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Diagnosis and Management of Aspergillus Diseases: Executive Summary of the 2017 ESCMID-ECMM-ERS Guideline

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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 aspergillosis. Of the numerous recommendations a few are summarized here. Chest computed tomography as well as bronchoscopy with bronchoalveolar lavage (BAL) in patients with suspicion of pulmonary invasive aspergillosis (IA) are strongly recommended. For diagnosis, direct microscopy preferably using optical brighteners, histopathology and culture are strongly recommended. Serum and BAL galactomannan is recommended as markers for the diagnosis of IA. PCR should be considered in conjunction with other diagnostic tests. Pathogen identification to species complex level is strongly recommended for all clinically relevant *Aspergillus* isolates; antifungal susceptibility testing should be done in patients with invasive disease in regions with resistance found in contemporary surveillance programmes. Isavuconazole and voriconazole are the preferred agents for first line treatment of pulmonary IA, while liposomal amphotericin B is moderately supported. Combinations of antifungals as primary treatment options are not recommended. TDM is strongly recommended for patients receiving posaconazole suspension or any form of voriconazole for IA treatment, and in refractory disease, where a personalized approach considering reversal of predisposing factors, switching drug class and surgical intervention is also strongly recommended. Primary prophylaxis with posaconazole is strongly recommended in patients with acute myelogenous leukaemia or myelodysplastic syndrome receiving induction chemotherapy. Secondary prophylaxis is strongly recommended in high-risk patients. 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 [1-9]. This part of the guideline regarding invasive and chronic aspergillosis is a condensation of all the recommendations made by the guideline subcommittees and presented in tables for easier and faster reading. More details on how the recommendations were arrived at are planned in supplementary publications. This *Aspergillus* guideline will follow the style of other guidelines by including diagnostic and therapeutic guidance. Other scientific groups have published guidelines on this topic previously 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 was similar to what was done previously [10]. In brief, experts in the field were nominated by the three societies ESCMID, ECMM, and ERS. The total 53 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 authors and sent to the ESCMID guideline director for public review. Then the final version was submitted to Clinical Microbiology and Infection for additional peer review and subsequent publication. Only the rationale of the chronic pulmonary aspergillosis (CPA) guideline was published ahead of time [11].

Questions were predefined and modified where appropriate and the strength of recommendation and quality of evidence was slightly modified (Table 1) [12]. Diagnostic tests are regarded as interventions.

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.

Thoracic Imaging

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)** [13-23]. 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 [24-26], 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 [27-32], PET-CT being of modest interest in the diagnostics of IA [33, 34].

No CT scanning technique is 100% sensitive or specific for pulmonary IA [35-37]: Classical CT findings of angioinvasive aspergillosis include macronodule(s) >1 cm, which may be surrounded by a halo of ground-glass attenuation (halo sign, early phase, inconstant) [36, 38-40], pleural based wedge-shaped areas of consolidation [41], alveolar consolidations [36, 42, 43], masses (especially in SOT recipients) [15, 38], internal low attenuation[44], reverse halo sign [45], cavity or air-crescent sign (delayed finding), ground glass opacities and pleural effusion [17, 35, 46]. Bronchoinvasive forms may appear as tracheal or bronchial wall thickening, centrilobular nodules with tree in bud appearance [14] in a patchy distribution, predominant peribronchial areas of consolidation [47] or bronchopneumonia [46] (Table 2).

Bronchoalveolar Lavage and Biopsies

Other diagnostic procedures include early bronchoalveolar lavage (BAL) **(AII)** [48-54], guided by CT-findings [55, 56], and less frequently CT-guided transthoracic biopsies, video-assisted thoracoscopic surgery (VATS), open lung biopsies, transbronchial biopsies or convex endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA), the latter technique appearing to be a promising procedure in this setting [28, 57-72]. Contraindications to these techniques need to be considered.

Imaging of other Sites

Moreover, according to clinical symptoms, paranasal CT, CT or MRI of the CNS as well as abdominal CT may also be required. In particular, findings of sinusitis with bone erosion may be observed, intracranial and/or intraorbital extension of the disease being best evaluated by MRI [73-75]. 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 [76-79].

Microscopy and Culture

Both microscopy and culture should be attempted on appropriate specimens from patients at risk for IA **(AII)** with a priority for culture in most cases where insufficient material is available**.** 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 [80]. 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 Blancophor™ have the advantages of increased sensitivity, rapid turnaround time, and broad applicability but are not specific for *Aspergillus* **(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 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

241 optimal recovery of *Aspergillus* from BAL fluid, centrifugation of the sample is advised with
242 investigation of the sediment **(AIII).** It is recommended that cultures of high volume untreated sputum
243 and BAL should be performed as opposed to culturing small volumes of digested, liquefied samples
244 [81] (Table 4). Specific media to support fungal growth are recommended. Species identification to the
245 complex level should be done for clinically relevant isolates from patients who need antifungal
246 treatment, and for epidemiological purposes (AIII) (Table 5).
247
248 **Non-Culture Based Assays**
249 Galactomannan (GM) detection in fluids (especially BAL) is more sensitive than culture for diagnosis of
250 IA. GM is reported as optical density index (ODI). In serum samples an ODI cut-off of 0.5 results in high
251 sensitivity in haematological patients in the absence of mould-active prophylaxis **(AI)** (Table 6). Serial
252 screening for serum GM in prolonged neutropenia and in allogeneic stem cell transplantation
253 recipients during the early engraftment phase has a high sensitivity and negative predictive value (NPV)
254 for IA **(AII)** [82]. Serial screening is not recommended in patients on mould-active prophylaxis [83].
255 Sensitivity of serum GM testing is significantly lower in non-neutropenic versus neutropenic patients
256 [84]. Decrease of the ODI during the first two weeks of antifungal therapy is a reliable predictor of a
257 satisfactory response in cancer patients [85]. GM detection in BAL specimens has an excellent
258 performance with evidence that ODI of 0.5–1.0 has decreased predictive values compared with results
259 of >1.0 [86] **(AII)** (Table 7). The test also has diagnostic value in patients undergoing lung
260 transplantation or who are in intensive care [87-89]; a sensitivity of 100% and a specificity of 90.4%
261 was defined at cut-off of 1.5 [87].
262 (1-3)-β-D-glucan (BDG) is a constituent of the cell wall of many species and genera of fungi and is
263 released into body fluids in association with fungal infection. A limited role is given for the exclusive
264 testing of the BDG in diagnosing IA **(BII)** (Table 8), however, the combination with GM or PCR improves
265 specific detection [90].

