Clinical Microbiology and Infection

Executive Summary of the 2017 ESCMID-ECMM Guideline for the Diagnosis and Management of Aspergillus Disease

Journal:	*Clinical Microbiology and Infection*
Manuscript ID	CLM-17-12576
Article Type:	Supplement Article
Date Submitted by the Author:	29-Sep-2017
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Key Words:	Haematology, Transplantation, Invasive Fungal Infection, Treatment, Aspergillosis, Diagnosis
Abstract:	The European Society for Clinical Microbiology and Infectious Diseases, the European Confederation of Medical Mycology and the European Respiratory Society Joint Clinical Guidelines focus on diagnosis and management of major forms of aspergillosis. Only a few of the numerous recommendations can be summarized here. The performance of a chest computed tomographic scan as well as a bronchoscopy with bronchoalveolar lavage (BAL) in patients with suspicion of pulmonary invasive aspergillosis (IA) is strongly recommended. For diagnosis, direct microscopy preferably using optical brighteners, histopathology and culture are strongly recommended. Serum and BAL galactomannan is recommended as accurate marker for the diagnosis of IA. PCR should be considered in conjunction with other diagnostic tests. Pathogen identification to species level by molecular methods is strongly recommended for all clinical relevant Aspergillus isolates; antifungal susceptibility testing should be done in patients unresponsive to treatment, or in regions with a high prevalence of azole resistance. Isavuconazole and voriconazole are the preferred agents for first line treatment of pulmonary IA, followed by liposomal amphotericin B. In refractory disease we strongly recommend a personalized approach considering therapeutic drug monitoring (TDM), reversal of predisposing factors, switching drug class and surgical intervention. Primary prophylaxis with posaconazole is strongly recommended in patients with haematological malignancy, secondary prophylaxis in high risk patients. TDM is strongly recommended for patients receiving posaconazole suspension or voriconazole for IA treatment. Combinations of antifungals as primary treatment options are not recommended. We strongly recommend treatment duration based on clinical improvement, degree of immunosuppression and response on imaging.

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Acknowledgement: Professor William Hope was a member of the TDM group, however, he stepped down during the process of guideline development due to his new post as guideline director of

ESCMID to avoid any conflicts of interest. His contributions were very much appreciated to the entry guideline group. We are thankful for his help.

Funding: European Society of Clinical Microbiology and Infectious Diseases (ESCMID), European Confederation of Medical Mycology (ECMM) and European Respiratory Society (ERS)

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Abstract

The European Society for Clinical Microbiology and Infectious Diseases, the European Confederation of Medical Mycology and the European Respiratory Society Joint Clinical Guidelines focus on diagnosis and management of major forms of aspergillosis. Only a few of the numerous recommendations can be summarized here. The performance of a chest computed tomographic scan as well as a bronchoscopy with bronchoalveolar lavage (BAL) in patients with suspicion of pulmonary invasive aspergillosis (IA) is strongly recommended. For diagnosis, direct microscopy preferably using optical brighteners, histopathology and culture are strongly recommended. Serum and BAL galactomannan is recommended as accurate marker for the diagnosis of IA. PCR should be considered in conjunction with other diagnostic tests. Pathogen identification to species level by molecular methods is strongly recommended for all clinical relevant *Aspergillus* isolates; antifungal susceptibility testing should be done in patients unresponsive to treatment, or in regions with a high prevalence of azole resistance. Isavuconazole and voriconazole are the preferred agents for first line treatment of pulmonary IA, followed by liposomal amphotericin B. In refractory disease we strongly recommend a personalized approach considering therapeutic drug monitoring (TDM), reversal of predisposing factors, switching drug class and surgical intervention. Primary prophylaxis with posaconazole is strongly recommended in patients with haematological malignancy, secondary prophylaxis in high risk patients. TDM is strongly recommended for patients receiving posaconazole suspension or voriconazole for IA treatment. Combinations of antifungals as primary treatment options are not recommended. We strongly recommend treatment duration based on clinical improvement, degree of immunosuppression and response on imaging.

Introduction

This is the third fungal diagnosis and management clinical guideline published in cooperation with various European scientific societies. This part of the guideline regarding invasive and chronic aspergillosis, despite its lengthiness, is a condensation of all the recommendations made by the group and are put into tables for easier and faster reading. More details on how the recommendations were arrived at will follow in a supplementary publication. This *Aspergillus* guideline will follow the style of other guidelines by including diagnostic and therapeutic guidance. Guidelines on this topic have been published previously by other scientific groups and all follow the common goal to provide clinicians with best guidance in their everyday working environment. Our goal was to provide a comprehensive European guideline focusing on the life-threatening diseases caused by *Aspergillus* spp.

Methods

Author panel recruitment and organisation is similar as done previously [1]. In brief, experts in the field were defined and approved by the three societies ESCMID, ECMM, and ERS. The total of 54 authors were grouped into their special fields of expertise. Subgroup coordinators were responsible for the first draft of recommendations. There were two face-to-face meetings followed by numerous electronic exchanges. Some of the first recommendations were presented at ECCMID 2014. This summary was reviewed and approved by all participating authors and sent to the ESCMID guideline director for public review. Then the final version was submitted to the Journal of Clinical Microbiology and Infection for additional peer review and subsequent publication. Only the rationale of the chronic pulmonary aspergillosis guideline was published ahead of time [2].

Questions were predefined and modified were appropriate and the strength of recommendation and quality of evidence was slightly modified (Table 1).

Summary of Recommendations

Diagnostic Procedures

Early diagnosis of invasive aspergillosis (IA) is a challenge and should be based on the integration of clinical, radiological and microbiological data.

In patients at risk for IA with fever of unknown origin or clinical symptoms of lower respiratory tract infection who remain febrile despite broad-spectrum antibacterial treatment, thin-section chest computed tomography (multidetector (MDCT), multislice (MSCT), spiral CT, high resolution CT) at optimized dose (according to ALARA (As Low As Reasonably Achievable) principle) is the imaging modality of choice **(AII)** [3-13]. Pulmonary CT angiography may be of interest in the early diagnosis of IA by depicting directly vessel occlusion at the level of a suspicious fungal lesion with a potential high negative predictive value regarding imaging evaluation [14-16], and is required in case of haemoptysis **(AII).** In selected patients where CT is not wanted or feasible, MRI of the lungs may represent an alternative imaging to thin-section MSCT [17-22], PET-CT being of modest interest in the diagnostics of IA [23, 24].

No CT scanning technique is 100% sensitive or specific for IPA [25-27]: Classical CT findings of angioinvasive aspergillosis including macronodule(s) >1 cm, which may be surrounded by a halo of ground-glass attenuation (halo sign, early phase, inconstant) [26, 28-30], pleural based wedge-shaped areas of consolidation [31], alveolar consolidations [26, 32, 33], masses (especially in SOT recipients) [5, 28], internal low attenuation[34], reverse halo sign [35], cavity or air-crescent sign (delayed finding), ground glass opacities and pleural effusion [7, 25, 36]. Bronchoinvasive forms may appear as tracheal or bronchial wall thickening, centrilobular nodules with tree in bud appearance [4] in a patchy distribution, predominant peribronchial areas of consolidation [37] or bronchopneumonia [36].

Other diagnostic procedures include early bronchoalveolar lavage (BAL) **(AII)** [38-44], guided by CT-findings [45, 46], and less frequently CT-guided transthoracic biopsies, video-assisted thoracoscopic surgery (VATS), open lung biopsies, transbronchial biopsies [18, 47-59] or convex endobronchial

ultrasound transbronchial needle aspiration (EBUS-TBNA), the latter technique appearing to be a promising procedure in this setting [60-62].

Moreover, according to clinical symptoms, paranasal CT, CT or MRI of the CNS as well as abdominal CT may also be required (Table 2). In particular, findings of sinusitis with bone erosion may be observed, intracranial and/or intraorbital extension of the disease being best evaluated by MRI [63-65]. In the brain, due to direct spread from paranasal sinuses or haematogenous dissemination, meningeal enhancement or empyema, cerebral abscess, mycotic aneurysms as well as haemorrhagic lesions and rarely stroke may be seen (Table 2) [66-69].

Both microscopy and culture should be attempted on appropriate specimens from patients at risk for IA with a priority for culture in case insufficient material is available **(AII).** Demonstrating tissue invasion by hyphae through microscopic examination of biopsy or autopsy material provides a diagnosis of proven invasive fungal infection. However, the sensitivity of microscopy for IA is 50% at best. Specimens may be examined as a wet mount preparation with or without the addition of 10% potassium hydroxide. Fluorescent dyes such as Calcofluor white or Blankophor have the advantages of relatively high sensitivity, rapid turnaround time, and broad applicability but are not specific **(AII).** Gomori's methenamine silver stain (GMS) and periodic acid-Schiff (PAS) can be applied to histological sections and smears and should be conducted in all cases in which IA is considered a diagnostic possibility (Table 3). Respiratory secretions from patients with suspected aspergillosis must be processed rapidly for culture to prevent overgrowth by bacteria and yeasts. To achieve optimal recovery of *Aspergillus* from BAL fluid, centrifugation of the sample is advised with investigation of the sediment **(AIII).** It is recommended that high volume untreated sputum and BAL cultures are performed as opposed to culturing small volumes of digested, liquefied samples [70] (Table 4). Specific media for fungal culture are recommended (Table 5). Galactomannan (GM) detection in fluids (especially BAL) is more sensitive than culture for diagnosis of IA. GM is reported as optical density index (ODI). In serum samples an ODI cut-off of 0.5 (currently under review by the EORTC/MSG-ERC) results in high sensitivity in haematological patients in the absence of mould-active

prophylaxis **(AI)** (Table 6). Serial screening for GM in prolonged neutropenia and in allogeneic stem cell transplantation recipients during the early engraftment phase has an excellent sensitivity and negative predictive value (NPV) for IA **(AII)** [71]. It is not recommended in patients on mould-active prophylaxis [72]. Sensitivity of serum GM testing is significantly lower in non-neutropenic versus neutropenic patients [73]. Decrease of the GM index during the first two weeks of antifungal therapy is a reliable predictor of a satisfactory response in cancer patients [74]. GM detection in BAL specimens has an excellent performance with evidence that GM index of 0.5–1.0 has decreased predictive values compared with results of >1.0 [75] **(AII)** (Table 7). (1-3)-β-D-glucan (BDG) is a constituent of the cell wall of many species and genera of fungi and is released into body fluids in association with fungal infection. A limited role is given for the exclusive testing of the BDG in diagnosing IA **(BII)** (Table 8), however, the combination with GM or PCR improves specific detection[76]. The *Aspergillus* lateral flow LFD assay can be performed on serum and on BAL samples. However, at the time of writing this test kit is not yet commercially available. According to the evidence so far, the recommendation to perform the LFD assay on BAL samples is moderate **(CIII)** [77] (Table 9). *Aspergillus* PCR has been applied to blood and BAL fluid, and is currently being considered by the EORTC / MSG-ERC for inclusion into the definitions of invasive fungal disease. For both sample types, a combination with other biomarkers increases the likelihood of IA [78, 79]. The performance of serum PCR is not significantly different from that of whole blood [80]. Prospective screening of high-risk haematological patients by a combination of GM and PCR improves the diagnostic accuracy and is associated with an earlier diagnosis [81, 82] (Table 10 and 11).

Molecular detection of fungi in biopsy samples is more sensitive on hyphal positive samples compared to hyphal negative samples **(AII)** (Table 12). Recommendations for storage of original samples and isolates are given in table 13. Antibody detection test are only marginally supported for the diagnosis of IA **(CII)** (Table 14).

Challenges in resistance development

Resistance to antifungal agents is an increasing problem in *Aspergillus* diseases [83, 84]. *Aspergillus* species can be intrinsically resistant to polyenes and azoles [85], or may acquire resistance following exposure to azole compounds [86]. Resistance may develop during azole therapy, and mainly occurs in patients with chronic (cavitary) pulmonary aspergillosis (CPA), especially those with aspergilloma [87, 88]. Individual *Aspergillus* colonies from a single specimen may harbour different resistance profiles [89]. Resistance may also develop through exposure to azole fungicides in the environment [90-93]. As resistant spores are present in ambient air, patients may present with azole-resistant *Aspergillus* disease without previous azole therapy [94, 95]. Acquired resistance to azoles is mainly found in *Aspergillus fumigatus* and is reported globally [83, 84, 96-99] (Table 15).

In clinical laboratories, species identification to complex level is recommended for all clinically significant isolates **(BIII)**. Some species are intrinsically resistant to either azoles or amphotericin B (AmB) (Table 16 and 17).

***Aspergillus fumigatus* species complex**

It is recommended that the MIC should be determined for all clinically relevant *Aspergillus* isolates **(AIII)** (Table 15), specifically if grown from patients previously exposed to or on antifungal therapy. If MIC-testing is not available, routine agar screening can be used to detect azole resistance, but there are no validated assays (Table 16). If growth is observed on the screening agar, the isolate should be referred to a mycology reference laboratory for MIC testing. Periodic MIC testing of at least 100 *A. fumigatus* is recommended for determination of local epidemiology of azole resistance (Table 15). Clinical breakpoints for interpretation of azole and AmB MICs against *Aspergillus* are currently available for European Committee on Antimicrobial Susceptibility Testing (EUCAST) microdilution method but remain undetermined for Clinical & Laboratory Standards Institute (CLSI) methodology. Accordingly, EUCAST **(AII)** or CLSI broth microdilution methods **(BII)** can be used for determination of routine MICs for clinical guidance and for epidemiological resistance surveillance **(AII).** Low to moderate correlation between Etest® and CLSI method has been reported, and in-house validation

and confirmation by reference method is warranted if Etest™ is used. Both itraconazole and voriconazole **(AII)** should be tested to ensure detection of the voriconazole-resistance mutation TR_{46}/Y121F/T289A (Table 3). Posaconazole resistance without itraconazole resistance has not been reported (Table 17). EUCAST **(BIII)** or CLSI broth microdilution methods **(CIII)** can be used to determine AmB MICs, but a correlation between MIC and clinical outcome is generally lacking, with exception of *A. terreus* and *A. flavus* (Table 17).

Voriconazole and isavuconazole are recommended for the treatment of IA due to species showing high AmB MICs (Table 18). Liposomal AmB (L-AmB) or AmB lipid complex (ABLC) are recommended for species with intrinsic high azole MICs (Table 19 and 20). In aspergillosis due to *A. fumigatus*, voriconazole is recommended if the isolate is voriconazole susceptible (EUCAST MIC ≤1 mg/l) **(AI).** If resistant (voriconazole MIC >2 mg/l), L-AmB therapy is recommended **(AII_u).** It is unknown if patients infected with *A. fumigatus* with voriconazole MIC 2 mg/l (intermediate), respond less well to voriconazole monotherapy. These patients may have an increased probability of failing voriconazole monotherapy, and combination therapy with an echinocandin or L-AmB monotherapy should be considered for invasive disease **(AIII)** (Table 20). In azole-resistant chronic pulmonary aspergillosis (CPA), L-AmB or micafungin can be considered **(BII)** if surgical intervention is precluded [2]. Inhaled AmB is an option for azole-resistant airway aspergillosis. In settings with environmental azole resistance, no change to the primary regimen for IA is recommended when resistance rates are <10% **(AIII).** If azole resistance rates are >10%, primary therapy with voriconazole plus echinocandin **(BIII)** or L-AmB **(BIII)** is recommended.

