

The overall UK response rate to the questionnaire was 35% (70/200). This response rate should ideally, have been higher but reflects a common return rate in such surveys. The majority of forms were returned by staff from microbiology departments who liaised with other specialties (histopathology, haematology, radiology and lead clinicians for transplantation and HIV/ID medicine where necessary). Four returns were submitted by histopathology departments and one by a haematology department who filled in their respective sections only.

Thirty-nine (56%) of the returns were from district general hospitals, 27 (38%) from University hospitals and four (6%) returns did not specify the hospital type.

All UK constituent countries were represented, including Northern Ireland ($n = 3$), Scotland ($n = 4$), Wales ($n = 14$), and all regions of England ($n = 47$). The majority of participants (81% (42/52)) demonstrated awareness of the previously published standards.

Microbiology standards

An average of 64 responses were received regarding the microbiology testing of specimens. A number of microbiology departments provided a service for specialist units, which included BMT/SCT unit ($n = 18$), SOT unit ($n = 11$), ICU ($n = 48$), SCBU ($n = 40$), burns unit ($n = 12$) and HIV/ID unit ($n = 28$).

The majority of departments identified *Candida* (94% (58/62)), *Aspergillus* (75% (49/62)) and other moulds (91% (57/63)) to species level from clinically relevant isolates in their own laboratory. All laboratories not speciating fungi locally sent their isolates to a reference laboratory.

The overall mycology service provided by microbiology departments varies in the UK. Adherence with the recommended standards is shown in Table 2. Overall compliance with the speciation of fungi from sterile sites including blood cultures, CAPD fluid, IV line tips and bronchoscopy specimens (excluding *Candida*) was 89% (Table 2 a). Microbiology departments that served high-risk units speciated *Candida* isolates and other fungi from vascular line tips in 73% (ITU 77% (37/48), SCBU 78% (31/40), BMT/SCT units 71% (12/17) and SOT units 67% (8/12)).

The overall rate of speciation of *Candida* and other fungi from urine of high-risk ICU, SCBU, burns and transplant patients from all participating hospitals was 66% (range 42–75%) but varied depending on the type of unit

Table 2 Microbiology standards of care.

Specimen (specialty)	Laboratories who speciate fungi from specific specimens/respondents (%)
a Blood cultures	63/64 (98%)
CAPD fluid	53/55 (96%)
intra-vascular line tips	46/64 (72%)
Bronchoscopy specimens	56/63 (89%)
Urine (ICU)	44/63 (70%)
Urine (SCBU)	44/59 (75%)
Urine (burns unit)	13/31 (42%)
Urine (transplantation)	38/51 (75%)
b Bronchoscopy specimens	Laboratories who perform test/respondents (%)
Microscopy for fungi	49/62 (79%)
Culture on 'fungal' media	65/66 (99%)
c Patient type	Laboratories that perform cryptococcal Ag test on CSF/respondents (%)
HIV patients	52/63 (83%)
Transplant patient	34/58 (59%)
Sarcoidosis patient	18/58 (31%)
Immunocompromised (other)	31/66 (47%)
Patient with abnormal CSF Glc*, protein, leucocytes	8/65 (12%)
Patient type	Laboratories that perform cryptococcal CSF culture/respondents (%)
Immunocompromised	49/65 (75%)
Sarcoidosis patient	23/58 (40%)
Any patient with abnormal CSF Glc*, protein, leucocytes	25/65 (39%)
CSF set up for culture on:	Laboratories who perform culture/respondents (%)
Fungal agar 30 °C up to 21d	20/65 (31%)
Bacterial agar incubated for ≥ 5 days	32/66 (48%)

*Glc = glucose.

(Table 2 a). Urine isolates were least commonly speciated from burns patients.

Only 49/62 (79%) of laboratories performed direct microscopy for fungal elements on bronchoscopy specimens, despite convincing data showing a substantially higher yield from microscopy combined with culture in patients than culture alone, and the essential need for microscopy to diagnose *Pneumocystis* pneumonia. Almost all participants used specialized fungal media for the culture of these specimens in order to maximize fungal growth (Table 2 b).

