



ECMM Excellence Centers Quality Audit

Person in charge	
Department	
Head of Department	
1st ECMM inspector	
2nd ECMM inspector	
Inspection date	

Application for*		Decision/Recommendation*	
Blue Status (ECMM Fungal Center)	<input type="checkbox"/>	Blue Status (ECMM Fungal Center)	<input type="checkbox"/>
Silver Status (ECMM Excellence Center)	<input type="checkbox"/>	Silver Status (ECMM Excellence Center)	<input type="checkbox"/>
Gold Status (ECMM Excellence Center)	<input type="checkbox"/>	Gold Status (ECMM Excellence Center)	<input type="checkbox"/>
Diamond Status (ECMM Excellence Center)	<input type="checkbox"/>	Diamond Status (ECMM Excellence Center)	<input type="checkbox"/>

*Requirements are given in Appendix 1

1st ECMM Inspector
2nd ECMM Inspector
Applicant

	Yes	No	Comments
Panel 1: Microbiology best practice recommendations which should be available			
Microscopy and stains			
<ul style="list-style-type: none"> Fluids from usually sterile sites and bronchoalveolar lavage (BAL) from patients with suspected infection should be examined by direct microscopy with suitable methods for fungal detection. 			
<ul style="list-style-type: none"> Optical brighteners are used for microscopy on all samples from patients with suspicion of invasive fungal infection. 			
<ul style="list-style-type: none"> Direct fluorescent-antibody staining, PCR, or both is available for patients with suspected pneumocystis infection in induced sputum or BALs. 			
<ul style="list-style-type: none"> India ink staining of cerebrospinal fluid and/or <i>Cryptococcus</i> capsule antigen (CRAG) testing is available. 			
Culture and identification			
<ul style="list-style-type: none"> Bronchoscopy fluids and other specimens are cultured in suitable media at different temperatures to support fungal growth. 			
<ul style="list-style-type: none"> All significant clinical isolates of <i>Aspergillus</i> & other fungi from patients who receive antifungal treatment are identified to species complex level. 			
<ul style="list-style-type: none"> All fungi (yeasts and moulds) obtained from sterile sites, including blood and continuous ambulatory peritoneal dialysis fluids, and intravenous line tips should be identified to species complex level. In addition susceptibility tested with a reference method should be done (EUCAST/CLSI). In severe immunosuppressed patients, bronchoscopy fluid and paranasal sinus material should be regarded as sterile in this context for all fungi except <i>Candida</i> spp. 			
<ul style="list-style-type: none"> If direct microscopy is positive for fungal mycelia all cultured fungi are potentially relevant. All <i>Aspergillus</i> isolates from patients with allergic bronchopulmonary aspergillosis, aspergilloma, chronic aspergillosis or acute invasive aspergillosis should be susceptibility tested for antifungals used for treatment if therapy is initiated; isolates should be stored for at least 6 months in case additional susceptibility testing is needed at a later date. 			
<ul style="list-style-type: none"> In immunosuppressed patients, fungi cultured from vascular-device tips are identified to species level and reported. 			
Respiratory specimens			
<ul style="list-style-type: none"> BAL fluid is recommended for diagnosis of pulmonary invasive fungal disease in immunosuppressed patients or with suspicion of suffering from invasive aspergillosis or invasive fungal infection. 			

	Yes	No	Comments
<ul style="list-style-type: none"> Respiratory and fluid samples should be concentrated by centrifugation at 1000 g or greater for at least 10 min or with the cytocentrifuge before microscopy. Respiratory samples should be liquified, especially for detection of <i>Pneumocystis jirovecii</i>. 			
<ul style="list-style-type: none"> Isolation of <i>Aspergillus</i> spp from respiratory samples: the laboratory provides interpretative comments according to patient risk group and likelihood of invasive, chronic, or allergic disease. 			
<ul style="list-style-type: none"> Sputum samples could be obtained for detection of respiratory fungi, especially in chronic cases of aspergillosis. 			
Cerebrospinal fluid (CSF) specimens			
<ul style="list-style-type: none"> All CSF specimens that are from patients with suspicion of cryptococcal meningitis (e.g. immunocompromised patients, patients with sarcoidosis or cancer, or who show abnormal concentrations of glucose, protein, or leucocytes without an adequate explanation) should be cultured and antigen tested for <i>Cryptococcus neoformans</i>; all bacterial plates should be incubated for a minimum of 5 days and fungal media incubated at 30°C for up to 28 days. 			
Fungal serological and molecular testing			
<ul style="list-style-type: none"> Serum samples from immunocompromised patients with presentations consistent with cryptococcal meningitis for whom a CSF specimen is not available (eg, cases in which lumbar puncture is contraindicated) should be tested for <i>Cryptococcus</i> spp antigen (CRAG). 			
<ul style="list-style-type: none"> Galactomannan screening of serum (two times per week) from patients with haematological malignancies at high risk of invasive aspergillosis should be considered in those not receiving mould-active prophylaxis. 			
<ul style="list-style-type: none"> Galactomannan testing of BAL from patients at high risk of invasive aspergillosis should be considered, although the current OD index cut-off of 0.5 might change. 			
<ul style="list-style-type: none"> β-D-glucan screening of serum from patients at high risk of invasive fungal disease could be considered; a negative result has a high negative predictive value, enabling invasive fungal disease to be excluded. 			
<ul style="list-style-type: none"> PCR screening of serum for <i>Aspergillus</i> from patients at high risk of invasive fungal disease could be considered; a negative result has a high negative predictive value, enabling invasive fungal disease to be excluded. 			
<ul style="list-style-type: none"> Combination testing with <i>Aspergillus</i> PCR plus another antigen test improves the positive and negative predictive values and diagnosis of invasive fungal disease. 			