Therapeutic drug monitoring (TDM)

Patients with IA often have multiple conditions associated with their underlying disease and its treatment that affects the absorption, distribution, metabolism, and clearance of antifungal medications [100]. As a result, standardized dosing recommendations for antifungals used in the prevention or treatment of IA may not achieve effective or safe drug exposures in all patients.

Moreover, a subset of patients with severe infections or difficult to treat sites (e.g. CNS) or infections caused by *Aspergillus* spp. with elevated MICs may require higher drug exposures. Therapeutic drug monitoring (TDM) is often the most direct laboratory approach for identifying patients at jeopardy for treatment failure or toxicity because of inadequate or excessive drug exposures, and can be used to fine-tune antifungal dosing to improve the probability of optimal outcomes (Table 21).

For itraconazole, a serum trough of 0.5-4 mg/L (measured by HPLC) is recommended for prophylaxis **(AII [efficacy], BII [safety])** and a trough of 1-4 mg/L is recommended during the treatment of IA **(AII [efficacy], BII [safety])** [101-106]. Itraconazole has an active metabolite, OH-itraconazole that is present in similar (1:1) concentrations as the parent itraconazole compound when patients are at pharmacokinetic steady state. OH-itraconazole concentrations may be reported separately when samples are analysed by HPLC or LC/MS/MS, but will included in the overall report of "itraconazole" concentrations if samples are analysed by bioassay [107, 108]. Therefore, the target range for itraconazole is higher when reported by bioassay (i.e. 3-17 mg/L) but may vary by lab depending on the reference standards used. Samples should be acquired within 5-7 days of starting therapy, and repeated as clinically indicated if there are changes in the patient's clinical condition, concomitant medications, or suspected toxicity (Table 22). Steady-state concentrations can often be predicted from earlier (non-steady) state samples through pharmacokinetic models or computerized dosage-assistance. In centres where these tools are available, sampling before day 5-7 may be preferable. Repeat TDM is recommended the following week to confirm the patient remains in the therapeutic range.

A plasma trough concentration of 1-6 mg/L is considered adequate for most patients receiving voriconazole prophylaxis or treatment **(AII, safety and efficacy)** [109-114]. However, a trough of 2-6 mg/L **(AII, safety and efficacy)** is recommended in patients treated for severe infections (multifocal or disseminated disease, CNS infections, infection with pathogen with elevated MICs) [111, 112]. TDM is strongly recommended in paediatric patients due to the much higher rates of drug

elimination and potential for underdosing, especially with the lower voriconazole doses recommended in the past **(AII)** [115, 116]. Plasma levels should be monitored between 2-5 days after initiation of therapy, and ideally repeated the following week to confirm the patient remains in the therapeutic range. Repeated monitoring is indicated if there are changes in the patient's clinical condition, concomitant medications, or suspected toxicity (Table 23).

For patients receiving posaconazole suspension, a plasma trough of >0.7 mg/L is recommended during prophylaxis **(BII efficacy)** [117, 118]; and a trough of >1 mg/L is recommended if the patient is receiving treatment for suspected or documented IA **(AII efficacy)** [119]. Currently, no studies have defined an upper plasma target that is associated with toxicity, although pharmacokinetic studies supporting the registration of the new posaconazole tablet formulation with the EMA used a provisional cut-off of 3.75 mg/L [120-122]. Posaconazole plasma trough levels should be monitored on day 5 of therapy or soon thereafter, and repeated as clinically indicated.

For most patients prescribed posaconazole, we recommend using the newer tablet formulation (or intravenous formulation if indicated) rather than the suspension **(AII),** as tablets are more likely to consistently achieve target plasma levels and are less affected by GI-dependent drug interactions [120]. Currently, there is limited evidence to suggest that all patients receiving posaconazole tablets or IV formulation for prophylaxis require routine TDM**;** however, our opinion is that when treating suspected or documented *Aspergillus* infections, TDM could still be useful if the pathogen has elevated MICs, is unresponsive to treatment, or in the event of unexplained toxicity **(BIII).** Until further data are available, we recommend using TDM monitoring strategies and plasma trough targets as detailed above suggested for the suspension formulation (Table 22).

Although dose-response and plasma concentration-response relationships for isavuconazole have been reported in animal models, limited data are currently available to define a target through therapeutic range or support the need for routine TDM for this agent [123]. Our opinion is that TDM could still be useful in the clinical assessment or monitoring of patients receiving isavuconazole therapy **(CIII)** if patients are unresponsive to treatment, have unexpected toxicity, pharmacokinetic

drug-drug interactions, or if isavuconazole is being used to treat pathogens with elevated MICs or sanctuary sites such as the CNS. In the absence of well-defined therapeutic targets, documentation of a plasma trough in the range of 2-3 mg/L (mean concentration range from phase II/III clinical studies) after day 5 (including loading doses) suggests adequate drug exposure (Table 24).

In rare circumstances, flucytosine may be used in combination with other antifungals for the treatment of triazole-resistant *Aspergillus* spp. In this scenario, weekly measurement of peak serum concentrations 2 hours following an oral dose **(AII)** are needed to confirm that peak concentrations are 50-100 mg/L in order to reduce the risk of toxicity. Trough concentrations of 25-50 mg/mL are required for efficacy [124, 125].

IA in the paediatric population

Presenting symptoms, distributions and patterns of diseases and vulnerability to IA are similar between children and adults. However, differences exist in epidemiology and underlying conditions, usefulness of newer diagnostic tools, pharmacology of antifungal agents and evidence from interventional phase III studies. Recommendations for paediatric patients are based on efficacy in phase II and III trials in adults (corresponding to adult ESCMID recommendation), the availability of paediatric pharmacokinetic data, safety data and supportive efficacy data. In addition, regulatory approval is considered as well. Therapeutic drug monitoring is always recommended when mould-active azoles are used as prophylaxis or treatment.

Primary antifungal prophylaxis may be indicated in paediatric patients at 'high risk' for developing invasive fungal diseases, and specifically IA. A natural incidence rate of IFDs of ≥10% is usually considered as high risk. High-risk populations include children with de novo or recurrent leukaemia (e.g. AML, ALL depending on treatment protocol), bone marrow failure syndromes with profound and persistent neutropenia (e.g. MDS, VSAA), allogeneic HSCT recipients, patients with chronic granulomatous disease and those undergoing lung transplantation. For patients with haematological disorders, the mould-active oral azoles are the first choice to prevent IA in children, although both

itraconazole and posaconazole are not licensed for use in patients <18 years of age. Due to the lack of paediatric data, recommendations for lung and high-risk liver transplant patients correspond to those made for adults [126, 127]. Secondary prophylaxis to prevent recurrence of IA when risk factors are persisting is recommended with an antifungal targeted at the previous *Aspergillus* species, which caused the first episode (Table 26).

Diagnostic procedures used in children are not different from those used in adults but their performance may differ. Typical abnormalities (e.g. halo sign, air crescent sign) on CT-chest as described in adults are less common in children in which unspecific masses or infiltrates predominate [128-130]. The GMI test on blood and BAL samples has a similar sensitivity and specificity profile compared to adults [131-139]. The BDG test is not specific for *Aspergillus* and is not validated in children. Higher baseline levels are reported in healthy children and therefore the cut-off is yet unknown [140-144].

General management principles of IA are consistent with those in adults and include prompt initiation of antifungal therapy, control of predisposing conditions (e.g. reduction or discontinuation of glucocorticosteroids in immunosuppressed, administration of colony-stimulating factors in neutropenic patients), and surgical interventions on a case by case basis using a multidisciplinary approach. Voriconazole is recommended as the first line agent to treat IA in all paediatric patients except for neonates **(AIIt)**. L-AmB is first choice for neonates **(AIII)** and may replace voriconazole as first line treatment in areas or institutions with a high prevalence of azole-resistant *A. fumigatus*. Upon diagnosis of invasive pulmonary aspergillosis thorough evaluation for further sites of infection is required and should include the CNS. The optimal duration of therapy is determined by the resolution of all signs and symptoms and reversal of the underlying deficit in host defences. For salvage therapy and breakthrough infections, a switch to a different class of antifungals is recommended [104, 113, 119, 145-154] (Table 27).

If a fever-driven (empiric) strategy is used in at risk paediatric haematological patients, caspofungin or L-AmB are recommended until resolution of fever and neutropenia [155-157]. Treatment

recommendations for a diagnostic-driven (pre-emptive) strategy correspond to those made for targeted treatment [158-161].

Aspergillosis in haematological malignancies including haematopoietic stem cell transplantation

In patients treated for haematological diseases, prolonged severe neutropenia is the most important risk factor for the development of IA. T cell depleted grafts, glucocorticosteroids and other immune suppressive drugs have been identified as further risk factors for IA in the later course after HSCT, even in non-neutropenic patients [162]. In fact, up to two thirds of patients with IA diagnosed after allogeneic HSCT are not neutropenic [163], and the median time of diagnosis of IA after allogeneic HSCT is 82 days (range, 3 - 6542 days) [164].

Environment

Standards for the hospital environment in this patient population (adults and paediatric) requires special attention. Patients need to be segregated from construction or renovation **(AII$_h$)**, potted plants **(BII)**, and flowers in wards and in patients' rooms **(CIII)** [165-170]. Published data support the recommendation to accommodate patients in special hospital rooms with positive air pressure and HEPA filters **(BII)** or laminar airflow **(BII$_h$).** However, data were with historical controls, underpowered, or described by multivariate analysis describing high-risk situations for IA [171-174]. Protective masks for patients are proven not to be effective outside of the protected area **(CII)** [175], filters for water supply especially in showers are recommended **(BII)** [176-180]. No data are available to support the regular environmental air sampling to prevent infections. However, indoor sampling is advisable to monitor filter efficacy **(BIII)** [181, 182].

Treatment

Providing a definite diagnosis of IA is a continuously challenging endeavour for clinicians. The EORTC definitions are only designed for clinical studies. For clinical decision-making, these definitions could

have a deleterious outcome since confirmation of a proven or probable diagnosis would delay the start of therapy [183]. Any patient at risk considered by the responsible clinician as having IA should receive therapy **(AIII)** (Tables 28-29). A consensus statement was made regarding duration of therapy. Physicians should consider IV to oral switch in stable and PK-reliable patients. Treatment duration depends on clinical response and on immune reconstitution or recovery from graft-versus-host disease (GvHD). Good partial or complete remission (radiographic imaging) requires no clinical (by radiographic imaging: scarring allowed) or microbiological evidence of disease. The range of the duration of treatment (3 to >50 weeks) is huge and the evidence base to support any particular recommendation is weak [146, 149, 184, 185]. Close monitoring (e.g. radiographic imaging [186, 187] or, if applicable, biomarkers) is suggested once antifungal treatment is discontinued.

Additional adjunctive therapy such as the administration of G-CSF or G-CSF-primed granulocyte infusions (data mainly from paediatric populations) received only a weak supportive recommendation (CIII). In refractory cases, G-CSF (or IFNγ) has immunomodulatory effects [188-193]. No controlled trials have been performed and only anecdotal data with small numbers of patients exist. Persistent neutropenia is related with treatment failure, recovery from neutropenia enhances the efficacy of antifungal agents. A recent Cochrane review investigating the efficacy of granulocyte transfusions indicates no mortality difference for any kind of infection in patients with neutropenia [194].

Secondary Prophylaxis

A further consensus statement regards the use of secondary prophylaxis: Secondary prophylaxis is a treatment strategy to prevent recurrence of IA during a subsequent risk period of immunosuppression. Patients with a history of IA previously successfully treated with antifungals entering a subsequent risk period of immunosuppression, e.g. allogeneic HCT (early phase), chemotherapy resulting in severe neutropenia (i.e. <500/µL and at least for 7 days), acute GvHD >I°

or extensive chronic GvHD, or T-cell suppressing therapy, including steroids, are at risk. Agents for secondary prophylaxis are listed in Table 30.

Other Treatment Options: Primary Prophylaxis, Fever-driven (Empiric), and Diagnostic-driven (Pre-emptive) Therapy

Two published studies by Chamilos and Sinko describe a number of patients who succumbed with IA missed prior to death [195, 196]. Current diagnostic procedures are apparently not satisfactory. For this reason, patients known to be at high risk for IA receive primary prophylaxis, especially patients with profound and prolonged neutropenia or with active GVHD (Table 31).

As an alternative to prophylaxis, patients could receive the classical empirical administration of antifungal agents during fever refractory to broad-spectrum antibacterial agents. Empiric treatment is defined as a fever-driven treatment approach. Patients who would qualify for this approach are patients receiving induction or remission chemotherapy for acute leukaemia or MDS or conditioning chemotherapy for haematopoietic stem cell transplantation. Empiric antifungal treatment is expected to reduce morbidity [158, 159, 197-200] and mortality [201] (Table 32). In our consensus statement the duration of empiric antifungal treatment is set by the following rules: If the patient is afebrile and has no active infection or infiltrates, then antifungal therapy can be discontinued after recovery of leukocyte counts.

Pre-emptive treatment is defined as a diagnostic driven procedure. In most cases, it is defined by positive GM testing. However, (low-dose) chest CT with pulmonary infiltrates would apply as well. The use of ß -D-glucan and PCR testing as alternative biomarkers for galactomannan have considerable merit [202, 203], though ß-D-glucan is not specific for *Aspergillus* disease. Some authors wait for *Aspergillus*-associated typical radiological signs (including nodules, halo sign, wedge-shaped areas of consolidation, or air crescent signs) before starting antifungal treatment (agents recommended as in targeted treatment).

The guideline group does not provide any recommendation, which approach is the most appropriate since various backgrounds, histories, and epidemiology drive that decision, in a given centre. Basically, there remain two possible ways to manage or monitor a patient besides vital signs (e.g. fever). The two classical options are that 1) patient receives primary prophylaxis or 2) a patient receives no prophylaxis but needs monitoring of biomarkers. The guideline group appreciates that breakthrough fungal diseases may appear through either symptoms or a disease-identifying biomarker or imaging result. Figure 1 depicts a consensus algorithm for patient management if the minimum recommended diagnostic tests are positive or negative.

Therapy for refractory disease

Refractory IA is defined as progression of disease and should be differentiated from stable disease [204]. Patients with radiological evidence of progression and persisting elevated GM have a very high probability of treatment failure resulting in death. Assessment of response should use composite outcome parameters including clinical, radiological, and mycological criteria. Radiological progression following or closely preceding neutrophil recovery should be carefully evaluated and is not necessarily indicative of failure. Keeping this in mind, assessing response 2 weeks after treatment initiation generally allows predicting the response, especially recognizing oncoming failure [205]. In case of GM negative IA, early assessment of response may be trickier and could require a longer time of therapy. If failure ascertained, look for poor vascular supply (i.e. sinusitis requiring surgical treatment), microbiological confirmation is recommended since identification of the fungus at the species level is pivotal. If a viable organism is recovered, susceptibility testing is recommended, especially regarding azole resistance. On the other hand, azole concentration should be monitored as well (see chapters on resistance and therapeutic drug monitoring within this guideline) [28, 204, 206-214]. The choices of antifungal agents in refractory disease are listed in Table 33.