The *Aspergillus* lateral flow LFD assay can be performed on serum and on BAL samples, but at the time of writing this assay is not commercially available [91] (Table 9).

Aspergillus PCR has been applied mostly to blood and BAL fluid. For both sample types, a combination with other biomarkers increases the likelihood of IA [92, 93]. The performance of serum PCR is not significantly different from that of whole blood [94-97]. 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 [98, 99] (Table 10 and 11).

On hyphal positive biopsy samples molecular detection of fungi is strongly recommended **(AII)**. If no hyphae are visible the diagnostic yield of molecular methods is lower (Table 12). Recommendations for storage of original samples and isolates are given in table 13. Antibody detection tests are not supported for the diagnosis of IA **(CII)** (Table 14).

Antifungal Susceptibility Testing

Resistance to antifungal agents is an increasing problem in *Aspergillus* diseases [100-102]. *Aspergillus* species can be intrinsically resistant to polyenes and azoles [103], or may acquire resistance following exposure to azole compounds [104]. Acquired resistance to azoles is mainly found in *Aspergillus fumigatus* and is reported globally [100, 101, 105-108]. Resistance may also develop through exposure to azole fungicides in the environment [109-112]. As resistant spores are present in ambient air, patients may present with azole-resistant *Aspergillus* disease without previous azole therapy [113, 114]. Individual *Aspergillus* colonies from a single specimen may harbour different resistance profiles [117], hence multiple colony testing (up to 5 colonies) is recommended to increase sensitivity for azole-resistance detection **(BIII**).

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) (Tables 5, 15, 16 and 17).

Antifungal susceptibility testing of *Aspergillus* isolates should be performed in patients with invasive disease with the exception of azole naïve patients in regions with no resistance found in contemporary surveillance programmes and regularly for epidemiological purposes including ≥100 isolates. This is particularly important in patients who are unresponsive to antifungal treatment, or in patients who are clinically suspected having an azole-resistant pathogen **(AIII)** (Table 15). If MIC-testing is not available, routine agar screening can be used to detect azole resistance (Table 16) [118]. However, such isolate should be referred to a mycology reference laboratory for MIC testing. 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)**. Both itraconazole and voriconazole **(AII)** should be tested to ensure detection of the voriconazole-resistance mutation TR_{46}/Y121F/T289A [118]. 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 although a correlation between MIC and clinical outcome exist for *A. terreus* and *A. flavus* it remains to be documented for *A. fumigatus* due to the scarcity of resistant isolates (Table 17).

Voriconazole and isavuconazole are recommended for the treatment of IA due to species showing high AmB MICs (Table 19). Liposomal AmB (L-AmB) or AmB lipid complex (ABLC) are recommended for species with intrinsic high azole MICs (Table 18 and 20). In aspergillosis due to *A. fumigatus* specifically, voriconazole or isavuconazole are 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 CPA, L-AmB or micafungin can be considered **(BII)** if surgical intervention is precluded [11]. 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%, first line 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 [119]. 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).

Itraconazole

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])** [120-125]. 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 [126, 127]. 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. Repeat TDM is recommended the following week to confirm the patient remains in the therapeutic range, and repeated thereafter as clinically indicated if there are changes in the patient's clinical condition, concomitant medications known to interact, 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.

Voriconazole

A plasma trough concentration of 1-5.5 mg/L is considered adequate for most patients receiving voriconazole prophylaxis or treatment **(AII, safety and efficacy)** [128-133]. 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, e.g. an MIC of 2 ml/L) [130, 131]. TDM is strongly recommended in children due to the much higher rates of drug elimination and potential for underdosing, especially with the lower voriconazole doses recommended in the past **(AII)** [134, 135]. Plasma levels should be monitored between 2-5 days after initiation of therapy, and repeated the following week to confirm the patient remains in the therapeutic range. Repeated monitoring is indicated until steady state level in the therapeutic range is confirmed, if there are changes in the patient's clinical condition, concomitant medications, or suspected toxicity (Table 23).

Posaconazole

For patients receiving posaconazole suspension, a plasma trough of >0.7 mg/L is recommended during prophylaxis **(BII efficacy)** [136, 137]; and a trough of >1 mg/L is recommended if the patient is receiving treatment for suspected or documented IA **(AII efficacy)** [138]. 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 and intravenous formulations with the EMA used a provisional cut-off of 3.75 mg/L [139-141]. 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 tablet formulation is contraindicated) 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 [139]. 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 24).

Isavuconazole

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 therapeutic range or support the need for routine TDM for this agent [142]. 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 25).

Flucytosine

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 required for efficacy are unknown but a level of 25-50 mg/mL is recommended based upon experience from cryptococcosis [143, 144].

Hospital Environment

Standards for the hospital environment in immunosuppressed adults and children 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)** [145-150]. 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 [151-154]. Protective masks for patients are proven not to be effective outside of the protected area **(CII)** [155]. Filters for water supply, especially in showers, are recommended **(BII)** [156-160]. No data are available to support regular environmental air sampling to prevent infections. However, indoor sampling is advisable to monitor filter efficacy **(BIII)** [161, 162].

Treatment Strategies

Two strategies are accepted for managing patients with haematological malignancy at risk for IA: 1) the patient receives primary prophylaxis or 2) the patient receives no prophylaxis but is monitored at least twice weekly using biomarkers. The decision between the two strategies depends on local epidemiology, access to rapid diagnostics and patient characteristics. 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.

Primary Prophylaxis

At least three studies describe a number of patients who succumbed with IA missed prior to death [163-165]. Although diagnostic procedures improved since then, they are not satisfactory. For this reason, patients known to be at high risk for IA may receive primary prophylaxis, especially patients with profound and prolonged neutropenia or with active graft-versus-host disease (GvHD) (Table 26).

Aspergillosis in Haematological Malignancy and 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 [166]. In fact, up to two thirds of patients with IA diagnosed after allogeneic HSCT are not neutropenic [167], and the median time of diagnosis of IA after allogeneic HSCT is 82 days (range, 3 - 6542 days) [168].

Treatment

Providing a definite diagnosis of IA is a continuously challenging endeavour for clinicians. The EORTC/MSG 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 [169]. Any patient at risk considered by the responsible clinician as having IA should receive antifungal therapy **(AIII)** (Tables 27-28). 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 GvHD. Good partial or complete remission requires no persistent clinical, including 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 [170-173]. Close monitoring (e.g. non-enhanced CT 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 [174-179]. 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 indicated no mortality difference for any kind of infection in patients with neutropenia [180].