The decision to test CSF for cryptococcal antigen greatly depended on the type of risk group (Table 2c). The test was most commonly used in HIV positive patients followed by transplant patients. The majority of laboratories (89% (25/28)) providing a direct service to an HIV/ID unit in their hospital use the cryptococcal antigen test on CSF samples of HIV positive patients although it remains unclear whether the decision to test was protocol driven or based on clinical request. The test was least commonly performed on patients diagnosed with sarcoidosis or those with an abnormal CSF glucose, protein and leukocyte count (Table 2c). Interestingly the majority of microbiology laboratories sent their CSF specimens away for cryptococcal antigen testing and only 23% (15/64) performed the test on site. Even those laboratories, who provide a direct service to an HIV/ID unit were only able to offer the test on site in 29% of hospitals. This was also reflected in the choice of routine CSF culture for *Cryptococcus neoformans*.

There are a number of other laboratory tests, which have a direct impact on the management of invasive fungal infections. The timely knowledge of the anti-fungal susceptibility for some anti-fungal drugs is highly desirable in order to guide effective therapy. Only 38% (24/63) of microbiology laboratories provide such service on site and 5% (3/63) of all laboratories do not provide sensitivity testing at all whether at a local level or via referral to a reference center. Even less common is the onsite monitoring of anti-fungal serum levels to assure a therapeutic range of agents (e.g. itraconazole) or to minimize drug toxicity (e.g. flucytosine). Only a minority (6% (4/62)) of participating UK laboratories currently undertake these tests in their own hospital and 23% (14/62) do not refer serum samples to a reference laboratory for testing.

The testing of galactomannan has become part of the criteria for defining invasive fungal infections.¹⁶ Based on the data provided by the participating laboratories this test is currently used in 72–75% of high-risk patients but only 2–17% of those laboratories are able to offer this test on site (Table 3). Molecular techniques for the detection of fungal DNA have also advanced in recent years but such techniques are still rarely (4% (9/64)) applied routinely in the UK.¹⁷

Histopathology standards

An average of 50 questionnaires were returned, which included a response to the histopathology standards. The overall compliance with the absolute histology standards was poor at 58%. The majority of histology departments routinely include fungal stains such as periodic acid Schiff or silver-based (Grocott) stain on tissue sections from immunocompromised patients when infection was suspected

Table 3 Galactomannan test performed by hospitals serving specific high-risk units.

Specialty or high-risk unit	Laboratories who offer galactomannan test/ respondents (%)	Laboratories who perform galactomannan test in house/ respondents (%)
BMT/SCT* Unit	13/18 (72%)	3/18 (17%)
Transplant Unit	9/12 (75%)	1/12 (9%)
Haematology/ oncology	31/42 (74%)	1/42 (2%)

*BMT/SCT = haematopoietic stem cell transplantation.

(Table 4) and positive results are immediately communicated to the clinicians in 71% (34/48).

The reporting on fungal morphology and their cellular location varied amongst the received responses. Most (82–84%) of histopathology departments provide a comment on the presence or absence of yeast forms or septate/non-septate hyphae in specimens that contained fungal elements (Table 4). Such information is critical to the mycological differential diagnosis and choice of anti-fungal therapy. Very few reports include comments on the presence of melanin, the relative size of fungi or special structures/forms, all features which contribute to the mycological differential diagnosis (Table 4). The cellular location of fungi such as intracellular position is reported by just over half of all respondents (Table 4).

Radiology standards

An average of 43 audit forms were returned, which included a response to the radiology standards. The overall compliance with the absolute radiology standards was 75%. A summary of the responses is shown in Table 5. The majority of BMT/SCT, leukaemic or neutropenic patients receive

Table 4 Histopathology standards: Laboratories that test and provide information on tissues from immunocompromised patients with suspected infection.

Standard of care	Histology laboratories reporting specific feature/all laboratories responding (%)
Routine use of 'fungal' stains	41/50 (82%)
Report on absence/presence of:	
Yeasts	42/50 (84%)
Hyphae and septae	42/51 (82%)
Melanin	9/51 (18%)
Comment on:	
Size of fungus	12/50 (24%)
Cellular location of fungus	28/48 (58%)
Special fungal structures/forms	22/49 (45%)

Table 5 Radiological standards.