IA in adults without haematological malignancies (e.g. solid organ transplantation)

Approximately 43-80% of the cases of IA appear in patients without a haematological malignancy [42, 215-218], although these patients are rarely included in the seminal studies of antifungals [146, 149, 185]. The proportion of these patients is even increased when exposed to spore concentrations of >25 cfu/m^3 in hospital air [219-222]. The non-haematological populations at risk for IA include among others solid organ transplant recipients (SOT), patients treated with prolonged high dose glucocorticosteroids, or with other immunosuppressants, patients with advanced AIDS or neoplasia, COPD, liver failure, liver cirrhosis as well as critically ill patients requiring ICU admission [42, 215-217, 223-226]. These patients frequently do not fulfil the EORTC criteria. Confirmation of diagnosis may be delayed resulting in high mortality rates. At the same time drug-drug interactions and toxicity can occur more frequently compared to haematological patients [42]. Physicians need to be aware of the specific risk factors, clinical manifestations and management challenges in order to improve outcome.

In SOT recipients the average incidence of IA ranges from 0.1 to 3% [227, 228], with the highest risk in small bowel (11.6%) and lung (8.6%) transplant recipients, followed by patients receiving liver (4.7%), heart (4.0%), pancreas (3.4%), and kidney (1.3%) grafts [227-229]. Half the cases will occur in the first three months after transplantation, in patients with post-surgical risk factors. Late aspergillosis is more common in elderly recipients, and patients with pronounced immunosuppression due to rejection or post-transplant neoplasia or chronically impaired graft function [228, 230]. With the exception of lung transplantation, in which universal prophylaxis is still common, antifungal prophylaxis will target SOT recipients with additional risk factors [229]. Risk factors for early IA in all SOT recipients – Including heart transplants – comprise renal failure requiring replacement therapy, re-intervention, CMV disease, and high environmental exposure to mould spores [126, 229, 231, 232]. In liver transplantation, high MELD score, transplantation in fulminant hepatic failure, high intraoperative transfusion needs or re-transplantation are considered indications for post-surgical prophylaxis [233-241]. In lung transplant recipients, risk factors include previous respiratory tract colonization with *Aspergillus,* single lung transplant, CMV disease and

acquired hypogammaglobulinaemia [242-244]. In kidney transplantation risk factors include COPD, delayed graft function, bloodstream infection, and acute graft rejection [245] and an >1.25 mg/kg/day average dose of prednisone [246]. Finally, some polymorphisms in defence genes have also been suggested to increase risk in transplant recipients [247, 248].

The incidence of IA in HIV patients has decreased since the advent of new antiretroviral therapy (2.2 cases per 10,000/year), but mortality remains high (38%) [249]. IA typically appears in patients with low CD4 counts and associated conditions such as neutropenia, advanced cirrhosis, liver transplantation or glucocorticosteroid therapy [250-258]. As in other non-haematologic populations, EORTC criteria only detect half of the IA cases diagnosed among HIV-infected patients [249] and in a recent series of autopsies, only 12% of the patients had been diagnosed ante mortem [259] (Table 34).

IA may affect 0.3% of patients with liver cirrhosis [260]. Both acute liver failure and advanced cirrhosis, mainly alcoholic hepatitis treated with glucocorticosteroids, have been recognized as risk factors for IA [223, 261-263]. Low level of suspicion explains that 53% of the cases of IA in cirrhotic patients are only recognized post-mortem [264] and that liver disease is independently associated with IA-related mortality [217, 265].

IA has also been described in apparently immunocompetent patients in a critical condition as a complication of ARDS, COPD, pneumonia, burns, severe bacterial infection, surgery, and malnutrition. Incidence is 4-6/1,000 ICU admissions and the mortality is higher than 70% in most series [262, 266-268]. Glucocorticosteroid treatment was the major host factor [269, 270] and as in cirrhotic or HIV positive patients delayed diagnosis is common [271, 272]. COPD patients requiring glucocorticosteroids represent a group with especially high mortality [266, 273 , 274]. Risk factors include admission to ICU, chronic heart failure, and antibiotic treatment and, above all, the cumulative dose of glucocorticosteroids [273].

Classic pulmonary and CNS aspergillosis predominates in these populations, but disseminated disease, fulminant and atypical forms may occur [221, 231, 242, 268, 275-283]. The sensitivity of

most diagnostic methods is lower in non-haematological patients. Isolation of *Aspergillus* from respiratory cultures has a much lower positive predictive value so overdiagnosis has to be prevented [215, 284-288]. Regarding imaging findings, angioinvasive presentation included in the EORTC criteria is uncommon in this setting [289]. Airway invasive radiological presentation was present in 37% of heart transplant recipients and was associated with delayed diagnosis and poorer prognosis [231, 290]. In COPD and HIV-positive patients, the most common radiological presentation was an alveolar infiltrate [289, 291, 292]. Experience with biomarkers and PCR is still scarce in these populations, but the combination of at least two different methods appears to be the best diagnostic approach [293-301] (Table 35).

Despite no comparative studies of antifungal therapy in non-haematologic patients voriconazole remains the first option, since it has been related to reduced mortality [233, 302-304] (Table 36). Combination therapy is uncommon, although retrospective data was encouraging in SOT recipients [305]. The risks of drug-drug interactions and toxicity are very important in these populations and TDM is especially advisable [306-311]. In patients with liver insufficiency, L-AMB is usually the first therapeutic option. Antifungal resistance is not a common problem despite prophylaxis [312, 313], although some cases have been reported [314-316]. Finally, immune reconstitution syndrome may occur after therapy initiation [317].

Most lung recipients receive antifungal prophylaxis. Targeted prophylaxis is preferred in the remaining SOT with risk factors [126, 229, 318-321]. However, significant variation in practice has been noted [238, 320, 322, 323]. In order to avoid drug-drug interactions and toxicity, echinocandins or inhaled amphotericin are preferentially used [324-327], although voriconazole has also demonstrated its efficacy and safety in this setting [234, 237, 328-330]. Duration of prophylaxis is adjusted to the presence of risk factors and, with the exception of lung recipients, is usually limited tor 3-4 weeks [232] (Table 37).

Chronic pulmonary aspergillosis (CPA)

CPA is an indolent destructive disease of the lungs usually complicating other pulmonary conditions occurring in non- or mildly immunocompromised patients [331]. Its manifestations include chronic cavitary pulmonary aspergillosis (CCPA), which if left untreated may progress to chronic fibrosing pulmonary aspergillosis (CFPA), *Aspergillus* nodule and single aspergilloma [2, 332]. Subacute invasive pulmonary aspergillosis (previously chronic necrotizing pulmonary aspergillosis) is also a cavitating destructive lung disease usually found in moderately immunocompromised patients which progresses more rapidly, typically over 1 to 3 months. The diagnosis of CPA requires a combination of characteristics: one or more cavities with or without a fungal ball present or nodules on thoracic imaging, either direct evidence of *Aspergillus* infection (culture or microscopy from biopsy) or an IgG antibody response to *Aspergillus* spp. and exclusion of alternative diagnoses (especially mycobacterial infection), all present for at least 3 months [2]. Over 90% of patients have circulating *Aspergillus* antibody (precipitins) **(AII)** [333]. A positive culture of *Aspergillus fumigatus* respiratory tract secretion (BAL, bronchoscopy aspiration) is not diagnostic because many different pathologies are attributable to the fungus, and it may be an airway colonizing fungus or a plate contaminant in the laboratory.

If a fungal ball is seen, then only a positive test of *Aspergillus* IgG or precipitins confirms pathogenicity. Patients may have CPA and other infections concurrently (see below).

The distinctive hallmark of CCPA is new and/or expanding cavities with thick or thin walls in those with chronic lung disease. An intracavitary fungal ball may be present, often with pleural thickening and extensive parenchymal destruction and/or fibrosis. Patients may have CPA and other infections concurrently, especially bacterial including *Pseudomonas aeruginosa* infection or tuberculosis and non-tuberculous mycobacterial infection. *Aspergillus* nodules, which may be single or multiple, are very similar in appearance to malignancy as well as those seen in rheumatoid arthritis, coccidioidomycosis, tuberculosis, non-tuberculous mycobacterial infection and – rarely – actinomycosis or rheumatoid arthritis. Typically, *Aspergillus* nodules appear rounded, some with low attenuation or cavitation within. Some are spiculated, a common feature of carcinoma [332].

If technically feasible single aspergilloma should be surgically removed, preferably via video-assisted thoracic surgery technique with due consideration to risks as recommended [334]. Long term oral antifungal therapy is strongly recommended in patients with CCPA, partly to reduce general and respiratory symptoms [335, 336], but also to minimise haemoptysis and prevent lung destruction and fibrosis **(AII)** itraconazole or voriconazole are effective for CCPA **(AIII)** [2]. Oral posaconazole is a potential alternative treatment **(BII)** [2]. Six months of therapy is the recommended minimum **(AI)** [2]. Relapse is common after discontinuation. Intravenous therapy for CPA is useful in patients who fail or are intolerant of triazoles or have triazole resistant *A. fumigatus*. Prednisolone may be considered for underlying symptom control only if patients are adequately treated with antifungals. Mild and moderate haemoptysis usually responds to tranexamic acid; severe haemoptysis should be arrested with bronchial artery embolization (Table 38).

Conclusions

This executive summary is a comprehensive guideline covering many aspects of *Aspergillus* diseases. It provides guidance for clinicians on prevention of disease, diagnostic procedures, resistance issues and treatment of IA as well as chronic pulmonary aspergillosis. The guideline group will provide additional publications supporting the rational of given recommendations.

Finally, the guideline group provides comprehensive tables explaining various options for specific situations. A follow-up manuscript is planned in approximately 5 years to update this guideline.

654 **Table 1. Strength of recommendation and quality of evidence**

Strength of Recommendation (SoR)	**Definition**
Grade A	Societies strongly support a recommendation for use
Grade B	Societies moderately support a recommendation for use
Grade C	Societies marginally support a recommendation for use
Grade D	Societies support a recommendation against use
Quality of Evidence (QoE)	**Definition**
Level I	Evidence from at least 1 properly* designed randomized, controlled trial (orientated on the primary endpoint of the trial)
Level II	Evidence from at least 1 well-designed clinical trial (incl. secondary endpoints), without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees
Added Index	**Source of Level II Evidence**
r	Meta-analysis or systematic review of RCT
t	Transferred evidence i.e. results from different patients' cohorts, or similar immune-status situation
h	Comparator group: historical control
u	Uncontrolled trials
a	For published abstract presented at an international symposium or

	meeting
* poor quality of planning, inconsistency of results, indirectness of evidence etc. would lower the SoR	

Table 2. Diagnostic imaging procedures

FUO, fever of unknown origin; CT, computed tomography; MDCT, multi-detector CT; BAL, bronchoalveolar lavage; PCR, polymerase chain reaction

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Neutropenia, fever or clinical symptom of pneumonia, empiric antibiotics, failing to achieve defervescence, e.g. FUO	Diagnostic Imaging	Chest CT and thin section MDCT	A	II	Within 12-24h after the beginning of fever	[11, 21, 25, 337]
Any	To identify possible underlying fungal or other infectious disease	BAL	A	II		[11]
Hemoptysis or feeding vessel	Identification of vessel erosion	Chest angio-CT / pulmonary CT angiography	A	II		[14-16]
Life-threatening haemoptysis	Bridging until neutrophil recovery	Arterial embolization	B	III		

Any	To send appropriate specimens for microscopy, culture and PCR	CT-guided BAL	A	III		

659 **Table 3. Microscopic examinations**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Any	To identify fungal elements in histological sections and stains	Histological examination Haematoxylin and eosin Gomori's methenamine silver stain Periodic acid-Schiff	A	III	Histopathology is an essential investigation Inability to definitively distinguish other filamentous fungi HE: difficult GMS: removes cellular background; more sensitive to hyphal elements PAS: advantage of counter stain to check cellular detail	[338-341]
Any	To identify fungal elements in histological sections and stains	Fluorescent dyes: Calcofluor white, Uvitex 2B, Blancophor	A	II	Not specific to *Aspergillus* but high sensitivity and the micromorphology may provide info on the fungal class (Mucorales, dichotomous 90% angle branching, budding) Rapid turnaround time Broad applicability May be applied to frozen sections, paraffin-embedded tissue	[342-346]

Any	To identify fungal elements in histological sections and stains	Immunohistochemistry Monoclonal antibody WF-AF-1 or EB-A1 In situ hybridization	B	II	In total 130 CNS cases with 73 cases of aspergillosis (56%) Culture positivity in only in 25% samples Have the potential to provide genus and species specific data Commercially available monoclonal antibodies WF-AF-1 is specific for *A. fumigatus*, *A. flavus*, and *A. niger*	[342-346]
Any	To identify fungal elements in fresh clinical specimens (e.g. BAL)	Application of fluorescent dyes Calcofluor white or Uvitex 2B or Blancophor	A	II	Essential investigation Not specific for *Aspergillus* species High sensitivity Rapid turn-around time Broad applicability Inability to definitively distinguish other filamentous fungi	[340, 341, 347]

BAL, bronchoalveolar lavage; HE, haematoxylin-eosin; GMS, Gomori's methenamine silver stain; PAS, Periodic acid-Schiff; CNS, central nervous system

662 **Table 4. Sample selection and pre-analytical respiratory sample treatment**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Any	To achieve a homogenous sample of viscous samples such as sputum	Liquefaction using a mucolytic agent, e.g. Pancreatin®, Sputolysin® Liquefaction using sonication and 1,4-dithiothreitol	A	III	Essential investigation High volume sputum culture (entire sample) shown to significantly increase recovery Combination increased PCR yield, with PCR being substantially more sensitive than culture	[70, 348]
Any	To achieve optimal recovery of *Aspergillus* from BAL by centrifugation and investigation of the	Centrifugation of BALs or bronchial aspirates	A	III	Essential investigation Isolation of *Aspergillus* dependent on volume cultured	[70]

	sediment					

BAL, bronchoalveolar lavage; PCR, polymerase chain reaction

Table 5. From culture to *Aspergillus* species identification

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Any	Primary isolation from deep sites samples (e.g. biopsies, blood, CSF)	Culture on SDA, BHI agar, PDA or PFA at 30ºC and 37ºC for 72 h	A	III	Blood inhibits conidiation; BHI can help to recover some isolates; Isolation of several colonies or isolation of the same fungus from a repeat specimen enhance significance	[70, 349, 350]
	Primary isolation from non-sterile samples, e.g. sputum, respiratory aspirates, skin	Culture on SDA, BHI agar, PDA with gentamicin plus chloramphenicol at 30ºC and 37ºC for 72 h	A	III	High volume sputum culture (entire sample) shown to significantly increase recovery; Quantitative cultures are not discriminative for infection or colonization	
	Identification of species complex	Macroscopic and microscopic examination from primary cultures	A	II	Colony colour, conidium size, shape and septation. Colour of conidia and conidiophore and conidiogenesis (tease or tape mounts are preferred); Expertise needed for interpretation	
	Identification of species complex	Culture on identification media at 25-30ºC and	A	II		

		37ºC (2% MEA and Czapek-Dox Agar) and microscopic examination				
	Identification at species level	MALDI-TOF MS identification	B	II	In house databases are often used to improve identification rates	[351-354]
	Identification at species level	Sequencing of ITS, beta-tubulin and calmodulin	A	III	Essential investigation in some clinical cases	[355, 356]
	To study outbreaks	Microsatellite and CSP analysis	C	II	To study outbreaks	[357-359]
			B	II	To study colonisation patterns	[360]