Fever-driven ("Empiric"), and Diagnosis-driven ("Pre-emptive") Therapy

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 [181-186] and mortality [187, 188] (Table 29). The duration of empiric antifungal treatment is set by the following rules applied in randomized clinical trials: If the patient is afebrile and has no active infection or infiltrates, then antifungal therapy can be discontinued after recovery of leukocyte counts [188-190]. Today, antifungal stewardship may warrant clinical trials on empiric treatment duration, but no such trial has been conducted so far.

Pre-emptive treatment is a diagnosis driven strategy. In most cases, it is defined by positive GM testing. However, chest CT with pulmonary infiltrates could apply as well. The use of BDG and PCR testing as alternative biomarkers for galactomannan have considerable merit [191, 192], though BDG is not specific for *Aspergillus* disease. In haematological patients, false positive BDG often results from contaminated infusions [193-196]. Very few authors wait for *Aspergillus*-associated suggestive

radiological signs including nodule, halo sign, wedge-shaped area of consolidation, or – late in the course of invasive aspergillosis – the air crescent sign, before starting antifungal treatment. Treatment choices are as recommended in targeted treatment.

Adult Patients without Haematological Malignancy

Epidemiology

Approximately 43-80% of the cases of IA appear in patients without a haematological malignancy [52, 197-200], although these patients are rarely included in the seminal studies of antifungals [170, 171, 173]. The proportion of these patients is even increased when exposed to spore concentrations of >25 cfu/m^3 in hospital air [201-204]. The non-haematological populations at risk for IA include 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, influenza as well as critically ill patients requiring ICU admission [52, 197-199, 205-208]. These patients frequently do not fulfil the EORTC/MSG criteria for invasive aspergillosis [169]. 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 [52]. 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 11.6% [209, 210], 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 [209-211]. 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 [210, 212]. With the exception of lung transplantation, in which universal prophylaxis is still common, antifungal prophylaxis will target SOT recipients with additional risk factors [211]. Risk factors for early IA in all SOT recipients – Including heart transplants – comprise renal failure requiring

497 replacement therapy, re-intervention, CMV disease, and high environmental exposure to mould
498 spores [211, 213-215]. In liver transplantation, high model for end-stage liver disease (MELD) score,
499 transplantation in fulminant hepatic failure, high intraoperative transfusion needs or re-
500 transplantation are considered indications for post-surgical prophylaxis [216-224]. In lung transplant
501 recipients, risk factors include previous respiratory tract colonization with *Aspergillus,* single lung
502 transplant, CMV disease and acquired hypogammaglobulinaemia [225-227]. In kidney transplantation
503 risk factors include COPD, delayed graft function, bloodstream infection, and acute graft rejection
504 [228] and an >1.25 mg/kg/day average dose of prednisone [229]. Finally, some polymorphisms in
505 defence genes have also been suggested to increase risk in transplant recipients [230, 231].
506 The incidence of IA in HIV patients has decreased since the advent of new antiretroviral therapy (2.2
507 cases per 10,000/year), but mortality remains high (38%) [232]. IA typically appears in patients with
508 low CD4 counts and associated conditions such as neutropenia, advanced cirrhosis, liver
509 transplantation or glucocorticosteroid therapy [233-241]. As in other non-haematological populations,
510 EORTC/MSG criteria only detect half of the IA cases diagnosed among HIV-infected patients [232] and
511 in a recent series of autopsies of AIDS patients, only 12% of the patients with IA had been diagnosed
512 ante mortem [242] (Table 30).
513 IA may affect 0.3% of patients with liver cirrhosis [243]. Both acute liver failure and advanced cirrhosis,
514 mainly alcoholic hepatitis treated with glucocorticosteroids, have been recognized as risk factors for
515 IA [205, 244-246]. A low level of clinical suspicion explains that 53% of the cases of IA in cirrhotic
516 patients are only recognized post-mortem [247] and that liver disease is independently associated with
517 IA-related mortality [199, 248].
518 IA has also been described in apparently immunocompetent patients in a critical condition as a
519 complication of ARDS, COPD, influenza, pneumonia, burns, severe bacterial infection, surgery, and
520 malnutrition. Incidence is 4-6/1,000 ICU admissions and the mortality is higher than 70% in most series
521 [245, 249-252]. Glucocorticosteroid treatment was the major host factor [253, 254] and as in cirrhotic
522 or HIV positive patients delayed diagnosis is common [255, 256]. COPD patients requiring

glucocorticosteroids represent a group with especially high mortality [249, 257 , 258]. Risk factors include admission to ICU, chronic heart failure, and antibiotic treatment and, above all, the cumulative dose of glucocorticosteroids [257].

Pulmonary and CNS aspergillosis predominates in these populations, but disseminated disease, fulminant and atypical forms may occur [203, 214, 225, 251, 259-267]. 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 over-diagnosis has to be prevented [197, 268-272]. Regarding imaging findings, angioinvasive presentation included in the EORTC/MSG criteria is uncommon in this setting [273]. Airway invasive radiological presentation was present in 37% of heart transplant recipients and was associated with delayed diagnosis and poorer prognosis [214, 274]. In COPD and HIV-positive patients, the most common radiological presentation was an alveolar infiltrate [273, 275, 276]. 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 [277-285] (Table 31).

Treatment

Despite no comparative studies of antifungal therapy in non-haematological patients voriconazole remains the first option, since it has been related to reduced mortality [216, 286-288] (Table 32). Combination therapy is uncommon, although retrospective data was encouraging in SOT recipients [289]. The risks of drug-drug interactions and toxicity are very important in these populations and TDM is advisable [290-295]. In patients with liver insufficiency, L-AMB is usually the first therapeutic option. Antifungal resistance is not a common problem despite prophylaxis [296, 297], although some cases have been reported [298-300]. Finally, immune reconstitution syndrome may occur after therapy initiation [301].