Standard of care	Hospitals that perform radiology investigation <i>n</i> (%)
HRCT of chest is performed on BMT/SCT*, leukaemic or neutropenic patients if:	
New cough, chest pain or haemoptysis	32/44 (73%)
Abnormal chest X-ray	37/43 (86%)
New <i>Aspergillus</i> /mould cultured	31/43 (72%)
Hyphae seen on microscopy in invasive specimen	34/42 (81%)
Unresolved fever after 7d antibiotics or anti-fungal agent	38/44 (86%)
Transplant patients receive CT within 48 h if:	
New positive <i>Aspergillus</i> or mould culture	32/40 (80%)

*BMT/SCT = haematopoietic stem cell transplantation.

high-resolution computerised tomography (HRCT) of their chest if there is a new cough, chest pain or haemoptysis, abnormal chest X-ray, new *Aspergillus* or mould culture or when hyphae are seen on microscopy in normally sterile sites. It has been known for over 10 years that a HRCT provides critical information for management including the potential for immediate surgery if invasive aspergillosis is localized adjacent to critical mediastinal structures. In 91% (42/46) of cases the CT scan is obtained within 48 h of the request and the result is reviewed by a consultant immediately in 87% (39/45) of cases. Likewise, the majority of SOT patients receive a chest CT within 48 h of a new positive *Aspergillus* or mould culture (Table 5). All participating UK hospitals provide a magnetic resonance image (MRI) or CT scan for immunocompromised patients that develop new neurological features or signs of meningitis.

Clinical standards of care

An average of 60 questionnaires were received regarding the clinical standards of care. In 52% (31/60) of hospitals, laboratory request cards for microbiology, histopathology or radiology do not state clearly if a patient is immunosuppressed.

The overall compliance with the management of candidaemia including vascular line removal and appropriate use of anti-fungal agents was 91%. Surprisingly 16% of central venous catheters were not changed within 48 h despite numerous data showing improved survival. While a positive culture of *Aspergillus* in immunocompromised patients prompted immediate therapy in 98% of cases, consistent radiology only led to treatment in 85% of cases. (Table 6). In the majority of responding hospitals, clinicians provide appropriate anti-fungal combination treatment and dosing for the management of cryptococcal meningitis (Table 6).

Discussion and prospects for improved practice

Over the past decades there has been an increase in invasive fungal infections and mycoses caused by rarer

Table 6 Clinical standards of care.

Standard of care	Appropriate management <i>n</i> (%)
Management of candidaemia	
CVC line removed/changed within 48 h	53/63 (84%)
Systemic anti-fungal agent given at appropriate dose	60/62 (97%)
Anti-fungal treatment of mould infection in neutropenic or transplant patient within 6 h if:	
New <i>Aspergillus</i> /mould culture positive	54/55 (98%)
New pulmonary/CNS abnormality consistent with fungal infection	55/65 (85%)
Management of cryptococcal meningitis	
Conventional amphotericin B >0.7 mg/d or lipid based >4 mg/kg/d plus 5FC* 75–100 mg/kg/d is given	47/54 (87%)

*5FC = flucytosine.

moulds and non-*Candida albicans* species are emerging particularly in the severely immunocompromised patient.^{4,18–20} The management of such infections involves expertise from many different disciplines including microbiology, histopathology, radiology and specialists looking after immunocompromised patients. The BSMM addressed this issue and published a set of multidisciplinary standards of care for the management of invasive fungal infections to promote best practice.¹⁴ The purpose of this national audit was to assess how widely these standards have been employed and to identify problem areas or possible barriers for their implementation.

The audit was designed to reflect the current working practice of a range of different types of hospitals including district general and teaching hospitals across the UK. The majority of hospital specialists recognize the importance of invasive fungal infections, which is reflected by the growing awareness of the BSMM standards over the years (82% in 2007 compared to 56% in the 2004 pilot audit study, unpublished data). However, the recent audit has shown that whilst many of the standards are implemented there are particular areas of concern in certain specialties that require further improvement in order to assure optimal patient care.

In the UK there are currently 187–208 microbiology laboratories that participate in one or more aspects of the UK NEQAS mycology scheme. Most of the surveyed laboratories provide a good basic mycology service particularly for the local speciation of yeasts and moulds from important

clinical sites including blood cultures, CAPD fluids and bronchoscopy specimens but less from IV line tips of at-risk patients. The speciation of yeasts from IV line tips is of clinical importance as they can be a cause of infection that may not be apparent at the time of culture, e.g. endogenous endophthalmitis. Speciation is critically important for the selection of appropriate therapy and tracking nosocomial infections.