CSF, cerebrospinal fluid; SDA, Sabouraud dextrose agar; BHI, brain heart infusion; PDA, potatodextrose agar; MEA, malt extract agar; MALDI-TOF MS, matrix-assisted laser desorption ionization time-of-flight mass spectometry identification; ITS, internal transcribed spacer

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667 **Table 6. Blood galactomannan testing in diagnosing IA**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Patients with prolonged neutropenic and allogeneic stem cell transplantation recipients not on mould-active prophylaxis	Prospective screening for IA	GM in blood* Draw samples every 3-4 days	A C	I III	Highest test accuracy requiring 2 consecutive samples with an ODI ≥ 0.5 or retesting the same sample Prospective monitoring should be combined with HRCT and clinical evaluation	[71, 80, 361-365]
Patients with prolonged neutropenic and allogeneic stem cell transplantation recipients on mould active prophylaxis	Prospective screening for IA	GM in blood*	D	II	Low prevalence of IA in this setting with consequently low PPV of blood GM test Prophylaxis may have a negative impact on sensitivity of the test	[366, 367]
Patients with a haematological malignancy • Neutropenic patients • Non-neutropenic patients	To diagnose IA	GM in blood*	 A B	 II II	Significantly lower sensitivity in non-neutropenic patients	[131, 362, 368, 369]

ICU patients	To diagnose IA	GM in blood*	C	II	Better performance in neutropenic than in non-neutropenic patients	[370, 371]
Solid organ recipients	To diagnose IA	GM in blood*	C	II	Low sensitivity, good specificity. Most data for lungTx (few other SOT patients with IA included)	[131, 372, 373]
Any other patient	To diagnose IA	GM in blood*	C	II	Diagnosis should be based on integration of clinical, radiological and microbiological signs False positive results reported due to ingestion of ice-pops, transfusions, antibiotics, Plasmalyt® infusion Piperacillin/tazobactam is no longer responsible for false positive results in recent studies Cross reactivity in case of histoplasmosis, fusariosis, talaromycosis (formerly: penicilliosis)	[369, 374-381]
Cancer patients	To monitor treatment	GM in blood*	A	II		[74, 214,

						382]

*, serum or plasma; GM, galactomannan; IA, invasive aspergillosis; ICU, intensive care unit; ODI, optical density index; PPV, positive predictive value; SOT, solid organ transplantation

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Any	To diagnose pulmonary IA	To apply GM test on BAL fluid	A	II	GM in BAL is a good tool to diagnose, optimal cut-off to positivity 0.5 to 1.0	[75, 383-387]
Any	To diagnose	To apply GM test on	B	II	No validated cut-off	[388, 389]

671 **Table 7. Galactomannan testing for diagnosing IA in other clinical samples**

	cerebral IA	cerebrospinal fluid				
Any	To detect GM in tissue	To apply GM test on lung biopsies	B	II	Cut-off 0.5; high sensitivity (90 %) and specificity (95%); specimens need to be sliced, precondition for doing so is that sufficient material is available; dilution in isotonic saline	[341, 390]

672 BAL, bronchoalveolar lavage; GM, galactomannan; IA, invasive aspergillosis

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674 **Table 8. *ß*-D-glucan assay in diagnosing IA**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Mixed population: adult ICU, haematological disorders, SOT	To diagnose IFD	Diagnostic assay	C	II	5 different assays. Fungitell FDA approved and available in US and Europe, others only available in Japan Overall sensitivity of 77% and specificity of 85% Specificity limits its value in this setting	[76, 391]
		Screening assays	C	II	Two or more consecutive samples: sensitivity: 65%; specificity: 93% Studies included once to thrice weekly. Varies with assay and cut-off: Wako assay sensitivity: 40-97%, specificity: 51-99%	[76, 391]
Adult haematological malignancy and HSCT	To diagnose IFD	Diagnostic assay	C	II	Overall sensitivity: 50-70%, specificity: 91-99%	[392-397]
ICU – mixed adult immunocompromised patients (haematology, SOT,	To diagnose IA	Diagnostic assay	C	II	Overall sensitivity: 78 -85%, specificity: 36-75%, NPV: 85-92% Specificity increased at higher cut-off values	[398, 399]

cancer, immunosuppressive therapy, liver failure, HIV)						
ICU – mixed adult population: SOT, liver failure, immunosuppressed		Screening assays	C	III	Sensitivity: 91%, specificity: 58%, PPV: 25%, NPV: 98%. Positive mean of 5.6 days before positive mould culture High false positive rate in early ICU admission	[400]
Adult haematological malignancy and HSCT	To diagnose IA	Diagnostic assay Screening assays	C C	II II	Overall sensitivity: 57-76%, specificity: 95-97% Overall sensitivity: 46%, specificity: 97% Confirmation with GM increases specificity Data suggests BDG is unsuitable for ruling out diagnosis of IA	[391, 392, 398]

675 FDA, Food and Drug Administration; HSCT, haematopoietic stem cell transplantation; ICU, intensive care unit; SOT, solid organ transplantation; IFD, invasive
676 fungal disease; PPV, positive predictive value; NPV, negative predictive value; GM, galactomannan; BDG, *ß*-D-glucan test; IA, invasive aspergillosis
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679 **Table 9. Lateral flow device for IA**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Haematological malignancy and solid organ transplant	To diagnose IA Evaluation of LFD using BAL samples	LFD for IFD diagnosis in BAL samples	B	II	Retrospective study. Sensitivity and specificity of BAL LFD tests for probable IPA were 100% and 81% (PPV 71%, NPV 100%), 5 pts with possible IPA had positive LFD, no proven IA	[401]
Haematopoietic stem cell transplantation	To diagnose IA Evaluation of LFD using serum samples	LFD for IFD diagnosis in serum samples	B	II	Prospective screening in 101 patients undergoing allogeneic HSCT Comparison to Asp-GM serum, IA: 1 proven, 9 probable, 20 possible cases 1 serum vs 2 serum samples positive: Sensitivity: 40%/20% Specificity: 86%/97% Diagnostic odds ratio 3.03/11.13	[402]

Immunocompromised patients (haematological malignancies 64%)	To diagnose IA Evaluation of LFD using BAL samples	LFD for IFD diagnosis in BAL samples	B	II	Retrospective study. Sensitivities for LFD, GM, BDG and PCR were between 70 and 88%. Combined GM (cut off >1.0 OD) with LFD increased the sensitivity to 94%, while combined GM (cut off >1.0 OD) with PCR resulted in 100% sensitivity (specificity for probable/proven IPA 95-98%).	[403]

IA, invasive aspergillosis; BDG, ß-D-glucan test; BAL, bronchoalveolar lavage; GM, galactomannan; HSCT, haematopoietic stem cell transplantation; IFD, invasive fungal diseases; LFD, lateral device flow; NPV, negative predictive value; PCR, polymerase chain reaction; PPV, positive predictive value

683 **Table 10. PCR and bronchoalveolar lavages or CSF in diagnosing IA**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Patients undergoing allogeneic stem cell transplantation recipients not on mould-active prophylaxis	To predict pulmonary IA	BAL PCR	B	II	In house assay	[404]
Patients with pulmonary infiltrates and haematological malignancies and prolonged neutropenia	To diagnose IA	BAL PCR	B	II	Methodically different in-house assays, better performance in patients without antifungal treatment, PCR and galactomannan: increases specificity	[214, 384, 403, 405-425]
ICU patients, mixed	To diagnose IA	BAL PCR	B	II	Methodically different assays: SeptiFast® and MycAssay Asp®	[70],[3

populations						83],[423],[426],[427],[428]
Patients with haematological malignancies	To diagnose CNS aspergillosis or meningitis	CSF PCR	B	II	113 CSF samples from 55 immunocompromised patients sensitivity 100%, specificity 93% (retrospective)	[388, 429-432]

IA, invasive aspergillosis ; BAL, bronchoalveolar lavage; PCR, polymerase chain reaction; ICU, intensive care unit; CNS, central nervous system; CSF, cerebrospinal fluid.

687 **Table 11. PCR on whole blood, serum and plasma in diagnosing IA**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Patients with haematological malignancies	To diagnose IA	PCR on blood samples	B	II	Meta-analysis: 16 studies, 1618 patients at risk, >10000 blood samples PCR single positive test: Sensitivity: 88%; Specificity: 75%; PCR 2 consecutive positive tests: Sensitivity: 75%; Specificity: 87%	[433]
	To diagnose IA	PCR on serum samples			97% of protocols detected threshold of 10 genomes/ml serum volume >0.5 ml, elution volume <100 µl, sensitivity: 86%; specificity: 94%	[434]
	To diagnose IA	PCR on whole blood samples	B	II	First blood PCR assay to be compatible with EAPCRI recommendations, fever driven: Sensitivity: 92%; Specificity: 95%; Negative PCR result to be used to rule out IA	[435]
Haematopoietic stem cell transplantation	To diagnose IA	Prospective screening PCR on whole blood samples	B	II	Combination of serum and whole blood superior, sensitivity 85 in serum, sensitivity 79% in whole blood	[80]

	To diagnose IA	Prospective screening PCR on blood samples	B	II	Addition of GM and PCR monitoring provides greater accuracy, PPV 50-80%, NPV 80-90%	[81]
	To diagnose IA	PCR and GM in BAL	A	II	randomized standard or biomarker-based diagnostic strategy, 32% patients in standard group, 15% in biomarker group, antifungal therapy (p=0.002), GM and PCR to direct treatment reduced empirical antifungal treatment, GM detection and PCR on blood	[364]

IA, invasive aspergillosis; PCR, polymerase chain reaction; EAPCRI, European *Aspergillus* PCR Initiative; GM, galactomannan, PPV, positive predictive value; NPV, negative predictive value; BAL, bronchoalveolar lavage

691 **Table 12. Molecular diagnostics on biopsy**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Biopsy with visible hyphae	To detect and specify a fungus	Broad range PCR in microscopic hyphal-positive and hyphal-negative specimens	A	II	High sensitivity (> 90 %) and high specificity (99 %); various molecular based techniques available	[341, 436]
Biopsy with no visible hyphae	To detect and specify a fungus	Broad range PCR in microscopic hyphal-positive and hyphal-negative specimens	C	II	Sensitivity (57 %) and specificity (96 %); ability to distinguish other fungi; performance only in addition to other tests	[341, 436]
Biopsy with visible hyphae	To detect and specify a fungus	Broad range PCR on wax embedded specimens	A	II	TaKaRa DEXPAT kit and QIAamp DNA mini kit detected less than 10 conidia/sample	[437, 438]
Any	To detect and specify a fungus	Fresh tissue samples	B	II	*Aspergillus* PCR performance analysis yielded sensitivity/specificity rates of 86% / 100% (79 patients, retrospective study)	[48]

692 PCR, polymerase chain reaction

693

694 **Table 13. Storage of original samples and isolates**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Any	To prevent loss of viability of *Aspergillus* in clinical samples, and to reflect the original fungal content	Clinical samples for culture - short-term storage: 4°C to prevent loss of viability and to reflect the original fungal content	A	III		[81, 349]
	To prevent degradation of biomarkers, e.g. GM in serum or BALs or bronchial washes	Complete assay soon after delivery to laboratory. Avoid short or long-term storage of serum at 4°C	A	I	GM in serum degrades with short-term and long-term storage at 4°C; BAL fluid GM ODI remain stable; testing of pos./neg. serum and BAL fluid pools showed no decline in GM index over 11 months at -20°C	[338-341, 363]
	Short-term maintenance of *Aspergillus* isolates	Repeated sub-culture	A	I	Viability maintained for several years by frequent sub-culture; Transfer once a month; Maintain at average ambient room temperature	[81, 349]

	Long-term preservation of *Aspergillus* isolates	Water storage/storage under mineral oil/silica gel storage/freeze-drying freezing (-80°C/ceramic beads/liquid nitrogen)	A	I	Long-term storage means storage periods of 5 years or longer; No further transfers required during this period	

695 GM, galactomannan; BAL, bronchoalveolar lavage; ODI, optical density index

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Table 14. Antibody based diagnosis in diagnosing IA

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Patients with IA	To diagnose IA	Detection of *Aspergillus*-specific Antibodies by EIA: Serion (Germany), Omega (France), Bio-Rad (France), Dynamiker (China)	C	II	Antibodies take a mean of 10.8 days to develop after onset of illness Detectable in 29% to 100% of patients during course of acute IA	[439-446]
		Detection of precipitating antibodies by agar gel double diffusion (Microgen Ltd. UK) or counterimmunoelectrophoresis	C	III		[447]
		Detection of agglutinating antibodies by indirect haemagglutination (EliTech/Fumouze, France)	C	II		[447]

		Detection of specific immunoglobulins to *Aspergillus* by ImmunoCap®	C	III	No data	

EIA, enzyme immunoassay; IA, invasive aspergillosis

699 **Table 15. Indications for testing for azole resistance in clinical *Aspergillus* isolates**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
All clinically relevant, *Aspergillus* isolates (in patient groups or regions with known azole resistance)	Identify isolates with intrinsic resistance	Species identification to complex level	A	III	Some species are intrinsically resistant – e.g. *A. calidoustus* (azole resistant), *A. terreus* and *A. flavus* (AmB resistant)	[85, 448]
Clinically relevant *A. fumigatus* isolates	Identify azole resistant *A. fumigatus*	Routine azole agar screening	B	III	If MIC is not available, but no validated assays	
Azole-resistant isolates	Determine nature and trends in Cyp51A mutation distribution	Cyp51A-gene mutation analysis	A	II	Test resistant isolates from surveillance survey	[98]

700 AmB, Amphotericin B; MIC, minimum inhibitory concentration

Table 16. Azole MIC testing: Timing, optimal number of colonies tested, method

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Any	Detect azole-resistant *A. fumigatus* genotypes in a single culture	MIC testing of multiple colonies (several colonies >5)	B	III	Multiple genotypes, i.e. azole-susceptible and azole-resistant, may be present.	[87, 449, 450]
Any	MIC testing of various *Aspergillus* spp.	Etest®	C	III	Not prone to very major errors, but major errors; confirmation by reference test recommended.	[451-455]

MIC, minimum inhibitory concentration

703 **Table 17. Which azole compounds need to be tested?**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Any	To determine susceptibility to itraconazole	MIC (EUCAST/CLSI)	A	III	In general, a sensitive marker for azole resistance in *Aspergillus; t*est itraconazole and voriconazole as a minimum	[456-462]
Any	To determine susceptibility to voriconazole	MIC (EUCAST/CLSI)	A	III	Resistance/reduced susceptibility to other azole(s) may accompany that of voriconazole; isolated voriconazole resistance described related to TR_{46} mutation	[95, 457, 460-464]
Any	To determine susceptibility to posaconazole	MIC (EUCAST/CLSI)	B	III	Posaconazole resistance without itraconazole resistance not reported so far; current EUCAST breakpoint will misclassify approximately 15% susceptible isolates as I/R	[316, 456, 457, 460-462, 464-467]
Any	To determine susceptibility to isavuconazole	MIC (EUCAST/CLSI)	A	III	MIC often similar to voriconazole, but needs testing separately, if isavuconazole is to be used; lower MIC of isavuconazole as compared	[456, 460, 461, 464, 468-470]

					to itraconazole and voriconazole for *A. lentulus* and *A. udagawae* (*A. fumigatus* complex) (CLSI)	

MIC, minimum inhibitory concentration; EUCAST, European Committee on Antimicrobial Susceptibility Testing; CLSI, Clinical & Laboratory Standards Institute

Table 18. Which antifungal regimen is recommended in intrinsic resistance?