Most lung recipients receive antifungal prophylaxis. Targeted prophylaxis is preferred in the remaining SOT with risk factors [211, 213, 302-305]. However, significant variation in practice has been noted

549 [221, 304, 306, 307]. In order to avoid drug-drug interactions and toxicity, echinocandins or inhaled
550 amphotericin are preferentially used [308-311], although voriconazole has also demonstrated its
551 efficacy and safety in this setting [217, 220, 312-314]. Duration of prophylaxis is adjusted to the
552 presence of risk factors and, with the exception of lung recipients, is usually limited to 3-4 weeks [215]
553 (Table 33).
554
555 **Special Considerations in Children**
556 Presenting symptoms, distributions and patterns of diseases and vulnerability to IA are similar
557 between children and adults. However, differences exist in epidemiology and underlying conditions,
558 usefulness of newer diagnostic tools, pharmacology of antifungal agents and evidence from
559 interventional phase III studies. Recommendations for paediatric patients are based on efficacy in
560 phase II and III trials in adults, the availability of paediatric pharmacokinetic data, safety data and
561 supportive efficacy data. In addition, regulatory approval is considered as well. Therapeutic drug
562 monitoring is always recommended when mould-active azoles are used as prophylaxis or treatment.
563 Primary antifungal prophylaxis may be indicated in paediatric patients at 'high risk' for developing
564 invasive fungal diseases, and specifically IA. An incidence rate of IFDs of ≥10% is usually considered as
565 high risk. High-risk populations include children with de novo or recurrent leukaemia (e.g. AML, ALL
566 depending on treatment protocol), bone marrow failure syndromes with profound and persistent
567 neutropenia (e.g. MDS, VSAA), allogeneic HSCT recipients, patients with chronic granulomatous
568 disease and those undergoing lung transplantation. For patients with haematological disorders, the
569 mould-active oral azoles are the first choice to prevent IA in children, although neither itraconazole
570 nor posaconazole are licensed for use in patients <18 years of age. Due to the lack of paediatric data,
571 recommendations for lung and high-risk liver transplant patients correspond to those given for adults
572 [213, 315]. Secondary prophylaxis to prevent recurrence of IA when risk factors are persisting is
573 recommended with an antifungal targeted at the previous *Aspergillus* species, which caused the first
574 episode (see below and Table 34).

575 Diagnostic procedures used in children are not different from those used in adults but their
576 performance may differ. Suggestive abnormalities (e.g. halo sign, air crescent sign) on CT-chest as
577 described in adults are less common in children in which non-specific masses or infiltrates predominate
578 [316-318]. The GM test on blood and BAL samples has a similar sensitivity and specificity profile
579 compared to adults [319-327]. The BDG test is not specific for *Aspergillus* and is not validated in
580 children. Higher baseline levels are reported in healthy children and therefore the cut-off is yet
581 unknown [328-332].
582 General management principles of IA are consistent with those in adults and include prompt initiation
583 of antifungal therapy, control of predisposing conditions (e.g. reduction or discontinuation of
584 glucocorticosteroids in immunosuppressed, administration of colony-stimulating factors in
585 neutropenic patients), and surgical interventions on a case by case basis using a multidisciplinary
586 approach. Voriconazole is recommended as the first line agent to treat IA in all children except
587 neonates **(AIIt)**. L-AmB is first choice for neonates **(AIII)** and may replace voriconazole as first line
588 treatment in areas or institutions with a high prevalence of azole-resistant *A. fumigatus*. Upon
589 diagnosis of invasive pulmonary aspergillosis, thorough evaluation for further sites of infection is
590 required and should include the CNS. The optimal duration of therapy is determined by the resolution
591 of all signs and symptoms and reversal of the underlying deficit in host defences. For salvage therapy
592 and breakthrough infections, a switch to a different class of antifungals is recommended [123, 132,
593 138, 170, 171, 177, 333-341] (Table 35).
594 If a fever-driven (empiric) strategy is used in at risk paediatric haematological patients, caspofungin or
595 L-AmB are recommended until resolution of fever and neutropenia [342-344]. Treatment
596 recommendations for a diagnosis-driven (pre-emptive) strategy correspond to those made for
597 targeted treatment [185, 186, 345, 346].
598
599 **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 36.

Treatment of Refractory Disease

Refractory IA is defined as progression of disease and should be differentiated from stable disease [349]. 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 [350]. In case of GM negative IA, early assessment of response may be difficult 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) [38, 349, 351-359]. The choices of antifungal agents in refractory disease are listed in 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 [360, 361]. 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 [11, 362]. 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 [11, 363]. Over 90% of patients have circulating *Aspergillus* antibody (precipitins) **(AII)** [364]. A positive culture of *A. 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, may mimic malignancy as well as nodules 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 [362].

If technically feasible single aspergilloma should be surgically removed, preferably via video-assisted thoracic surgery technique with due consideration to risks as recommended [365]. Long term oral

antifungal therapy is strongly recommended in patients with CCPA, partly to reduce general and respiratory symptoms [366, 367], but also to minimise haemoptysis and prevent lung destruction and fibrosis **(AII)** itraconazole or voriconazole are effective for CCPA **(AIII)** [11]. Oral posaconazole is a potential alternative treatment **(BII)** [11]. Six months of therapy is the recommended minimum **(AI)** [11]. 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 intends to provide additional publications supporting the rationale of recommendations given.

Finally, the guideline group provides comprehensive tables explaining various options for specific situations.

669 **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	

670

671 **Table 2. Recommendations for imaging and bronchoalveolar lavage**

Population	Intention	Intervention*	SoR	QoE	Comment	Ref.
Neutropenia, fever or clinical symptom of pneumonia, empiric antibiotics, failing to achieve defervescence, e.g. FUO	To detect pulmonary infiltrates	Chest CT and thin section multi-detector CT (MDCT)	A	II	Within 12-24h after the beginning of fever, dose optimization recommended	[21, 31, 35, 368]
Haemoptysis	To identify vessel occlusion	Chest angio-CT / pulmonary CT angiography	B	II		[24-26]
Haemoptysis	To identify vessel erosion	Chest angio-CT / pulmonary CT angiography	A	II		[24-26, 369, 370]

Any	To identify possible underlying fungal or other infectious disease	BAL	A	II		[21, 49-54]
Any	To obtain appropriate specimens for microscopy, culture and PCR	CT-guided BAL	A	III		[55, 56]

*, Diagnostic tests are interventions; SoR, Strength of recommendation; QoE, Quality of evidence; FUO, fever of unknown origin; CT, computed tomography; BAL, bronchoalveolar lavage; PCR, polymerase chain reaction

675 **Table 3. Microscopic examinations**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Any	To identify fungal elements in histological sections and stains	Histological examination Gomori's methenamine silver stain Periodic acid-Schiff	A	III	Histopathology is an essential investigation Inability to definitively distinguish other filamentous fungi GMS: removes cellular background; more sensitive to hyphal elements PAS: advantage of counter stain to check cellular detail	[80, 371-373]
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 (e.g. *Aspergillus*: typically dichotomous and septate, Mucorales: pauci-septate and 90° angle branching, yeast: budding) Rapid turnaround time Broad applicability May be applied to frozen sections, paraffin-embedded tissue	[374-378]