	Yes	No	Comments
<ul style="list-style-type: none"> • PCR testing of biopsy samples should be considered in case fungal hyphae are detected but culture remains negative. 			
<ul style="list-style-type: none"> • Patients with pulmonary cavities of uncertain cause (with or without an aspergilloma) should have serum samples tested for antibodies to <i>Aspergillus</i> (IgG). 			
<ul style="list-style-type: none"> • Patients with suspected allergic bronchopulmonary aspergillosis should have serum samples tested for total IgE and <i>Aspergillus</i>-specific IgE. 			
Antifungal drug-susceptibility testing			
<ul style="list-style-type: none"> • Isolates of <i>Candida</i> spp and yeasts from sterile sites, or from patients not responding to therapy at a minimum should have their susceptibility tested against a standard panel of antimycotic drugs or the specific drug given. 			
<ul style="list-style-type: none"> • Significant clinical isolates of <i>Aspergillus</i> species should have their susceptibility tested against antifungal agents used. 			
<ul style="list-style-type: none"> • Reporting MIC data should include whether the values given display epidemiological (ECOFFs) or clinical breakpoints; there is need to underline that ECOFFs divide the wild type (WT) and non-wild type (NWT) population; NWT harbour one or more resistance mechanisms but, depending on the values of the clinical breakpoints, WT and NWT fungi may or may not respond clinically to treatment with the agent. 			
Therapeutic drug monitoring			
<ul style="list-style-type: none"> • Therapeutic drug monitoring of itraconazole, voriconazole, and posaconazole (oral solution only) is usually needed. Specifically, voriconazole monitoring is needed in most patients, and certainly in children, including repeat monitoring after dose changes and shift from intravenous to oral treatment; dose optimization during long-term therapy needs such monitoring. 			
<ul style="list-style-type: none"> • Flucytosine serum level monitoring is recommended for all patients receiving treatment. 			
Clinical requests and reporting			
<ul style="list-style-type: none"> • Background information regarding the patients' immune status should be available for any interpretation of the results obtained. 			
<ul style="list-style-type: none"> • All intravascular devices should be removed promptly if clinically feasible after diagnosis of candidaemia irrespective of the species identified. 			
<ul style="list-style-type: none"> • All new fungaemia, positive results of microscopy on sterile tissues or fluids, and positive cryptococcal antigen and galactomannan results should be communicated by laboratory staff to clinicians within 2 h of their availability. 			

Panel 2: Histopathology best practice recommendations which should be available*

Specialized stains			
Specialized stains should be done in parallel with standard stains if mycosis or another infection is to be assessed or excluded.			
<ul style="list-style-type: none"> Standard stain: haematoxylin and eosin (H&E) on histopathology slides; Giemsa or Papanicolaou on smears. 			
<ul style="list-style-type: none"> Triple set of stains: Ziehl–Neelsen stain for acid-fast organisms; Gram stain for bacteria, fungi, and others; Grocott silver stain, or periodic acid–Schiff, Fontana-Masson to highlight fungi. 			
Reporting of results			
Report fungal morphology (yeast or hyphae), including the following:			
<ul style="list-style-type: none"> Whether a yeast is small, medium, or large. 			
<ul style="list-style-type: none"> Whether a yeast has cross walls or septa (i.e., is splitting rather than budding). 			
<ul style="list-style-type: none"> Whether a hyphal form has usual width, or has a dilated, bizarre shape, how the fungus branches (<i>Aspergillus</i> like or not). 			
<ul style="list-style-type: none"> Whether H&E-stained fungi are pigmented and brown or are unpigmented and colourless or pale blue. 			
Positive results should be telephoned to clinicians immediately. Review of the stains by a mycologist is encouraged in case of a positive histology.			