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Amphotericin B MIC ≥1 mg/L	To cure IA	Replace AmB with azole, if azole tested susceptible	B	II		[7, 146, 471-476]
IA due to *A. terreus*	To cure IA	Voriconazole	A	II	Avoid AmB	[182, 477, 478]
		Isavuconazole	A	II		
		Posaconazole	B	III		
		Itraconazole	B	III		
IA due to *A. calidoustus*	To cure IA	Lipid formulation of AmB	A	II	Avoid azoles	[85, 479]
IA due to *A. tubingensis* (*A. niger* complex)	To cure IA	Other than azole monotherapy	C	III	Higher azole MIC common, but no data on clinical impact	[455, 480, 481]
IA due to *A. lentulus* (*A. fumigatus* complex)	To cure IA	Other than azole monotherapy				
IA due to *A. alliaceus* (*A. flavus* complex)	To cure IA	Other than AmB monotherapy	C	III	Avoid AmB	[482]
IA due to *A. niger*	To cure IA	Other than itraconazole and isavuconazole	B	III	Isavuconazole, posaconazole, and	[455, 470]

complex					voriconazole MIC in general 1 step higher compared to *A. fumigatus*; itraconazole MIC in general 2 steps higher; limited clinical data	
IA due to *A. nidulans*	To cure IA	Voriconazole	C	III	AmB MIC elevated, poor clinical responses in chronic granulomatous disease	[483, 484]

AmB, amphotericin B; IA, invasive aspergillosis; MIC, minimum inhibitory concentration

709 **Table 19. Recommendations for amphotericin B susceptibility testing for *Aspergillus* strains**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Clinically relevant isolate	Confirm or reject AmB resistance when antifungal treatment is considered	MIC test	C	III	Limited correlation with clinical outcome could be demonstrated in general; high MIC associated with poor outcome (Etest®)	[485-488]
Clinically relevant isolate	Interpretation of MIC (EUCAST)	MIC test using EUCAST method and EUCAST break points (S, I, R)	B	III	MIC break points proposed for *A. fumigatus* and *A. niger* Epidemiologic cut-offs established for *A. flavus*, *A. fumigatus*, *A. niger* and *A. terreus* *A. terreus* is not considered a good target for AmB. A concern is raised for *A. flavus* due to higher MIC	[456, 489, 490]
Clinically relevant isolate	Interpretation of MIC (CLSI)	MIC test using CLSI method and CLSI ECVs (wild-type/non-wild-type)	B	III	ECVs proposed for *A. fumigatus*, *A. flavus*, *A. nidulans*, *A. niger*, *A. terreus*, *A. versicolor.* No clinical break points. *A. terreus* and *flavus*, e.g. with MIC below the ECV are not good targets for AmB. No clinical data that *A. fumigatus* with MIC 2 will respond to AmB although classified as wildtype according	[491]

					to CLSI ECVs.	

AmB, amphotericin B; CLSI, Clinical & Laboratory Standards Institute; ECV, epidemiological cut-off value; EUCAST, European Committee on Antimicrobial Susceptibility Testing; MIC, minimum inhibitory concentration

Table 20. Optimal therapy for documented azole-resistant IA

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Isolate with voriconazole MIC =2 mg/ml	To cure IA	Voriconazole + echinocandin or L-AmB for IA (as well as for CPA)	A	III	The probability of voriconazole treatment failure may be higher than in voriconazole MIC <2.	[492-494]
Isolate with posaconazole MIC >0.5 mg/ml [495]	To cure IA	L-AmB	A	II_u		[94, 95, 496]
		AmB lipid complex	C	III		
		Voriconazole & anidulafungin	B	III		[492]
		Posaconazole & caspofungin	C	III	Posaconazole not licensed for primary treatment	[497]
		Caspofungin or micafungin	C	III	Patients with contra-indications to AmB & other azoles	

AmB, Amphotericin B; CPA, chronic pulmonary aspergillosis; IA, invasive aspergillosis; L-AmB, Liposomal amphotericin B; MIC, minimum inhibitory concentration

717 **Table 21. TDM to be considered**

Clinical scenarios where antifungal therapeutic drug monitoring may be indicated	**Examples, comments**
Populations with increased pharmacokinetic variability	Impaired gastrointestinal function; hepatic dysfunction; paediatric patients, elderly patients, obese patients, critically-ill patients
Changing pharmacokinetics	Intravenous to oral switch, changing gastrointestinal function, changing hepatic or function, physiological-instability
Interacting medications	Patient receiving medication known to induce cytochrome P450 enzymes especially CYP3A4, antacids, proton-pump inhibitors (itraconazole capsules, posaconazole suspension), antiretroviral medications. Patients should have medication records screened using drug interactions screening database before starting and stopping antifungals (example: www.fungalpharmacology.org, fungal-druginteractions.org, or http://www.aspergillus.org.uk/content/antifungal-drug-interactions
Poor prognosis disease	Extensive or bulky infection, lesions contiguous with critical structures, CNS infection, multifocal or disseminated infection
Compliance concerns	Important issue with longer-term consolidation therapy or secondary prophylaxis in outpatient setting

Suspected breakthrough infection	TDM can establish whether fungal disease progression occurred in the setting of adequate antifungal exposure
Suspected drug toxicity, especially neurotoxicity (voriconazole)	Exposure-response relationships are described for other toxicities (e.g., hepatotoxicity), the utility of TDM to prevent their occurrence is less well established

718 CNS, central nervous system; TDM, therapeutic drug monitoring

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Table 22. Itraconazole therapeutic drug monitoring

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
All patients receiving itraconazole treatment for IA	Improve efficacy	Measure serum trough level on day 5 of therapy or soon after	A	II	Target itraconazole level >1 mg/L to 4 mg/L by HPLC. Hydroxy-itraconazole metabolite concentrations generally reported separately by HPLC or LC/MS/MS methods, but included in "itraconazole" concentration report by bioassay. Therapeutic range by bioassay may vary by laboratory but typically fall in the range of (3-17 mg/L). Need for repeat determinations should be determined by clinical status, or change in concomitant medications; may be less important with suspension however compliance is a concern	[103, 108, 498-500]
All patients receiving itraconazole for prophylaxis for IA	Improve efficacy	Measure serum trough level on day 5 of therapy or soon after	A	II	Target itraconazole level >0.5 mg/L (HPLC) or > 3 mg/L (bioassay)	[105]

Patients receiving itraconazole	Reduce toxicity	Measure serum trough level on day 5 of therapy or soon after	B	II	Toxicity was associated with itraconazole levels >17.1 mg/L by itraconazole bioassay, which correspond to ~4 mg/L by HPLC	[108]

721 IA, invasive aspergillosis; HPLC, high performance liquid chromatography; LC, liquid chromatography; MS, mass spectrometry

722

723 **Table 23. Voriconazole therapeutic drug monitoring**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
All patients receiving voriconazole treatment for IA	Improve efficacy, safety and compliance	Measure plasma trough level after 2-5 days of therapy or soon after	A	I	Target range of 1-6 mg/L	[109-112, 114, 501-503]
All patients receiving voriconazole treatment for IA	Improve efficacy, safety and compliance	Repeat plasma trough level	B	II	Repeat during second week of therapy, additional samples as clinically indicated, or upon relevant change in concomitant medication	[109-112, 114, 501-503]
All patients receiving voriconazole prophylaxis for IA	Improve efficacy, safety and compliance of prophylaxis	Measure serum trough level after 2-5 days of therapy or soon after, and 4 days after change of dose	A	IIt	As above; most studies investigated voriconazole treatment rather than prophylaxis	[113, 504, 505]
Patients with IA due to *Aspergillus* strains	Improve efficacy of treatment for	Measure serum trough level after 2 to 5 days of therapy	A	III	Trough >2 mg/L recommended on the basis of PK/PD analysis, however other therapies are	[112, 506]

of reduced azole susceptibility MIC >2 mg/ml	isolates with MIC>2 mg/ml	or soon after and 4 days after change of dose			recommended (Table 20)	

724 IA, invasive aspergillosis; MIC, minimum inhibitory concentration; PK, pharmacokinetic; PD, pharmacodynamic

Table 24. Posaconazole therapeutic drug monitoring

Population	Intention	Intervention	SoR	QoE	Comments	Ref.
Patients receiving posaconazole suspension for treatment of IA	Improve efficacy, compliance	Serum trough level on day 5 of therapy or soon after	A	II	Target level >1 mg/L. Gastroresistant tablet or intravenous formulation are the preferred formulations for most patients, consider switch to tablet or IV, if no therapeutic levels with oral suspension. Repeat determination as clinically appropriate, for example upon relevant change in concomitant medications. Prolonged half-life gives similar results for random sampling and true trough samples.	[119]
Patients receiving posaconazole suspension for	Improve efficacy, compliance	Serum trough level on day 5 of therapy or soon after.	C	II	Target level >0.7 mg/L. Adequate tissue concentrations may occur despite serum concentration <0.7 mg/L. Repeat determination as clinically appropriate, for	[117, 118, 507-510]

prophylaxis to prevent IA					example upon relevant change in concomitant medications.	
Patients receiving posaconazole	Improve safety	Measure serum trough level on day 5 of therapy or soon after	C	III	If treatment failure or toxicity suspected, TDM may be indicated in patients receiving gastroresistant delayed release tablet or intravenous formulation. Posaconazole exposures between 0.5-3.75 mg/L are well studied and considered safe and effective with all three formulations. Posaconazole plasma levels above this exposure range may be associated with toxicity.	[120,121]

726 IA, invasive aspergillosis; IV, intravenous; TDM, therapeutic drug monitoring; AML, acute myeloid leukaemia; HSCT, haematopoietic stem cell

727 transplantation; GVHD, graft versus host disease

728 **Table 25. Isavuconazole therapeutic drug monitoring**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
All patients receiving isavuconazole	Improve efficacy safety and compliance	Measure serum trough level on D5 of therapy or soon after	C	III	Limited data to support routine TDM but may be indicated in the setting of treatment failure, drug interactions, or if toxicity is suspected. The long half-life of isavuconazole (130 hours) may support use for TDM in some clinical situations to confirm drug clearance prior to starting medications metabolized by CYP3A4, especially chemotherapy agents.	FDA advisory briefing documents.

729 TDM, therapeutic drug monitoring; FDA, Food and Drug Administration

Population	Intention	Intervention	SoR	QoE	Comment	Ref

730 **Table 26. Prevention of IA in high risk paediatric patients**

Allogeneic HSCT, pre-engraftment phase; Allogeneic HSCT, post-engraftment phase, GvHD and augmented immunosuppression; High-risk patients with de novo or recurrent leukaemia, bone marrow failure syndromes with prolonged and profound neutropenia	Prevention of IA	Itraconazole	A/B*	II_t	Not approved for <18 years; TDM recommended; Approved indication; not approved EU < 18 years.	[103, 511-521]
		Posaconazole	A	II_t	TDM recommended; only supportive paediatric data for ≥ 13 years of age.	[117, 118, 152, 522-530]
		Voriconazole	A	II_t	Not approved for <2 years; Inference from efficacy from HSCT trials and supportive studies; TDM recommended.	[111, 112, 116, 504, 531-539]
		Liposomal amphotericin B	B	II_t/III*	Not approved for prophylaxis; Optimal dose of alternate administration unknown; Alternative if triazoles are not tolerated / contraindicated	[540-546]
		Micafungin	B	II_t/III*	No definite evidence (trend only) for prophylactic efficacy against *Aspergillus* spp. Alternative if triazoles are not tolerated or contraindicated.	[547-552]
Chronic granulomatous disease (CGD) patients	Prevention of IA	Itraconazole	A	II	Approved indication; not approved in the EU for < 18 years; TDM recommended.	[103, 517-520, 553,

						554]
		Posaconazole	A	III	Not EU approved for children < 18 years; TDM recommended; PK and safety data for children ≥ 4 years	[117, 118, 526-529]

* SoR = B for allogeneic HSCT post-engraftment phase, GvHD (graft versus host disease) and augmented immunosuppression

* QoE = III for allogeneic HSCT post-engraftment phase, GvHD and augmented immunosuppression

IA, invasive aspergillosis; TDM, therapeutic drug monitoring; HSCT, haematopoietic stem cell transplantation

735 **Table 27. Treatment of IA in paediatric patients**

Population	Intention	Intervention	SoR	QoE	Comment	Ref
Any paediatric population other than neonates	Treatment proven/probable IA	Voriconazole 18 mg/kg/d iv day 1, followed by 16 mg/kg/d iv or 18 mg/kg/d po in 2 divided dosages (up to 14 years and < 50 kg); if >15 yrs or >12 yrs and >50 kg use adult dosing recommendations	A	II_t	Not approved in patients <2 yrs; TDM recommended.	[111, 112, 116, 145, 146, 504, 535-538, 555-561]
Any paediatric population other than neonates	Treatment proven/probable IA	L-AmB 3 mg/kg/d	B	II_t	Comparison between 2 dosages of L-AmB, no comparison to voriconazole	[149, 544, 546, 562-565]
Any paediatric population other than neonates	Treatment proven/probable IA	Caspofungin 70 mg/m^2 day 1, followed by 50 mg/m^2/d (max. 70 mg/d)	C	II_t	Study prematurely stopped due to low accrual	[564, 566-576]
Neonates	Treatment proven/probable IA	L-AmB 3 mg/kg/d	A	III		[577-580]

736 IA, invasive aspergillosis; TDM, therapeutic drug monitoring; L-AmB, liposomal amphotericin B

737 **Table 28. Targeted therapy of pulmonary IA: Choice of antifungal drugs for first line therapy**

Population	Intention	Intervention	SoR	QoE 1	QoE 2	QoE 3	Comment	Ref.
[1] Neutropenia (non- allo HSCT recipients)	To increase response and survival rate	Voriconazole 2x 6 mg/kg IV (oral 400 mg bid) on D1, then 2x 4 mg/kg IV (oral 200 to 300 mg bid)	A	I	II_t	II_t	C III for start with oral; D III, if mould active azole prophylaxis; TDM	[146, 184, 470, 581]
		L-AmB 3 mg/kg	B	II	II_t	II_t		[149]
[2] Allo-HCT (during neutropenia)		Caspofungin 70/50 mg	C	II	II	II		[566-568]
		Micafungin 100 mg	C	III	III	III		[582-584]
[3] Allo-HCT (w/o neutropenia) or other non-		Itraconazole 200 mg q12h iv on D1, then 200 mg/qd	C	III	$II_{t,a}$	$II_{t,a}$	D III for start with oral, TDM D III, if mould active azole prophylaxis	[470, 500]

neutropenic patients		Isavuconazole 200 mg iv tid D1-2, then 200 mg qd oral	A	I	II_t	II_t	D III, if mould active azole prophylaxis	[185, 470]
		Conventional AmB 1-1.5 mg/kg	D	I	II_t	II_t		[146]
		AmB lipid complex (ABLC) 5 mg/kg	C	III	III	III		[585]
		AmB colloidal dispersion (ABCD) 4-6 mg/kg	D	I	II_t	II_t		[586]
		Voriconazole 6/4 mg/kg bid after one week oral possible (300mg bid) + Anidulafungin 200/100 mg	C	I	$II_{t,}$	$II_{t,}$	No significant difference compared to voriconazole, in GM positive (subgroup) better survival; TDM	[184, 581]
		Other combinations	D	III	III	III	Efficacy unproven	[587]