Any	To identify fungal elements in histological sections and stains	Immunohistochemistry Monoclonal antibody WF-AF-1 or EB-A1 In situ hybridization	B	II	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* Time consuming and not broadly available	[374-378]
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 No species identification but the micromorphology may provide info on the fungal class (e.g. *Aspergillus*: typically dichotomous and septate, Mucorales: pauci-septate and 90° angle branching, yeast: budding)	[80, 373, 379]

676 SoR, Strength of recommendation; QoE, Quality of evidence; BAL, bronchoalveolar lavage; HE, haematoxylin-eosin; GMS, Gomori's methenamine silver
677 stain; PAS, Periodic acid-Schiff; CNS, central nervous system
678

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®, or using sonication and 1,4-dithiothreitol	A	III	Essential investigation High volume sputum culture (entire sample) shown to significantly increase recovery	[81, 380]
Any	To achieve optimal recovery of *Aspergillus* from BAL by centrifugation and investigation of the sediment	Centrifugation of BALs or bronchial aspirates	A	III	Essential investigation Isolation of *Aspergillus* dependent on volume cultured	[81]

SoR, Strength of recommendation; QoE, Quality of evidence; BAL, bronchoalveolar lavage; PCR, polymerase chain reaction

682 **Table 5. Culture and *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 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	[81, 381, 382]
	Primary isolation from non-sterile samples, e.g. sputum, respiratory aspirates	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 (and species	Culture on identification media at 25-30ºC, 37ºC	A	II		

	identification of *A. fumigatus* specifically)	and 50ºC (2% MEA and Czapek-Dox Agar) and microscopic examination			Thermotolerance test (growth at 50 °C for species confirmation of *A. fumigatus*)	
	Identification at species level	MALDI-TOF MS identification	B	II	In house databases are often used to improve identification rates	[383-386]
	Identification at species level	Sequencing of ITS, beta-tubulin and calmodulin	A	III	Not necessary in organisms with typical growth, but in cases of atypical growth	[387, 388]
	To study outbreaks	Microsatellite and CSP analysis	C	II	To study outbreaks (which in general may comprise more than one genotype)	[389-391]
			B	II	To study colonisation patterns	[392]

SoR, Strength of recommendation; QoE, Quality of evidence; CSF, cerebrospinal fluid; SDA, Sabouraud dextrose agar; BHI, brain heart infusion; PDA, potato dextrose agar; MEA, malt extract agar; MALDI-TOF MS, matrix-assisted laser desorption ionization time-of-flight mass spectometry identification; ITS, internal transcribed spacer; CSP, Cell surface protein

683

684 **Table 6. Galactomannan testing in blood samples**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Patients with prolonged neutropenia or allogeneic stem cell transplantation recipients **not on mould-active prophylaxis**	Prospective screening for IA	GM in blood*	A	I	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	[82, 94, 393-397]
		Draw samples every 3-4 days	C	III		
Patients with prolonged neutropenic or 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 or the low yield may be due to decreased incidence of IA	[398, 399]
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	[319, 394, 400, 401]

ICU patients	To diagnose IA	GM in blood*	C	II	Better performance in neutropenic than in non-neutropenic patients	[89, 402]
Solid organ recipients	To diagnose IA	GM in blood*	C	II	Low sensitivity, good specificity Most data for lung SOT	[319, 403, 404]
Any other patient	To diagnose IA	GM in blood*	C	II	Piperacillin/tazobactam may no longer be responsible for false positive results according to recent studies Cross reactivity in case of histoplasmosis, fusariosis, talaromycosis (formerly: penicilliosis)False positive results reported due to ingestion of ice-pops, transfusions, antibiotics, Plasmalyt® infusion	[401, 405-412]
Cancer patients	To monitor treatment	GM in blood*	A	II		[85, 359, 413]

685 SoR, Strength of recommendation; QoE, Quality of evidence; *, serum or plasma; GM, galactomannan; IA, invasive aspergillosis; ICU, intensive care unit;

686 ODI, optical density index; PPV, positive predictive value; SOT, solid organ transplantation

687

688 **Table 7. Galactomannan testing in samples other than blood**

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	[86, 414-418]
Any	To diagnose cerebral IA	To apply GM test on cerebrospinal fluid	B	II	No validated cut-off	[419, 420]
Any	To detect GM in tissue	To apply GM test on lung biopsies	B	II	Using a cut-off 0.5 resulted in a sensitivity of 90 % and a specificity of 95%; specimens need to be sliced, precondition for doing so is that sufficient material is available; dilution in isotonic saline	[373, 421]

689 SoR, Strength of recommendation; QoE, Quality of evidence; BAL, bronchoalveolar lavage; GM, galactomannan; IA, invasive aspergillosis

690

691 **Table 8. *ß*-D-glucan assays**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Mixed population: adult ICU, haematological disorders, SOT	To diagnose IFD	Diagnostic assay	C	II	5 different assays Overall sensitivity of 77% and specificity of 85% Specificity limits its value in this setting	[90, 422]
		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%	[90, 422]
Adult haematological malignancy and HSCT	To diagnose IFD	Diagnostic assay	C	II	Overall sensitivity: 50-70%, specificity: 91-99%	[193-195, 423-428]
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	[429, 430]

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	[431]
Adult haematological malignancy and HSCT	To diagnose IA	Diagnostic assay	C	II	Overall sensitivity: 57-76%, specificity: 95-97%	[422, 423, 429]
		Screening assays	C	II	Overall sensitivity: 46%, specificity: 97% Confirmation with GM increases specificity Data suggests BDG is unsuitable for ruling out diagnosis of IA	

692 SoR, Strength of recommendation; QoE, Quality of evidence; HSCT, haematopoietic stem cell transplantation; ICU, intensive care unit; SOT, solid organ
693 transplantation; IFD, invasive fungal disease; PPV, positive predictive value; NPV, negative predictive value; GM, galactomannan; BDG, ß-D-glucan test; IA,
694 invasive aspergillosis

Table 9. Lateral flow device antigen test for IA

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Haematological malignancy and solid organ transplant	To diagnose IA	LFD applied on 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	[432]
Haematopoietic stem cell transplantation	To diagnose IA	LFD applied on serum samples	B	II	Prospective screening in 101 patients undergoing allogeneic HSCT	[433]
Immunocompromised patients	To diagnose IA	LFD applied on 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%).	[434]

SoR, Strength of recommendation; QoE, Quality of evidence; 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

700 **Table 10. PCR on bronchoalveolar lavage or cerebrospinal fluid**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Patients undergoing allogeneic stem cell transplantation recipients not on mould-active prophylaxis	To diagnose IA	BAL PCR	B	II		[435]
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	[359, 415, 434, 436-456]

ICU patients, mixed populations	To diagnose IA	BAL PCR	B	II	Commercially available Aspergillus PCR assays with good performance data.	[81][414][454][457][458][459]
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)	[419, 460-463]

701 SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis ; BAL, bronchoalveolar lavage; PCR, polymerase chain reaction; ICU,

702 intensive care unit; CNS, central nervous system; CSF, cerebrospinal fluid.