Similarly, yeasts cultured from urine may be significant in high-risk (ICU, SCBU or SOT) patient groups. Approximately three quarters of participating laboratories identify and speciate fungal isolates from urines in these patients, but less in burns patients (50%). This is surprising as these patients should also be considered to be a high-risk group due to the fact that extensive burns can lead to an impaired cellular immunity.²¹ Urinary isolates may be representative of a bloodstream infection strain, which may not be cultured from blood. It is therefore recommended that burns patients, in particularly those receiving late wound coverage, artificial dermis and multiple broad spectrum antibiotics, are monitored for *Candida* infections.²²

While knowledge of the species of fungi is important for the choice of treatment because of intrinsic anti-fungal resistance, acquired resistance also plays a role. Surveillance of anti-fungal drug resistance is therefore encouraged both locally and nationally. Only 38% of participating laboratories performed anti-fungal susceptibility testing locally. A recent laboratory audit from the northwest of England has identified that there is general willingness to introduce in house sensitivity testing on yeasts but staff feel they require more training and guidance.²³ Although laboratories can purchase international standardized protocols for anti-fungal susceptibility testing and a UK NEQAS scheme has been introduced, there is no UK guidance on the choice, use and interpretation of results of simple methods such as disk diffusion or E-testing for the routine implementation in general diagnostic microbiology laboratories. This may explain why few hospitals currently perform susceptibility testing in their own laboratories. Shared UK wide standard operating procedures on cost effective, easy to perform methods may help to encourage and increase local testing in future.

The use of non-culture methods such as antigen and antibody detection can often aid the diagnosis of certain invasive fungal infections. A good example is cryptococcal meningitis. This infection can be diagnosed by prolonged CSF culture at both 37 °C and 25–30 °C to improve recovery of *Cryptococcus neoformans* and *Cryptococcus gattii*, respectively. Only one-third of microbiology laboratories currently perform fungal culture on CSF with extended incubation to maximize the chance of recovering small numbers of this pathogen. Reliance is placed on the cryptococcal agglutination latex test performed on CSF which the majority of participating laboratories use on abnormal CSF samples of symptomatic HIV positive patients. However, the test is rarely performed on other vulnerable risk groups such as transplant, sarcoidosis or other immunocompromised patients presenting with abnormal CSF parameters. Laboratories may mistakenly believe that a serum cryptococcal antigen is adequate to exclude cryptococcal meningitis, but it is falsely negative in 15% of cases, especially in non-AIDS patients.²⁴ Interestingly compared with a laboratory

survey in 1994, there seems to be very little change in the number of laboratories who currently perform this test on site (21% in 1994 versus 23% in 2007).²⁵ Some of the reasons could be that since the introduction of anti-retroviral therapy for HIV, the numbers of cryptococcal infections have decreased and the test is no longer cost effective for single laboratories to perform.²⁶ However, the need to send CSF specimens away for testing is likely to cause significant delay in making a diagnosis and in initiating appropriate treatment for patients suffering from a potentially life threatening infection.

A similar observation can be made for the galactomannan antigen test, which can guide the diagnosis of invasive aspergillosis but is currently only offered on site by 2–27% of the surveyed laboratories and who are mainly reference mycology centers.

Overall, the audit has shown that microbiology laboratories that participated in the audit are providing a good basic mycology service but more specialist tests are less established. However, we do not know the level of service provided by the remaining 70% of laboratories that did not respond. The barriers to implementing some of the standards are likely to be multi-factorial such as low incidence of invasive fungal infections in individual hospitals and lack of resources (cost and manpower). With the introduction of the UK Clinical Mycology Network (UKCMN) under the umbrella of the Health Protection Agency (HPA) this difficulty may be overcome by concentrating already scarce resources and expertise at regional level in the form of regional reference laboratories with good infrastructure to local hospitals.²⁷