738 IA, invasive aspergillosis; IV, intravenous; TDM, therapeutic drug monitoring; GM, galactomannan

739 **Table 29. Targeted therapy of other than pulmonary IA: Choice of antifungal drugs for first line therapy**

Population	Intention	Intervention	SoR	QoE	Comment	Ref
Suspected or proven IA of the central nervous system	To increase response and survival rate	Surgical debridement, if surgically possible	A	II_u		[588, 589]
		Voriconazole	A	II_u	N=5/5	[146]
					N=81, 48 proven cases, 33 probable cases, TDM recommended targeting trough concentration of 2-5 mg/L	[588]
		Posaconazole	D	III	8 patients documented in studies (5xfailure)	[590]
		Itraconazole	D	III	Not specified in studies	
		Lipid formulations of AmB	B	III	Case collections, animal data	[591-593]
		cAmB	D	I	Renal toxicity	[594-597]
		Echinocandins	D	III	No satisfying tissue penetration	[592]
Sinus						
Patients w/ clinical	To cure	Surgery	A	III	Need to be considered on an individual basis and decision	

suspicion of or proven invasive sinus aspergillosis		Local antifungal therapy	C	III		
Patients with invasive sinus aspergillosis (all levels of certainty: suspected through proven)		Voriconazole	A	II_t	N=8/7, TDM recommended	[146, 598]
		L-AmB	A	II_t	Active against mucormycosis as well since mixed infections occur or cannot be differentiated	[149]
		Posaconazole, itraconazole, echinocandins	C	III	Not well specified in studies, TDM recommended for posaconazole and itraconazole	[599, 600]

TDM, therapeutic drug monitoring; AmB, Amphotericin B, cAmB, conventional amphotericin B; L-AmB, liposomal amphotericin B

742 **Table 30. Secondary Prophylaxis**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Previous IA and undergoing allogeneic HSCT or entering risk period with non-resectable foci of *Aspergillus* disease	To reduce risk of IA recurrence	Secondary prophylaxis with an *Aspergillus* active antifungal, i.e. voriconazole OR any alternative proven to be effective in the actual patient	A	II	Results compared to historical data, mostly in allogeneic HSCT setting	[601-606]
		Voriconazole	A	II_h	IA: 31/45 pts, 1 year cumulative incidence of IFD 6.7±3.6%, TDM	[601]
		Caspofungin 70/50 mg IV until stable engraftment, followed by 400 mg itraconazole suspension PO	B	II_h		[605]
		L-AmB followed by voriconazole	C	II	Fungal infection related mortality 28% despite lipid-based AmB	[604, 607]
Previous IA and with resectable foci of *Aspergillus* disease	To reduce risk of IA recurrence	Surgical resection following by secondary prophylaxis	B	III	Timing and methods of surgery important. Concomitant administration of appropriate antifungal compound justified.	[608-612]

before entering risk period					Indication for surgical intervention by appropriate specialist. Interdisciplinary consensus needed.	

HSCT, haematopoietic stem cell transplantation; IA, invasive aspergillosis, IFD, invasive fungal disease; TDM, therapeutic drug monitoring, PO, per os; L-AmB, liposomal amphotericin B

745 **Table 31. Primary Prophylaxis**

Population	Intention	Intervention	SoR	QoE	Comment	Ref
Haematological malignancies, e.g. AML with prolonged and profound neutropenia	Lower incidence of IA	Posaconazole 200 mg TID suspension or 300mg tablet QD	A	I	AML/MDS induction only. TDM especially with oral suspension. Tablets more bioavailable, bridging with posaconazole IV formulation possible	[522]
		ABLC 3 mg/kg 3x/weekly	C	II_h	No difference to L-AmB regimen	[613]
		Itraconazole 400mg/d, oral solution	D	II	No difference to fluconazole (n=195) and more toxicity	[102, 512, 614, 615]
		Micafungin (50 mg per day)	C	II_t		[547, 616]
		L-AmB 10 mg/kg q7d	C	II	Phase II trial low participation	[617]
		L-AmB 50mg abs q2d	C	II		[543]
		L-AmB 15 mg/kg q14d	C	II	Phase II trial low participation	[618]
		L-AmB 12.5 mg biw, nebulized, with fluconazole	B	I	AML	[619, 620]

		Voriconazole	C	II_t	Not better than fluconazole	[621]
Acute lymphoblastic leukaemia, remission induction chemotherapy	Lower incidence of IA	L-AmB 5 mg/kg biw	D	I	L-AmB more toxic than placebo, no significant reduction in IA rate	[622]
Treatment of haematological malignancies besides acute leukaemia	Lower incidence of IA	Any mould active agent	D	III	No study demonstrated outcome advantage	
Autologous HSCT	Lower incidence of IA	Any mould active agent	D	III	No study demonstrated outcome advantage	
Allogeneic HSCT (until neutrophil recovery)	Lower incidence of IA	Posaconazole 200mg TID suspension or 300mg tablet once a day	B	II_t	Neutropenia duration approximately identical, TDM*	[522]
		Voriconazole 200mg BID	C	I	Not better than fluconazole, TDM	[531, 532]
		Itraconazole 400mg/d oral solution	D	I	Toxicity issues; TDM	[512]
		Micafungin 50mg/d	C	I	But no difference in subgroup analysis for aspergillosis	[547]
		L-AmB 12.5mg biw, nebulized, with	B	II_t		[619]

		fluconazole				
Allogeneic HSCT (after neutrophil recovery and no GVHD)		Any antifungal agent	D	III	No study demonstrated outcome advantage	
Allogeneic HSCT (with moderate to severe GvHD and/or intensified immuno-suppression)		Posaconazole 200mg TID suspension	A	I	TDM	[523]
		Voriconazole 200mg BID	C	II	Not better than fluconazole; TDM	[531, 532]
		Itraconazole 400mg/d, oral solution	C	II	Toxicity issues; TDM	[512]
		Micafungin 50mg/d	C	III	Only few patients with GVHD	[547]
Allogeneic HSCT (until neutrophil recovery)	To reduce IA attributable mortality	Posaconazole 200mg TID suspension	B	II_t	Neutropenia duration approximately identical. TDM	[522]
Allogeneic HSCT (after neutrophil recovery, without GVHD)		Any other antifungal	D	III	No study demonstrated outcome advantage	
Allogeneic HSCT (with moderate to severe GVHD and/or intensified immuno-		Posaconazole 200mg TID suspension	A	II	Mainly IFD-attributable mortality, TDM	[523]

suppression)						

QD, once daily; BID, twice daily; TID, thrice daily; AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; TDM, therapeutic drug monitoring; ABLC, amphotericin B lipid complex; L-AmB, Liposomal amphotericin B; HSCT, haematopoietic stem cell transplantation; GVHD, graft versus host disease; IFD, invasive fungal disease

Table 32. Fever-driven strategy: Choice of antifungal agents

Population	Intention	Intervention	SoR	QoE	Comment	Ref
Chemotherapy for haematological malignancies or HSCT, neutropenia <500/µL ≥ 96 h, fever (>38°C), and parenteral broad spectrum antibacterial therapy ≥ 96 h (some centres consider 48h)	Reduce of the incidence of IA and/or related mortality	Caspofungin 70/50 mg	A	I	Caspofungin was associated with a significantly higher rate of survival than L-AmB (subgroup analysis).	[623]
		L-AmB 3 mg/kg	B	I	Less toxicity in comparison to cAmB but more renal toxicity compared to echinocandin	[597, 623]
		Voriconazole 2x 6 mg/kg IV (oral 400 mg bid) on D1, then 2x 4 mg/kg IV (oral 200 to 300 mg bid)	B	II	Failed the 10% non-inferiority cut-off when compared with L-AmB, but first-line for aspergillosis. Activity of azoles empirical therapy for persistent fever may be limited in patients receiving prophylaxis with an agent of the same class. TDM*	[624]
		Itraconazole 200 mg/day iv	C	II	Activity of azoles empirical therapy for persistent fever may be limited in patients receiving prophylaxis with an agent of the same class. TDM*	[625]
		ABLC 5 mg/kg	C	I	Infusion-related toxicity (fever, chills, hypoxia)	[626]

		ABCD 4 mg/kg	C	I	Same as above	[627]
		cAmB (0.5-1 mg/kg)	D	I	Poor tolerance due to extreme toxicity	[155, 595-597, 625, 627]
		Micafungin 100 mg	B	II		[628]
		Fluconazole	D	II_r	No activity against Aspergillus	[629]

751 L-AmB, liposomal amphotericin B; cAmB, conventional amphotericin B; IV, intravenous; TDM, therapeutic drug monitoring; ABLC, amphotericin B lipid

752 complex; ABCD, amphotericin B colloidal dispersion

Population	Intention	Intervention	SoR	QoE	Comment	Ref

753 **Table 33. Antifungal drugs for refractory disease**

Haematological patients with refractory IA	Achieve complete or partial response, or stable disease, improve survival	Switch to another drug class	A	III		
		Any combination	C	III	No prospective study demonstrated superiority of combination therapy over monotherapy	[630]
		Voriconazole	A	II		[145, 631-633]
		L-AmB 3-5 mg/kg	B	II	Majority voted for BII others for AII	[545, 634, 635]
		ABLC 5 mg/kg	C	II		[585, 635-637]
		ABCD	D	--	No longer commercially available	[638, 639]
		Caspofungin 70 mg, then 50 mg (if body weight <80kg)	B	II	Very few data in case of voriconazole/posaconazole failure	[148, 633, 640-646]
		Micafungin 75-200 mg/d	C	II		[583, 647]
		Posaconazole 200 mg qid or 400 mg bid	B	II		[119, 150, 648, 649]

		Itraconazole	D	III	In case of refractoriness to voriconazole	
		Itraconazole oral forms	C	II	Poor bioavailability	[107]
		Itraconazole IV formulation	NR	--	Commercially not available everywhere	[500, 650]

754 L-AmB, Liposomal amphotericin B; ABLC, amphotericin B lipid complex; ABCD, amphotericin B colloidal dispersion; IV, intravenous; TDM, therapeutic drug
755 monitoring; QD, once daily; BID, twice daily; TID, thrice daily
756

Table 34. Risk factors of IA in non-haematological patients

Population	Intention	Intervention	Risk factor	SoR	QoE	Comment	Ref.
Lung Tx	To identify a subset of SOT recipients at high risk of IA	To provide prophylaxis and increase the index of suspicion of the disease	Pre-transplantation colonization and *Aspergillus* in intraoperative culture	B	III	independent risk factor for bronchiolitis obliterans	[228, 243, 651]
			Repeated acute and chronic rejection	B	II_t		[652, 653]
			CMV disease	B	III		[654]
			Donor age, ischaemia time and use of daclizumab	B	III		[655]
			Bronchial anastomotic ischemia or bronchial stent placement	B	III	Airway ischemia increases risk for IA	[656]
			Single-lung transplant	B	III		[232]
Heart Tx	To identify a subset of SOT recipients at high risk	To provide prophylaxis and increase the index of suspicion of	Re-operation, CMV infection, haemodialysis, other episode of IA in the program within 2 months	A	II_h	Allows the administration of targeted prophylaxis to less than 10% of heart transplant recipients	[222]
			High concentration of spores in ICU	A	II		[221, 222]
			Sirolimus and tacrolimus	B	II_h	Predictors of late onset IA	[230]

	of IA	the disease	Hypogammaglobulinemia	B	II_h		[657]
Liver Tx	To identify a subset of SOT recipients at high risk of IA	To provide prophylaxis and increase the index of suspicion of the disease	Requirement for dialysis	B	II_h		[228, 229, 234, 241, 324, 327, 555, 658-661]
			Retransplantation				
			Fulminant hepatic failure				
			Model for end-stage liver disease (MELD) score >30				
			ICU admission or corticosteroid requirement previous 2-4 weeks to transplant	C	III	2 or more of these risk factors were considered in clinical trials as minor criteria for receiving specific antifungal prophylaxis	
			>15 units of packed red blood cells during transplant surgery				
			Reoperation involving the intraabdominal cavity				
			Choledochojejunostomy				

Kidney Tx	To identify a subset of SOT recipients at high risk of IA	To provide prophylaxis and increase the index of suspicion of the disease	Pre-transplant COPD, delayed graft function, post-transplant blood stream infection and acute graft rejection within the 3 months prior to the diagnosis of IA	A	II_h		[245]
COPD	To identify populations at high risk of IA	Rapid suspicion of the disease	Cumulative glucocorticosteroid dose Refractory to antibiotic therapy Admission to the intensive-care unit	A	II_t	Severe COPD with corticosteroids, with recent exacerbation of dyspnoea, abnormal chest imaging, refractory to antibiotic therapy and positive culture or positive galactomannan (probable IA, Bulpa criteria)	[249, 273, 662, 663]

HIV	To identify populations at high risk of IA	Rapid suspicion of the disease	CD4 count <100 cells/µl	A	II_h	Only 50% of the cases fulfilled EORTC criteria	[249]
ICU patients	To identify populations at high risk of IA	Rapid suspicion of the disease	COPD	A	II_h	Putative IA: *Aspergillus* in respiratory tract + compatible signs and symptoms + abnormal chest imaging + either: a) host risk factors (neutropenia or cytotoxic agents or corticosteroids therapy or immunodeficiency) or b) Aspergillus in BAL (no bacteria) and branching hyphae (Vandewoude criteria)	[273, 662, 663]
			Corticosteroid therapy required				
			Acute liver failure, burns, severe bacterial infection, malnutrition	B	III		
			Acute respiratory distress syndrome, pneumonia				

ICU patients and SOT recipients	To identify populations at high risk of IA	To provide prophylaxis and increase the index of suspicion of the disease	Increased environmental exposure	A	II		[221, 222, 664, 665]
Liver insufficiency	To identify populations at high risk of IA	To provide prophylaxis and increase the index of suspicion of the disease	Alcoholic hepatitis treated with corticosteroids, acute liver failure	B	II_h		[261, 666]
Burns	To identify populations at high risk of IA	Rapid suspicion of the disease	Positive fungal cultures	A	II_h	Mortality (logistic regression): culture of mould or *Aspergillus* (OR: 12-fold)	[667, 668]
			Percentage of total body surface area burn injury; length of stay	B	III		[665]

Monoclonal antibodies	To identify populations at high risk of IA	Rapid suspicion of the disease	Risk of IA in patient receiving TNF-α blockers and other	C	III	Risk increased: basiliximab, daclizumab, infliximab, etanercept, alemtuzumab (prophylaxis may be indicated); risk may be increased: adalimumab, rituximab, abatacept	

758 IA, invasive aspergillosis; CMV, cytomegalovirus; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; BAL, bronchoalveolar lavage