703

704 **Table 11. PCR on whole blood, serum or plasma**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Patients with haematological malignancies	To diagnose IA	PCR on blood samples	B	II	Meta-analysis: 16 studies PCR single positive test: Sensitivity: 88%, specificity: 75%; PCR 2 consecutive positive tests: Sensitivity: 75%, specificity: 87%	[464]
	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%	[465]
	To diagnose IA	PCR on whole blood samples			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	[466]
Haematopoietic stem cell transplantation	To diagnose IA	Prospective screening PCR on whole blood samples	B	II	Combination of serum and whole blood superior	[94-97]

	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%	[98]
	To diagnose IA	PCR and GM in BAL	A	II		[396]

SoR, Strength of recommendation; QoE, Quality of evidence; 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

708 **Table 12. Molecular diagnostics on biopsies**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Biopsy with visible hyphae	To detect and specify a fungus	Broad range PCR	A	II	High sensitivity (> 90 %) and high specificity (99 %); various molecular based techniques available	[373, 467]
Biopsy with no visible hyphae	To detect and specify a fungus	Broad range PCR	C	II	Sensitivity (57 %) and specificity (96 %); ability to distinguish other fungi; performance only in addition to other tests	[373, 467]
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	[468, 469]
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)	[58]

709 SoR, Strength of recommendation; QoE, Quality of evidence; PCR, polymerase chain reaction

710 **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		[98, 381]
	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	[80, 371-373, 395]
	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	[98, 381]

	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	

711 SoR, Strength of recommendation; QoE, Quality of evidence; GM, galactomannan; BAL, bronchoalveolar lavage; ODI, optical density index

712

713 **Table 14. Antibody based diagnosis of invasive aspergillosis[11]**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Any	To diagnose IA	*Aspergillus*-specific antibodies by EIA: Serion (Germany), Omega (France), Bio-Rad (France), Dynamiker (China)	C	II	Antibodies take a mean of 11 days to develop after onset of illness; detectable in 29% to 100% of patients during course of acute IA	[470-477]
		Precipitating antibodies by agar gel double diffusion (Microgen Ltd. UK) or counter-immuno-electrophoresis	C	III	Consider false-negative results due to hypogammaglobulinaemia	[478]
		Agglutinating antibodies by indirect haemagglutination (EliTech/Fumouze, France)	C	II		[478]
		Specific immunoglobulins to *Aspergillus* by ImmunoCap®	C	III		No reference found

714 SoR, Strength of recommendation; QoE, Quality of evidence; EIA, enzyme immunoassay; IA, invasive aspergillosis

715 **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 azole resistance	Reference MIC testing	A	II	In situations where rapid testing is available	[105, 111, 114, 116, 300, 479-489]
Clinically relevant *Aspergillus* isolates in patient groups with high prevalence of azole resistance or patients unresponsive to treatment	Identify isolates with intrinsic resistance	Species identification to complex level	A	III	Some species are intrinsically resistant – e.g. *A. calidoustus* (azole resistant) *and A. terreus* (AmB resistant)	[103, 490]
Clinically relevant *A. fumigatus* isolates	Identify azole resistant *A. fumigatus*	Routine azole agar screening	B	III	Identifies resistant colonies that require MIC-testing	[118, 491]
All isolates –resistance surveillance	Determine the local epidemiology of azole resistance	Periodical reference MIC testing of *A. fumigatus* complex	A	II	Test at least 100 isolates	[105, 111, 114, 300,

						482-485, 487-489]
Azole-resistant isolates	Determine nature and trends in Cyp51A mutation distribution	Cyp51A-gene mutation analysis	A	II	Test resistant isolates from surveillance survey	[107]

716 SoR, Strength of recommendation; QoE, Quality of evidence; AmB, Amphotericin B; MIC, minimum inhibitory concentration

717 **Table 16. Azole susceptibility testing: Timing, methods, and number colonies**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Any	Confirm or reject azole resistance in clinical *A. fumigatus* isolates when antifungal treatment is considered	Azole agar screening test followed by reference MIC test where needed	A	III	MIC testing as soon as the strain is isolated and without waiting for species ID	[103, 114]
	Detect azole-resistant *A. fumigatus* genotypes in a single culture	Reference MIC testing of multiple colonies (up to 5 colonies)	B	III	Multiple genotypes, i.e. azole-susceptible and azole-resistant, may be present	[115, 492, 493]
		Routine azole agar screening (up to 5 colonies)	B	III	One resistant colony can be identified among 4 susceptible samples together as recently validated.	[118, 491]
	Confirm or reject azole resistance by a validated method	MIC test using EUCAST method and EUCAST BPs (S, I, R)	A	III	Applicable to all *Aspergillus* spp. Breakpoints established for most species	[494-496]

		MIC test using CLSI method and CLSI ECVs (wild-type/non-wild-type)	B	III	Breakpoints not established	[496]
	MIC testing of various *Aspergillus* spp.	Etest®	C	III	Confirmation by reference test recommended.	[497-501]

718 SoR, Strength of recommendation; QoE, Quality of evidence; MIC, minimum inhibitory concentration

719 **Table 17. Azole MIC testing: Choice of azole compounds**

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	[495, 496, 502-506]
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	[114, 494, 496, 504-507]
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	[300, 486, 495, 496, 504-509]
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	[495, 504, 505, 507, 510-512]

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

720 SoR, Strength of recommendation; QoE, Quality of evidence; MIC, minimum inhibitory concentration; EUCAST, European Committee on Antimicrobial

721 Susceptibility Testing; CLSI, Clinical & Laboratory Standards Institute

722

723 **Table 18. Amphotericin B susceptibility testing**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Clinically relevant isolate	Confirm or reject AmB resistance when antifungal treatment is considered	MIC test	C	III	Acquired resistance to amphotericin B is very rare and therefore correlation with clinical outcome has not been documented apart from the poorer outcome for high MIC species (*A. terreus* and *A. flavus* compared to *A. fumigatus)*.	[513-516]
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. flavus* may be in vitro resistant	[495, 517, 518]
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	[519]

					will respond to AmB although classified as wildtype according to CLSI ECVs.	