Panel 3: Radiology best practice recommendations which should be available

<p>Patients with leukaemia, and patients who have undergone haemopoietic stem cell or solid organ transplantation</p> <p>All patients with acute leukaemia or another hematological malignancy and patients who have undergone haemopoietic stem cell transplantation, who are, or who have been, profoundly neutropenic (<500 neutrophils/μL) with any of the following should have a high-resolution (or spiral) or, preferably, multidetector CT scan of the entire thorax within 48 h, with immediate consultant review:</p>			
<ul style="list-style-type: none"> a new cough, chest pain, or haemoptysis 			
<ul style="list-style-type: none"> an abnormal chest radiograph 			
<ul style="list-style-type: none"> a new positive culture of an <i>Aspergillus</i> spp or other mould from any site 			
<ul style="list-style-type: none"> microscopic evidence of hyphae in any invasive sample 			
<ul style="list-style-type: none"> unresolved temperature under antibiotics 			
<ul style="list-style-type: none"> positive fungal biomarkers (i.e., galactomannan, β-D glucan, PCR) 			

All solid organ transplant recipients who test positive by microscopy, PCR, galactomannan, or culture of <i>Aspergillus</i> spp or other mould should have a CT scan of the chest (as above) within 48 h.			
Immunocompromised patients with new neurological features All immunocompromised patients with new neurological features (e.g., change in mental status, seizure, stroke, or persistent headache) or possible or proven meningitis should have MRI of the brain within 48 h (or if not possible, a contrast-enhanced CT scan, but not a non-enhanced CT scan).			
Suspected invasive fungal sinus infection All patients with suspected invasive fungal paranasal sinus infection receive a non-contrast CT scan within 48 h.			
Suspected disseminated fungal infection Patients undergoing investigation for disseminated fungal infection should have an MR or dual-phase CT scan of the abdomen.			
A low threshold for repeat scanning in patients with suspected cerebral and hepatosplenic fungal infection is in place.			
Suspected pneumocystis infection in patients without HIV In patients not infected with HIV and possible <i>Pneumocystis</i> pneumonia, a CT scan of the chest should be made for differential diagnoses, in combination with respiratory sample testing for <i>Pneumocystis jirovecii</i> .			
Participation in external quality control programmes for identification and antifungal susceptibility testing of fungi with good performance.			
Panel 4: Clinical best practice recommendations which should be available			
Treatment infrastructure			
<ul style="list-style-type: none"> • Access to all antifungal drug classes (incl. azoles, echinocandins, liposomal or lipid complex amphotericin B). 			
<ul style="list-style-type: none"> • Access to experienced thoracic, visceral and neurosurgery for diagnosis and treatment of IFD. 			
<ul style="list-style-type: none"> • Access to a second level ICU. 			
Diagnostic infrastructure			
Access to timely diagnostic intervention.			
<ul style="list-style-type: none"> • CT scanning within 24 hours. 			
<ul style="list-style-type: none"> • CT guided biopsy within 24-72 hours. 			
<ul style="list-style-type: none"> • MRI scanning within 24 hours. 			
<ul style="list-style-type: none"> • Bronchoscopy within 24-48 hours. 			

Research infrastructure			
• Patient enrolment in clinical trials.			
• Participation in registry studies.			
Experienced in and currently actively consulting in IFD and willing to accept			
• National patient referrals and to consult physicians from external centers.			
• Consultation from other ECMM EC.			
<i>Panel 5: Publishing, teaching, education, and others</i>			
• Active publishing in the field of IFD.			
• Active teaching and lecturing locally and nationally.			
• Networking and multidisciplinary sessions within the hospital.			
• Presence of a multidisciplinary group within the hospital being involved in managing fungal infections (i.e., ID, Clinical Mycologist, Clinical pharmacologist, ...) and /or antifungal stewardship.			
<i>Panel 6: Clinical and epidemiological studies</i>			
• Collaboration and networking with other appointed ECMM EC.			
• Active support of studies endorsed by ECMM.			
• Studies the applicant currently contribute to.			

Comments:

Appendix 1 - Requirements

The audit takes place by collecting data on how laboratory diagnosis is made and on how clinical management of invasive fungal infections is effectively executed.

As a basis of the laboratory audit, the best practice recommendations for the diagnosis of serious fungal diseases will be used (Schelenz S et al. Lancet Infect Dis. 2015;15:461-474, Ullmann AJ et al. CMI 2018;24:e1-e38, Cuenca-Estrella M et al. CMI 2012;18:9-18, Chen SCA et al. Lancet Infect Dis. 2021;21:e375-e386).

The minimum requirements for the **Blue Status** (ECMM Fungal Centers, possibly ECMM Excellence Center candidates) for laboratories consist of:

- Identification of medical important yeasts and moulds
- Susceptibility testing on yeasts and moulds according to standard procedures
- Performance of antigen ELISA for *Aspergillus* or equivalent assay
- Cryptococcal antigen test

The clinical minimum requirements for the **Blue Status** in part depend on the type of patients cared for.

- Timely CT scan in immunosuppressed patients with suspected pneumonia
- Timely CT or MRI scan in immunocompromised patients with suspected brain infection
- Timely bronchoscopy and BAL
- Access to azoles, amphotericin B, and an echinocandin
- Access to appropriate surgery
- Access to second level ICU

Silver Status (laboratory or clinical): Excellence in either laboratory mycology **or** clinical mycology. 2/3 of the practice recommendations according to the audit plan should be implemented.

Gold Status: Excellence in both, laboratory mycology **and** clinical mycology.

Diamond Status: Gold Status **and** participation in ECMM endorsed clinical or epidemiological studies.

Applicants should send the audit plan to the auditors two weeks before the audit takes place.