759

Table 35. Diagnostic approach to IA in non-haematological patients

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
COPD	To diagnose IA	Culture	A	II_u	IPA affects at least 22% of patients with COPD and isolation of *Aspergillus* in culture	[273]
COPD	To diagnose IA	Culture	B	II_h	Sensitivity 11-42%	[273, 297, 298, 669]
COPD	To diagnose IA	GM BAL	B	II_u	Sensitivity/specificity of BAL GM >1.0 cut-off is 67% / 96%, at GM >0.5 cut-off is 89% / 88%	[297]
Underlying respiratory disease	To diagnose IA	Lateral flow device BAL	C	II	Sensitivity / specificity 77% / 92%	[301]
HIV	To diagnose IA	Direct microscopy	A	II_h	50% positive	[249]
HIV	To diagnose IA	GM BAL	B	II_u	53% positive	[249]
HIV	To diagnose IA	GM serum	B	II_u	34% positive	[249]

HIV	To diagnose IA	Histology	A	II_u	75% positive	[249]
ICU	To diagnose IA	BDG serum	B	II_u	Autopsy study, non-haematological immunocompromised critically ill patients with lower respiratory tract infection. Using 140 pg/ml cut-off, sensitivity/specificity 100% / 70%	[398]
ICU	To diagnose IA	BDG serum	B	II_u	BG appeared a mean of 6.5 days before *Aspergillus* was grown	[670]
ICU	To diagnose IA	Culture	B	II_u		[371, 671, 672]
ICU	To diagnose IA	GM BAL	C	II_u	Using cut-off ODI 0.5 sensitivity/specificity 88-90% / 87-100%	[371, 671, 672]
ICU	To diagnose IA	SeptiFast®	C	II_h	Sensitivity/specificity 66% / 98%, PPV 93%, NPV 88%	[673, 674]
Non haematological	To diagnose IA	Culture	A	II_h	Very low PPV of *Aspergillus* spp. culture from respiratory samples	[215]
Non haematological	To diagnose IA	Culture	A	II_h	Sensitivity of BAL higher for non-neutropenic patients	[42]

Non-haematological	To diagnose IA	GM serum	C	II	Using cut-off of 0.5 ng/ml sensitivity/specificity 60% / 89%	[669]
Non-haematological	To diagnose IA	MycAssay Aspergillus®	C	II	Sensitivity, specificity, PPV, and NPV of first sample/any sample were 87%/93%, 87%/82%, 34%/34%, 92%/100%	[294]
SOT, any	To diagnose IA	Culture	D	II	Low sensitivity and specificity	[298, 675]
SOT, any	To diagnose IA	GM BAL	B	II	Using cut-off ODI 1.0 sensitivity/specificity 100% / 91%	[676]
SOT, any	To diagnose IA	High-resolution computed tomography	A	III	Bilateral bronchial wall thickening and centrilobular opacities, tree-in-bud pattern (65%), ground-glass opacities and/or bilateral areas of consolidation (23%)	[231, 677]
SOT, any	To diagnose IA	Lateral flow device BAL	C	II	N=11 SOT	[300, 403, 678]
SOT Heart	To diagnose IA	Culture	A	II_h	Overall positive predictive value (PPV) 60-70%, PPV 88-100% with respiratory specimens other than sputum; recovery of *A. fumigatus* PPV 78-91%	[287]

SOT Heart	To diagnose IA	High-resolution computed tomography	A	II_h	provided significant additional information in 41%; positive with a normal chest X-ray in 18%	[290]
SOT Lung	To diagnose IA	BDG serum	C	II_u	Sensitivity/specificity 64%, 9%, PPV 14%, NPV 50%	[679]
SOT Lung	To diagnose IA	GM BAL	B	II	Using cut-off ODI 1.5 sensitivity/specificity 100% / 90%	[675, 680-682]
SOT Lung	To diagnose IA	PCR	B	II		[682]

BDG, ß-D-glucan; IA, invasive aspergillosis; ICU, intensive care unit; SOT, solid organ transplantation; PPV, positive predictive value; GM, galactomannan; ODI, optical density index; NPV, negative predictive value; BAL, bronchoalveolar lavage

763 **Table 36. Therapy of IA in non-haematological patients**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
HIV	To treat IA	Voriconazole	A	III	Consider drug-drug interactions with antiretroviral drugs.	[683]
SOT Heart	To treat IA	Itraconazole	C	III	6 HT cured with itraconazole 200-400 mg/d Erratic absorption and interaction with calcineurin inhibitors and other agents	[684]
SOT, any	To treat IA	Voriconazole	A	III	Herbrecht study 11 SOT; voriconazole increases the levels of anti-calcineurin immunesuppressors, TDM; monitor liver function tests especially in liver transplant recipients.	[145, 146, 231, 303, 555-557, 632, 685-687]
SOT, any	To treat IA	L-AmB	A	II		[637, 688, 689]
SOT, any	To treat IA	Voriconazole &	B	II	40 SOT voriconazole & caspofungin (n=40) vs AmB (n=47). Survival	[305]

		caspofungin			benefit in pts with *A. fumigatus* or renal insufficiency	
SOT, if voriconazole contraindicated	To treat IA	Caspofungin	B	III	Complete response 83%; response 7/9 monotherapy and 7/10 combination	[569, 570, 645, 690]

764 IA, invasive aspergillosis; SOT, solid organ transplantation; L-AmB, Liposomal amphotericin B; SOT, solid organ transplantation

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766 **Table 37. Prophylaxis strategies of IA in non-haematological patients**

Population	Intervention	Intention	SoR	QoE	Comment	Reference
SOT Lung	Universal* prophylaxis	To prevent IA	A	I	Invasive fungal infection appeared at a median of 35 days	[127, 320, 691]
	Targeted* prophylaxis	To prevent IA	C	III		[127, 655, 692]
	Inhaled cAmB	To prevent IA	B	II_h	25 mg/day for 4 days, followed by 25 mg/week for 7 weeks. More adverse events in inhaled deoxycholate vs lipid-based	[693]
	Inhaled cAmB	To prevent IA	B	II_h	Breakthrough IA in 7-10%	[694]
	Inhaled lipid-based AmB	To prevent IA	A	I	More adverse events with inhaled deoxycholate vs lipid-based but similar efficacy; various possible protocols: 50mg/day for 4 days, then 50mg/week for 7 weeks; 50mg/day for 2 weeks, then once weekly for 10 weeks; 25mg thrice weekly between day 1 and day 60 post SOT and once weekly between day 60 and day 180	[685, 693-696]

	Voriconazole	To prevent IA	A	III	Voriconazole 2x200 mg/d more hepatotoxic than itraconazole 2x200 mg/d. Usual duration of prophylaxis 3-6 months; monitor liver and skin toxicity	[127, 319, 320, 692, 697]
	Voriconazole pre-emptive, if colonized	To prevent IA	B	II_u	Breakthrough IA <2% at 6 months	[692]
	Voriconazole for three months	To prevent IA	C	II	No effect of voriconazole on the incidence of IA (45% vs 49%)	[319]
SOT Heart	Universal* prophylaxis with itraconazole or inhaled AmB	To prevent IA	C	I		[231, 698, 699]
	Universal* prophylaxis with itraconazole or inhaled AmB	To prevent IA	C	II	IA rates 5% without prophylaxis, 1.5% with itraconazole 2x200 mg, 0% with inhaled AmB	[231, 698, 699]
	Targeted* prophylaxis with echinocandins	To prevent IA	A	II_t	Prophylaxis in 10% of patients, IA rate reduced from 9% to 2%, attributable mortality from 6% to 2%; duration dependant of risk	[232]

					factors persistence	
SOT Liver	Targeted* prophylaxis with lipid AmB	To prevent IA	B	III	IA rate reduced, mortality unaffected	[555, 700-702]
	Targeted* prophylaxis with echinocandins	To prevent IA	A	I	Standard dosed echinocandins reduced IA rate; duration of prophylaxis usually 21 days post SOT	[234, 324, 327, 703]

* targeted prophylaxis = only if additional risk factors; universal prophylaxis = to all patients in population; IA, invasive aspergillosis; SOT, solid organ transplantation; AmB, Amphotericin B

Table 38. Key recommendations for chronic pulmonary aspergillosis

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Cavitary or nodular pulmonary infiltrate in non-immuno-compromised patients	Diagnosis or exclusion of CPA	Direct microscopy for hyphae	A	II_t	Positive microscopy is a strong indicator of infection, not studied in CPA, but in ABPA	[704]
		Histology	A	II	In CPA histology distinguishes between CNPA and CCPA	[705]
		Fungal culture (respiratory secretion)	A	III	Bacterial culture plates are less sensitive than fungal culture plates	[285]
Cavitary or nodular pulmonary infiltrate in non-immuno-compromised patients	Diagnosis or exclusion of CPA	*Aspergillus* IgG antibodies	A	II	IgG and precipitins test standardization incomplete	[333]
CPA patients with progressive disease	Control of infection	Itraconazole: Start 200 mg bid, adjust with TDM	A	II	No data to indicate which agent is preferable	[333, 706]
		Voriconazole Start 150-200 mg bid, adjust with TDM			Voriconazole preferred for CNPA and patients with fungal balls to minimize risk	[335, 707,

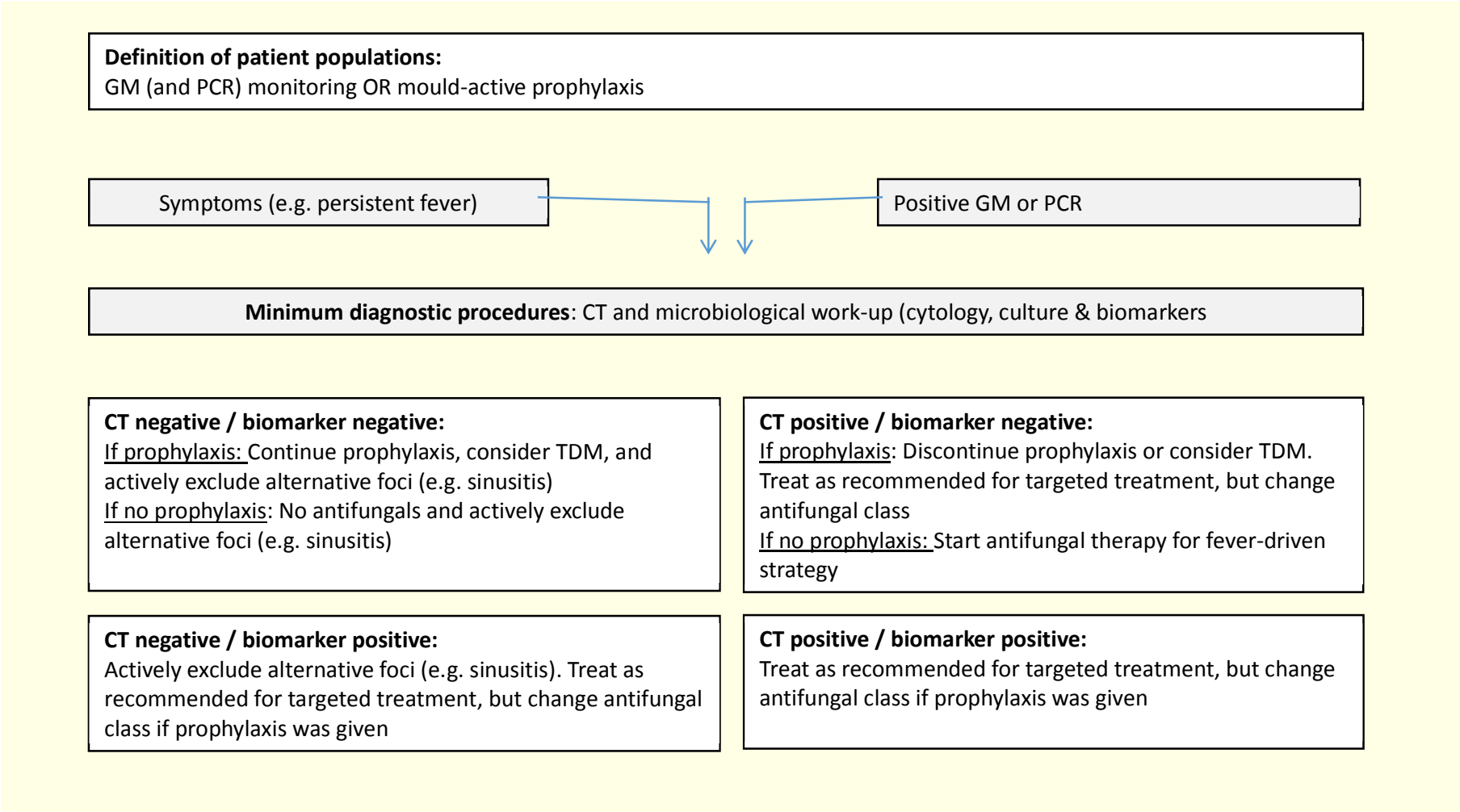
					of resistance	708]
		Posaconazole 400 mg bid (oral suspension) 300mg qd (delayed release tablets)	B	II	Higher rate of adverse events, if some adverse events with itraconazole and voriconazole.	[709]

771 CPA, chronic pulmonary aspergillosis; ABPA, allergic bronchopulmonary aspergillosis; SAIA, ; CNPA, chronic necrotising pulmonary aspergillosis; CCPA,

772 chronic cavitary pulmonary aspergillosis; TDM, therapeutic drug monitoring

773

774 **Figure 1. Management in Neutropenia**



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Comments during consultation:

Please send any comments on this guideline, with supporting data or references where appropriate, to the ESCMID Publications and Medical Guidelines Manager (nancy.gerits@escmid.org) before 09 May 2017. Please use this form for your comments.
Important note: all comments as well as the authors' response to them will be published along with the final version of the guideline.

Page/Line	Comment from (name, contact details)	Comment	Reply
70/-	Francisco López-Medrano – Unit of Infectious Diseases – University Hospital 12 de Octubre, Madrid, Spain	Table 34 – HIV patients – reference 241 is not correct for this population (it refers to solid organ transplant recipients)	Many thanks. Good catch. Replaced this reference.
76/-	Francisco López-Medrano – Unit of Infectious Diseases – University Hospital 12 de Octubre, Madrid, Spain	Table 36 – Treatment with voriconazole – consider to add reference 298	Added.
7/146	Hossein Zarrinfar, Zarrinfarh@mums.ac.ir; Department of Medical Mycology and Parasitology, Allergy research centre, Faculty of medicine, Mashhad University of Medical Sciences, Mashhad, IRAN	One of the reasons for the increase in antifungal resistance is to pay no attention to the dominant species of *Aspergillus* in a region and doing empirical therapies. For example, in the Middle East among *Aspergillus* species, *A. flavus* is the most common cause detected. In addition, *A. niger* is nearly the second most common cause detected; Unlike most reports from throughout the world that *A. fumigatus* is the dominant and most frequent causative agent for fungal infections and environment airborne. The high frequency of *A. flavus* isolation from here may be because of the higher prevalence of the fungus in the environment, for example air, water, and different geographic location (1-3). 1. Fereshteh Zarei, Hossein Mirhendi, Marjan Motamedi, Bahram Ahmadi, Sadegh Nouripour-Sisakht, Hossein Zarrinfar, Nilufar Jalalizand, Jamal Hashemi. Black Aspergillus species isolated from clinical and environmental samples in Iran. Journal of medical microbiology 2015; 64(11): 1454-6. 2. Zarrinfar H, Mirhendi H, Fata AA, Khodadadi H, Kordbacheh P. Detection of *Aspergillus flavus* and *A. fumigatus* in Bronchoalveolar Lavage Specimens of Hematopoietic Stem Cell Transplants and Hematological Malignancies Patients by Real-Time Polymerase Chain Reaction, Nested PCR and Mycological Assays. Jundishapur J Microbiol 2015; 8(1): e13744.	Agree that local epidemiology is a basis to empirical treatment. Another example is *A. terreus* in Innsbruck.