724 SoR, Strength of recommendation; QoE, Quality of evidence; AmB, amphotericin B; CLSI, Clinical & Laboratory Standards Institute; ECV, epidemiological cut-

725 off value; EUCAST, European Committee on Antimicrobial Susceptibility Testing; MIC, minimum inhibitory concentration

726

727 **Table 19. Antifungal regimens 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		[17, 170, 520-525]
IA due to *A. terreus*	To cure IA	Voriconazole	A	II	Avoid AmB	[162, 526, 527]
		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	[103, 528]
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	[501, 529, 530]
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	[531]

IA due to *A. niger* complex	To cure IA	Other than itraconazole and isavuconazole	B	III	Isavuconazole, posaconazole, and voriconazole MIC in general 1 dilution higher compared to *A. fumigatus*; itraconazole MIC in general 2 steps higher; limited clinical data	[501, 512]
IA due to *A. nidulans*	To cure IA	Voriconazole	C	III	AmB MIC elevated, poor clinical responses in chronic granulomatous disease	[532, 533]

728 SoR, Strength of recommendation; QoE, Quality of evidence; AmB, amphotericin B; IA, invasive aspergillosis; MIC, minimum inhibitory concentration

729 **Table 20. Optimal therapy in documented azole-resistance**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Isolate with voriconazole MIC =2 mg/ml	To cure IA	Voriconazole + echinocandin combination therapy or L-AmB monotherapy for IA (as well as for CPA)	A	III	The probability of voriconazole treatment failure may be higher than in voriconazole MIC <2.	[534-536]
Isolate with posaconazole MIC >0.5 mg/ml [537]	To cure IA	L-AmB	A	II_u		[113, 114, 538]
		AmB lipid complex	C	III		No reference found.
		Voriconazole & anidulafungin	B	III		[534]
		Posaconazole & caspofungin	C	III	Posaconazole not licensed for primary treatment	[539]
		Caspofungin or micafungin	C	III	Patients with contra-indications to AmB & other azoles	No reference found.

730 SoR, Strength of recommendation; QoE, Quality of evidence; AmB, Amphotericin B; CPA, chronic pulmonary aspergillosis; IA, invasive aspergillosis; L-AmB,

731 Liposomal amphotericin B; MIC, minimum inhibitory concentration

732 **Table 21. Therapeutic drug monitoring**

Clinical scenarios where antifungal therapeutic drug monitoring may be indicated	**Examples, comments**
Populations with increased pharmacokinetic variability	Impaired gastrointestinal function; hepatic dysfunction; children, 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

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

734

735 **Table 22. Itraconazole therapeutic drug monitoring**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
All patients receiving itraconazoletreatment 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)	[122, 127, 540-542]
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)	[124]
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	[127]

736 SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis; HPLC, high performance liquid chromatography; LC, liquid

737 chromatography; MS, mass spectrometry

738 **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	II	Target range of 1-5.5 mg/L	[128-131, 133, 543-545]
		Repeat plasma trough level	B	II	Repeat during second week of therapy, additional samples as clinically indicated and outlined in the text	[128-131, 133, 543-545]
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	[132, 546, 547]
Patients with IA due to *Aspergillus* strains of reduced azole	Improve efficacy of treatment for isolates with MIC=2 mg/ml	Measure serum trough level after 2 to 5 days of therapy or soon after and 4 days after change of dose	A	II	Trough >2 mg/L recommended on the basis of PK/PD analysis	[131, 548]

susceptibility MIC =2 mg/ml						

SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis; MIC, minimum inhibitory concentration; PK, pharmacokinetic; PD, pharmacodynamic

741 **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 preferred for most patients, consider switch to tablet or IV, if no therapeutic levels with oral suspension Repeat determination as clinically appropriate Longed half-life gives similar results for random sampling and true trough samples	[138]
Patients receiving posaconazole suspension for **prophylaxis to prevent IA**	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	[136, 137, 549-552]

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 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]

742 SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis; IV, intravenous; TDM, therapeutic drug monitoring; AML, acute

743 myeloid leukaemia; HSCT, haematopoietic stem cell transplantation; GvHD, graft versus host disease

744

745 **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

746 SoR, Strength of recommendation; QoE, Quality of evidence; TDM, therapeutic drug monitoring; FDA, Food and Drug Administration

747 **Table 26. 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 300 mg tablet qd	A	I	AML/MDS induction only. TDM especially with oral suspension. Tablets more bioavailable, bridging with posaconazole IV formulation possible	[553]
		L-AmB 12.5 mg biw, nebulized, with undetermined dose of fluconazole	B	I	AML	[554, 555]
		ABLC 3 mg/kg 3x/weekly	C	II_h	No difference to L-AmB regimen	[556]
		Micafungin 50 mg qd	C	II_t		[560, 561]
		L-AmB 10 mg/kg q7d	C	II_u		[562]
		L-AmB 50 mg abs q2d	C	II_u		[563]
		L-AmB 15 mg/kg q14d	C	II_u		[564]
		Voriconazole	C	II_t	Not better than fluconazole	[565]

		Itraconazole 400 mg/d, oral solution	D	II	No difference to fluconazole (n=195) and more toxicity	[121, 557-559]
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	[566]
Autologous HSCT or treatment of haematological malignancies besides acute leukaemia	Lower incidence of IA	Any mould active agent	D	III		No reference found.
Allogeneic HSCT (until neutrophil recovery)	Lower incidence of IA	Posaconazole 200 mg tid suspension or 300 mg tablet qd	B	II_t	Neutropenia duration approximately identical, TDM*	[553]
		L-AmB 12.5 mg biw, nebulized, with fluconazole	B	II_t		[554]
		Voriconazole 200 mg bid	C	I	Not better than fluconazole, TDM	[567, 568]

		Micafungin 50 mg/d	C	I	But no difference in subgroup analysis for aspergillosis	[560]
		Itraconazole 400 mg/d oral solution	D	I	Toxicity issues; TDM	[554, 559]
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 200 mg tid suspension or 300 mg tablet qd	A	I	TDM	[569]
		Voriconazole 200 mg bid	C	II	Not better than fluconazole; TDM	[567, 568]
		Itraconazole 400 mg/d, oral solution	C	II	Toxicity issues; TDM	[559]
		Micafungin 50 mg/d	C	III	Only few patients with GVHD	[560]
Allogeneic HSCT (until neutrophil recovery)	To reduce IA attributable mortality	Posaconazole 200 mg tid suspension or 300 mg tablet qd	B	II_t	Neutropenia duration approximately identical. TDM	[553]
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-suppression)		Posaconazole 200 mg tid suspension or 300 mg tablet qd	A	II	Mainly IFD-attributable mortality, TDM	[569]