The audit also reviewed the reporting practice of histopathology departments. A tissue diagnosis is often vital in confirming invasive fungal disease, which may be clinically suspected, or may be a chance finding particularly when conventional fungal culture or serology is negative. The majority of histopathology laboratories use fungal stains such as PAS or Grocott routinely on tissues of immunocompromised patients suspected to have an infection. Although it is generally not possible to identify the fungus at species level, the structure, form and appearance of fungal elements can provide useful information about the class of fungus (e.g. dichotomous branching septate hyphae are unlikely to be zygomycosis), which may guide appropriate treatment. However, most histopathologists infrequently (18–46%) report on fungal characteristics such as melanin, size, location and structures or forms. This may be because of the rarity of such infections and the variable knowledge and experience of individual histopathologist. Regular training and guidance on the specific tissue appearance of invasive fungi or even standard operating procedures for reporting fungal elements may help to increase the knowledge and awareness of such infections and the quality of reporting.

In many symptomatic high-risk patients, radiological imaging is used to assess whether a patient has any abnormal signs suggestive of invasive fungal infection. Although these signs are often non-specific or indistinguishable from other infectious agents, some changes, e.g. halo sign in HRCT have been particularly associated with invasive pulmonary aspergillosis.²⁸ The use of anti-fungal agents is often guided by imaging signs in combination

with clinical symptoms. It was reassuring to see that the majority of participating hospitals are able to perform and report radiological investigations such as HRCT or MRI in a timely manner on high-risk patients.

The clinical management of patients with invasive fungal infections also depends on the early and appropriate use of anti-fungal agents. The audit has shown that the majority of participating hospital patients with invasive fungal infections are appropriately managed. In candidaemia, intra-vascular lines are removed within 48 h of diagnosis in 84% of hospitals, which will help to improve morbidity and mortality.¹¹ Similarly patients with febrile neutropenia or transplant patients are treated promptly with appropriate anti-fungal agents if they have pulmonary or neurological signs of infection suggestive of a serious fungal infection or if a new fungus has been isolated. This demonstrates that there is a high UK wide clinical awareness of the importance of invasive fungal infections in the 'high risk' group of patients.

Nevertheless good clinical management depends on the confirmation of the diagnosis based on positive microbiological, histopathological or radiological reports. The test selection, processing and interpretation of pathology or radiology results depend greatly on the quality of the clinical information provided. Unfortunately, this audit has identified that there is a significant problem with such information. This may lead to missed or delayed diagnosis, increased morbidity and mortality of patients with an invasive mycosis and under reporting of the infection. The introduction of electronic information technology requesting systems by hospitals is an opportunity to design 'compulsory' clinical information codes that will help to guide laboratory test selection and reporting in future.

Acknowledgement

We would like to thank P. Cowling and the staff from the Professional Standards Unit, Royal College of Pathology in London for their help with the coordination of the audit. The audit was undertaken on behalf of the BSMM working party on the standards of care for patients with invasive fungal infections.