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6/139	Hossein Zarrinfar, Zarrinfarh@mums.ac.ir; Department of Medical Mycology and Parasitology, Allergy research centre, Faculty of medicine, Mashhad University of Medical Sciences, Mashhad, IRAN	However, due to the high sensitivity of PCR technique especially nested PCR; the false positive results may increase because of contamination or colonization. Therefore, this method is not recommended for the specimens of non-sterile sites, although it can be helpful for immunocompromised patients at risk of invasive aspergillosis (1-2). 1. Zarrinfar H, Makimura K, Satoh K, Khodadadi H, Mirhendi H. Incidence of pulmonary aspergillosis and correlation of conventional methods with Nested-PCR and Real-time PCR assay using BAL fluid in Intensive Care Unit patients. Journal of Clinical Laboratory Analysis 2013; 27(3): 181-185. 2. Zarrinfar H, Mirhendi H, Makimura K, Satoh K, Khodadadi H, Paknejad O. Use of mycological, nested-PCR and real-time PCR methods on BAL fluids for detection of *Aspergillus fumigatus* and *A. flavus* in solid organ transplant recipients. Mycopathologia 2013; 176(5-6): 377-385.	No action taken.
14/336	Hossein Zarrinfar, Zarrinfarh@mums.ac.ir; Department of Medical Mycology and Parasitology, Allergy research centre, Faculty of medicine, Mashhad University of Medical Sciences, Mashhad, IRAN	During the past two decades, the incidence of invasive aspergillosis has increased in hospitalized patients, who are particularly immunosuppressed patients. Therefore, assessment of airborne fungal spores can help decrease hospital-acquired infections (HAI) rates (1). 1. Nasrin Rostami, Hossien Alidadi, Hossein Zarrinfar, Pegah Salehi. Assessment of indoor and outdoor airborne fungi in an Educational, Research and Treatment Center. Italian Journal of Medicine. 2017; 11: 52-56.	No action taken.
65/-	David Andresen, St Vincents Hospital Sydney Australia	In Table 32, since many of the agents listed are 'no better than fluconazole", and often more toxic, why isn't fluconazole in the table?	Because we strictly focus on aspergillosis.
-	David Andresen, St Vincents Hospital Sydney Australia	Itraconazole gets only a "D" recommendation but has prophylaxis efficacy equivalent to voriconazole. In our experience the capsules are better tolerated than the suspension and many patients will get good serum levels, so the suspension (which has more gut side-effects) can be reserved for those patients who do not achieve adequate therapeutic levels on the capsules. Several studies have shown good tolerability of the suspension. Itraconazole use has the advantage of "preserving" the more modern azoles for use as treatment if there is persistent fever or suspected breakthrough infection (see for instance Clinical effectiveness	Don't agree. You likely refer to David Marks study, where there was no efficacy difference between voriconazole and itraconazole. Toxicity/tolerability though was different. No action taken.

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		of itraconazole as antifungal prophylaxis in AML patients undergoing intensive chemotherapy in the modern era. C. L. Keighley1,2,3 & P. Manii3 & S. R. Larsen4 & S. van Hal1. Eur J Clin Microbiol Infect Dis (2017) 36:213–217)	
66/-	David Andresen, David.Andresen@svha.org.au St Vincents Hospital Sydney Australia	In Table 33, fluconazole gets a "D" for fever-driven therapy, presumably because of its lack of mould efficacy. However most fungal infections in this setting are yeasts so – if a CT chest can be performed to exclude aspergillosis – it's a perfectly reasonable choice. See for instance the 2000 RCT by Winston which showed Fluconazole as effective but much better tolerated than amphotericin.	The group consensus is D, because of the lack of activity against aspergillosis.
6/119-123 And Table 6 (p32)	Zekaver Odabasi zekaver@marmara.edu.tr, Marmara University, department of infectious diseases Istanbul, Turkey	Regarding the reference 72 saying that "Serial screening for GM in prolonged neutropenic patients and allogeneic stem cell transplantation recipients during the early engraftment phase has an excellent sensitivity and negative predictive value (NPV) for IA [71] but is not recommended in patients on mould-active prophylaxis [72]" may cause misunderstanding. We should also notice that using GM testing is not recommended in patients on mould active prophylaxis but the test remains useful to diagnose patients with a clinical suspicion of invasive fungal disease in patients under mould active prophylaxis as noted in reference 72. It is recommended in figure 1 too. So, although not recommended routinely in surveillance, GM testing in patients on antimould prophylaxis is still useful for the diagnosis of IA (ref 72).	Agree. GM in BAL fluid is particularly useful in case of persistent fever and lung infiltrates on CT. This is addressed in the following lines.
35/- Table 8	Zekaver Odabasi zekaver@marmara.edu.tr, Marmara University, department of infectious diseases Istanbul, Turkey	Adult haematological malignancy and HSCT: reference 389 is a study of nosocomial candidemia in ICU patients not in haematological malignancy patients, so this reference should be removed or replaced with another beta glucan study performed for the diagnosis of general IFD in haematological cancer patients (eg: odabasi z clin infect dis 2004, or ostrosky zeichner l, clin infect dis 2005 etc).	Thanks for pointing out this mistake, ref. should move down one line, inserted the proposed very appropriate references.
57/- Table 28	Zekaver Odabasi zekaver@marmara.edu.tr, Marmara University, department of infectious diseases Istanbul, Turkey	It is generally recommended that using another class of antifungal agent for the treatment of invasive aspergillosis in patients with mould active azole prophylaxis. In table 28 you noticed that voriconazole is D III in such a condition as mentioned above but there is no recommendation about other azoles in the same table such as for itraconazole and isavuconazole. From this table, it can be misunderstood that isavuconazole or	Important point. Added this to the respective table.

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		itraconazole may be used in İA developed under mould active azole prophylaxis. I know that for the isavuconazole we have very limited clinical studies but the references given for voriconazole are also very poor. I think the same recommendations should also be done for isavuconazole and itraconazole at least as an expert opinion level because we know that cross resistance is can be seen in Aspergillus fumigatus isolates for all mould active azoles (ref: Gregson L, AAC 2013). Otherwise it will be a kind of bias I think.	
62/- Table 31	Zekaver Odabasi zekaver@marmara.edu.tr, Marmara University, department of infectious diseases Istanbul, Turkey	Haematological malignancies, e.g. AML with prolonged and profound neutropenia: For the prophylaxis there is no recommendation for voriconazole, although we know that there is very limited number of clinical studies for evaluation of voriconazole in this group of patients (Vehreschild JJ, A double-blind trial on prophylactic voriconazole or placebo during induction chemotherapy for acute myelogenous leukaemia (AML), J infect. 2007) Most of the other guidelines (ECIL 5, NCCN 2015 and German hematology etc.) recommended voriconazole as an alternative agent for the primary prophylaxis of IFD in AML patients. If you do not recommend it in AML, I think it should be noticed in table 31 at least saying that no clinical data or no recommendation or CIII etc	We have it in allogeneic SCT, and not in the neutropenic population / AML, added it.
63/- Table 31	Zekaver Odabasi zekaver@marmara.edu.tr, Marmara University, department of infectious diseases Istanbul, Turkey	Allogeneic HCT (until neutrophil recovery): I couldn't see a recommendation for Fluconazole, although it has AI recommendation in all guidelines in low risk groups,	Yes, this is the specifics of focussing on aspergillosis only, which is somewhat artificial in the prophylaxis scenario, where other pathogens play a role, too.
63, 64/- Table 31, 31b	Zekaver Odabasi zekaver@marmara.edu.tr, Marmara University, department of infectious diseases Istanbul, Turkey	Transferring the data or results from posa prophylaxis study results (ref 525, which was performed in patients undergoing chemotherapy for acute myelogenous leukemia or the myelo-dysplastic syndrome) to neutropenic Allogeneic bone marrow transplant patients seems disrupting the homogeneity and reliability of this table and may be a kind of bias I think. The risk of aspergillosis in any kind of neutropenia then accepted as a good candidate for posa prophylaxis by this data extraction from ref 525. Even risk factors in Allo BMT cases for aspergillosis changes according to type of BMT, match or mismatch condition, age, underlying disease etc.	I see the point, but I don't follow. The group stays in line with the grading system by downgrading from A to B.

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		as you know.	
65/- Table 32	Zekaver Odabasi zekaver@marmara.edu.tr, Marmara University, department of infectious diseases Istanbul, Turkey	Table 32 is for empirical antifungal therapy of IFD in febrile neutropenic patients. Considering the Walsh study on comparison of caspo vs LamB, caspo was better with treatment of baseline IFI, especially in cases with aspergillosis. So you accepted caspo as AI. I would like to ask that how many people in your group accept the caspo as the first choice agent for the treatment of IA. I think initially the committee must vote for the value of the fever based treatment of IA and made a recommendation for this kind of approach even by using data of the C cordonier, Girmenia and L pagano studies. Even recommendations in this table have great discrepancies with figure 1 which is the guideline group's recommended diagnostic approach.	We did not vote on caspofungin first line, and there are arguments and data to support its use. No action taken.
66/- Table 33	Zekaver Odabasi zekaver@marmara.edu.tr, Marmara University, department of infectious diseases Istanbul, Turkey	I would like to vote for Liposomal AmB as AII for the treatment of refractory aspergillosis.	Should have had you there!
27/- Table 2	Zekaver Odabasi zekaver@marmara.edu.tr, Marmara University, department of infectious diseases Istanbul, Turkey	CT imaging is one of the most important diagnostic tool for IA, as guideline group made a strong recommendation on it (AII). CT is also noticed as major determinant of therapy in Figure 1. I think it is necessary to add another table to table 2 or somewhere else, and make recommendations or grading on CT findings of invasive aspergillosis (nodule with or without halo, cavity, etc). We need a recommendation on frequency of CT imaging too (2 weeks etc ?) And also we need recommendations on therapeutic success or failure indicators in CT imaging especially for pulmonary aspergillosis: for clinical studies there are definitions for success, stable or progressive disease as ref 201.	Very challenging, but it is indeed separate papers we work on. The paper for public consultation is the executive summary only.
-/- (General feedback)	J Peter Donnelly p.donnelly@usa.net De Hoefkamp 1096; 6545 MD Nijmegen; The Netherlands	• Decide on which English spelling is to be adopted British or US. If the former use "mould, pathological, haematology" throughout, if the latter use "mold", pathologic, hematology" throughout • Congratulations in giving diagnosis an equal billing to prophylaxis and treatment. Given the size of the document would it not be better to	BE, otherwise no action taken. Thanks for the compliment, it will be several papers following this executive summary.

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		split it into 4 papers 1) instruction 2) diagnosis, 3) prophyalxis and 4) treatment as JAC did with the Ecil pneumocystis guidelines? Just a thought	
90/-	J Peter Donnelly p.donnelly@usa.net De Hoefkamp 1096; 6545 MD Nijmegen; The Netherlands	Other diagnostic procedures include early bronchoalveolar lavage (BAL) [38-44]. Should be BAL fluid throughout	BAL occurs 76 times, for readability we skipped "fluid" 75 times.
102/-	J Peter Donnelly p.donnelly@usa.net De Hoefkamp 1096; 6545 MD Nijmegen; The Netherlands	Both microscopy and culture should be attempted on appropriate specimens from patients at risk for IA	added
114/-	J Peter Donnelly p.donnelly@usa.net De Hoefkamp 1096; 6545 MD Nijmegen; The Netherlands	To achieve optimal recovery of *Aspergillus* from BAL centrifugation of the sample is advised with investigation of the sediment. Shouldn't the original volume be noted to allow estimation of the cfu/mL?	Appears more appropriate in the diagnostic full paper.
118/-	J Peter Donnelly p.donnelly@usa.net De Hoefkamp 1096; 6545 MD Nijmegen; The Netherlands	for diagnosis of IA and a 0.5 cut-off in serum results in a high sensitivity in haematological patients in the absence of anti-mould prophylaxis Please consider adding this cut-off is currently under review by the EORTC and MSG-ERC	Added.
134/-	J Peter Donnelly p.donnelly@usa.net De Hoefkamp 1096; 6545 MD Nijmegen; The Netherlands	Aspergillus PCR has been applied to blood and BAL and is being considered by the EORTC and MSG-ERC for inclusion into the definitions of invasive fungal disease.	Pleasure to add this. And I added fluid to BAL, too.
160/-	J Peter Donnelly p.donnelly@usa.net De Hoefkamp 1096; 6545 MD Nijmegen; The Netherlands	It is recommended that the MIC should be determined for all clinically relevant *Aspergillus* isolates	Rephrased accordingly.
317/-	J Peter Donnelly p.donnelly@usa.net De Hoefkamp 1096; 6545 MD Nijmegen; The Netherlands	Consider adding "In fact, recent history of neutropenia, receipt of an allogeneic stem cell transplant and prolonged use of corticosteroids are considered sufficient to meet the host factors for defining invasive fungal disease."	No action taken.
372/-	J Peter Donnelly p.donnelly@usa.net De Hoefkamp 1096; 6545 MD Nijmegen; The Netherlands	Please consider reversing the terminology to fever-driven (empiric) therapy, and diagnostic driven (pre-emptive) therapy as the latter allows for imaging, biomarkers or both to be used to start treatment	Agree.
27/- Table 2	J Peter Donnelly p.donnelly@usa.net De Hoefkamp 1096; 6545 MD Nijmegen;	Neutropenia, fever or clinical symptom of pneumonia, empiric antibiotics failing to achieve defervescence, e.g. FUO	Agree. Thanks!

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	The Netherlands		
27/- Table 2	J Peter Donnelly p.donnelly@usa.net De Hoefkamp 1096; 6545 MD Nijmegen; The Netherlands	To identify possible underlying fungal or other infectious disease.	Rephrased.
27/- Table 2	J Peter Donnelly p.donnelly@usa.net De Hoefkamp 1096; 6545 MD Nijmegen; The Netherlands	What does Bridging to recovery mean?	Bridging until neutrophil recovery
27/- Table 2	J Peter Donnelly p.donnelly@usa.net De Hoefkamp 1096; 6545 MD Nijmegen; The Netherlands	To send appropriate specimens for microscopy, culture and PCR	Agree.
32-33/- Table 6	J Peter Donnelly p.donnelly@usa.net De Hoefkamp 1096; 6545 MD Nijmegen; The Netherlands	Please consider Galactomannan in blood (serum or plasma)	Now in a footnote.
32-33/- Table 6	J Peter Donnelly p.donnelly@usa.net De Hoefkamp 1096; 6545 MD Nijmegen; The Netherlands	Please add to the comments for patients not n mould-active prophylaxis	?
34/- Table 7	J Peter Donnelly p.donnelly@usa.net De Hoefkamp 1096; 6545 MD Nijmegen; The Netherlands	Galactomannan: Optimal cut-off ranging from 0.5 to 1.0 is not consistent with the text. Also use the terminology Optical Density Index (ODI) when referring to galactomannan	Refers to BAL fluid. ODI is now used on various occasions throughout the document.