References

- Kibbler CC, Seaton S, Barnes RA, Gransden WR, Holliman RE, Johnson EM, et al. Management and outcome of bloodstream infections due to *Candida* species in England and Wales. *J Hosp Infect* 2003;54:8–24.
- Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003;348(16):546–54.
- McNeil MM, Nash SL, Hajjeh RA, Phelan MA, Conn LA, Plikaytis BD, et al. Trends in mortality due to invasive mycotic diseases in the United States, 1980–1997. *Clin Infect Dis* 2001;33:641–7.
- Heath Protection Agency. Candidaemia in England, Wales and Northern Ireland 2005. *Commun Dis Rep Wkly* 2006;16(42).
- Odd FC, Hanson MF, Davidson AD, Jacobsen MD, Wright P, Whyte JA, et al. *J Med Microbiol* 2007;56:1066–75.
- Pai MP, Turpin RS, Gary KW. Association of fluconazole area under the concentration time curve/MIC ratios with mortality in non-neutropenic patients with candidaemia. *Antimicrob Agents Chemother* 2007;51(1):35–9.
- Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of *Candida* bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. *Antimicrob Agents Chemother* 2005;49(9):3640–5.
- Meersseman W, Lagrou K, Maertens J, Van Wijngaerden E. Invasive aspergillosis in the intensive care unit. *Clin Infect Dis* 2007;45:205–16.
- Bulpa P, Dive A, Sibille Y. Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2007;30(4):782–800.
- Spanakis EK, Aperis G, Mylonakis E. New agents for the treatment of fungal infections: clinical efficacy and gaps in coverage. *Clin Infect Dis* 2006;43:1060–8.
- Rex JH, Bennett JE, Sugar AM, Pappas PG, Serody J, Edwards JE, et al. Intravascular catheter exchange and duration of candidaemia. NIAID Mycoses Study Group. *Clin Infect Dis* 1995;21:994–6.
- Von Eiff M, Roos N, Schulten R, Hesse M, Zühlendorf M, van de Loo J, et al. Pulmonary aspergillosis: early diagnosis improves survival. *Respiration* 1995;62:341–7.
- Taur Y, Cohen N, Dubnow S, Paskovaty A, Seo SK. The effect of antifungal timing on mortality in cancer patients with candidemia. In: abstracts of the 47th interscience conference on antimicrobial agents and chemotherapy, Chicago; 2007 [Abstract no. K-2173].
- Denning DW, Kibbler CC, Barnes RA. British Society for Medical Mycology proposed standards of care for patients with invasive fungal infections. *Lancet Infect Dis* 2003;3:230–40.
- Royal College of Pathology. National audit of the investigation and management of invasive fungal diseases: an invitation to participate. In: The bulletin of the royal college of pathologists. Number 138. Available via DIALOG: <http://www.rcpath.org/resources/pdf/BulletinApril07_WEB.pdf> [cited 13 November 2007].
- De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group; National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008;15(46):1813–21.
- White PL, Barton R, Guiver M, Linton CJ, Wilson S, Smith M, et al. A consensus on fungal polymerase chain reaction diagnosis? a United Kingdom–Ireland evaluation of polymerase chain reaction methods for the detection of systemic fungal infections. *J Mol Diagn* 2006;8:376–84.
- Groll AH, Shah PM, Menzel C, Schneider M, Just-Nuebling G, Huebner K. Trends in the postmortem epidemiology of invasive fungal infections at a university hospital. *J Infect* 1996;33:23–32.
- Malani AN, Kauffman CA. Changing epidemiology of rare mould infections: implications for therapy. *Drugs* 2007;13:1803–12.
- Lamagni TL, Evans BG, Shigematsu M, Johnson EM. Emerging trends in the epidemiology of invasive mycoses in England and Wales (1990–9). *Epidemiol Infect* 2001;126:397–414.
- Munster AM, Eurenus K, Katz RM, Canales L, Foley FD, Mortensen RF. Cell-mediated immunity after thermal injury. *Ann Surg* 1993;177(2):139–43.
- Cochran A, Morris SE, Edelman LS, Saffle JR. Systemic *Candida* infection in burns patients: a case control study of management patterns and outcomes. *Surg Infect (Larchmt)* 2002;3(4):367–74.
- Hassan IA, Critten P, Isalska B, Denning DW. Audit of laboratory mycology services for the management of patients with fungal infections in the northwest of England. *J Clin Pathol* 2006;59:759–63.

24. Dromer F, Mathoulin-Pelissier S, Launary O, Lortholary O, the French Cryptococcosis Study Group. Determinants of disease presentation and outcome during cryptococcosis: the CryptoA/D study. *PLoS Med* 2007;4(1):e21.
25. Barnes RA, Denning DW, Evans EG, Hay RJ, Kibbler CC, Prentice AG, et al. Fungal infections: a survey of laboratory services for the diagnosis and treatment. *Commun Dis Rep CDR Rev* 1996;5:R69–75.
26. Mirza SA, Phelan M, Rimland D, Graviss E, Hamill R, Brant ME, et al. The changing epidemiology of cryptococcosis: an update from population-based active surveillance in 2 large metropolitan areas, 1992–2000. *Clin Infect Dis* 2003;36(6):789–94.
27. Health Protection Agency. Fungal diseases in the UK – the current provision of support for diagnosis and treatment: assessment and proposed network solution In: Report of a working group of the HPA advisory committee for fungal infections and superficial parasites. Health Protection Agency. Available via DIALOG: <http://hpa.org.uk/publications/2006/fungal_disease/fungal_disease_report_06.pdf>; 2006 [cited 13 November 2007].
28. Greene RE, Schlamm HT, Oestmann JW, Stark P, Durand C, Lortholary O, et al. Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. *Clin Infect Dis* 2007;44(3):373–9.