748 SoR, Strength of recommendation; QoE, Quality of evidence; qd, once daily; bid, twice daily; tid, thrice daily; AML, acute myeloid leukaemia; MDS,
749 myelodysplastic syndrome; TDM, therapeutic drug monitoring; ABLC, amphotericin B lipid complex; L-AmB, Liposomal amphotericin B; HSCT,
750 haematopoietic stem cell transplantation; GvHD, graft versus host disease; IFD, invasive fungal disease
751

752 **Table 27. Targeted therapy of pulmonary disease – First line**

Population	Intention	Intervention	SoR	QoE[1]	QoE[2]	QoE[3]	Comment	Ref.
[1] Neutropenia (non- allo HSCT recipients) [2] Allo-HSCT (during neutropenia) [3] Allo-HSCT (w/o neutropenia) or other non-	To increase response and survival rate	Isavuconazole 200 mg iv tid day 1-2, then 200 mg qd oral	A	I	II_t	II_t	D III, if mould active azole prophylaxis less adverse effects than voriconazole	[173, 512, 633, 634]
		Voriconazole 2x 6 mg/kg IV (oral 400 mg bid) on day 1, 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 prior mould active azole prophylaxis; TDM	[170, 172, 512, 635]
		L-AmB 3 mg/kg	B	II	II_t	II_t		[171]
		Combination of voriconazole 6/4 mg/kg bid (after one week oral possible (300 mg bid)) + anidulafungin 200/100 mg	C	I	$II_{t,}$	$II_{t,}$	No significant difference compared to voriconazole, in GM positive (subgroup) better survival; TDM	[172, 635]
		Caspofungin 70 mg qd day 1, followed by 50 mg qd (if body weight <80kg)	C	II	II	II		[618-620]

neutropenic patients		Itraconazole 200 mg q12h iv on day 1, 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	[512, 542]
		AmB lipid complex (ABLC) 5 mg/kg	C	III	III	III		[636]
		Micafungin 100 mg	C	III	III	III		[637-639]
		AmB colloidal dispersion (ABCD) 4-6 mg/kg	D	I	II_t	II_t		[142]
		Conventional AmB 1-1.5 mg/kg	D	I	II_t	II_t		[170]
		Other combinations	D	III	III	III	Efficacy unproven	[640]
Life-threatening haemoptysis	Bridging until neutrophil recovery	Arterial embolization, emergency surgical intervention	B	III	III	III		[641]

753 SoR, Strength of recommendation; QoE, Quality of evidence; allo-HSCT, allogeneic haematopoietic stem cell transplantation; bid, twice daily; tid, thrice

754 daily, qd, once daily; IA, invasive aspergillosis; IV, intravenous; TDM, therapeutic drug monitoring; GM, galactomannan

755 **Table 28. Targeted therapy of extrapulmonary disease – First line**

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		[642, 643]
		Voriconazole	A	II_u	N=5/5	[170]
					N=81, 48 proven cases, 33 probable cases, TDM recommended targeting trough concentration of 2-5.5 mg/L	[642]
		Posaconazole	D	III	8 patients documented in studies (5 failures)	[644]
		Itraconazole	D	III		
		Lipid formulations of AmB	B	III	Case collections, animal data	[645-647]
		cAmB	D	I	Renal toxicity	[189, 648-650]
		Echinocandins	D	III	Insufficient tissue penetration	[646]

Patients with clinical suspicion of or proven invasive sinus aspergillosis	To cure	Surgery	A	III	Need to be considered on an individual basis and decision	
		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	[170, 651]
		L-AmB	A	II_t	Active against mucormycosis as well since mixed infections occur or cannot be differentiated	[171]
		Posaconazole, itraconazole, echinocandins	C	III	Not well specified in studies, TDM recommended for posaconazole and itraconazole	[652, 653]

SoR, Strength of recommendation; QoE, Quality of evidence; TDM, therapeutic drug monitoring; AmB, Amphotericin B, cAmB, conventional amphotericin B; L-AmB, liposomal amphotericin B

759 **Table 29. Fever-driven ("empiric") approach**

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)	Reduction in the incidence of IA and/or related mortality	Caspofungin 70 mg qd day 1, followed by 50 mg qd (if body weight <80kg)	A	I	Caspofungin was associated with a significantly higher rate of survival than L-AmB (subgroup analysis).	[188]
		L-AmB 3 mg/kg	B	I	Less toxicity in comparison to cAmB but more renal toxicity compared to echinocandin	[188, 189]
		Voriconazole 6 mg/kg bid IV (oral 400 mg bid) on day 1, then 4 mg/kg bid 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*	[190]
		Itraconazole 200 mg qd 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*	[666]
		ABLC 5 mg/kg qd	C	I	Infusion-related toxicity (fever, chills, hypoxia)	[667]

		ABCD 4 mg/kg	C	I	Same as above	[668]
		cAmB 0.5-1 mg/kg qd	D	I	Poor tolerance due to extreme toxicity	[189, 342, 649, 650, 666, 668]
		Micafungin 100 mg qd	B	II		[669]
		Fluconazole	D	II_r	No activity against Aspergillus	[670]

SoR, Strength of recommendation; QoE, Quality of evidence; L-AmB, liposomal amphotericin B; cAmB, conventional amphotericin B; IV, intravenous; TDM, therapeutic drug monitoring; ABLC, amphotericin B lipid complex; ABCD, amphotericin B colloidal dispersion

762 **Table 30. Non-haematological patients at high risk**

Population	Intention	Intervention	SoR	QoE	Ref.
SOT lung with pre-transplantation colonization and *Aspergillus* in intraoperative culture OR CMV disease OR higher donor age OR prolonged ischaemia time OR receiving daclizumab OR bronchial anastomotic ischemia OR bronchial stent OR single lung SOT	To identify patients with high risk of IA	Consider prophylaxis	B	III	[210, 226, 692] [215, 693-695]
SOT lung with repeated acute and chronic rejection			B	II_t	[696, 697]
SOT heart with re-operation, CMV infection, haemodialysis, other episode of IA in the program within 2 months	To identify patients with high risk of IA	Consider prophylaxis	A	II_h	[204]
SOT heart with airborne *Aspergillus* spores in ICU			A	II	[203, 204]
SOT heart with sirolimus OR tacrolimus OR hypogammaglobulinemia			B	II_h	[212, 698]
SOT liver with one of the following characteristics: requirement for dialysis OR retransplantation OR fulminant hepatic failure OR MELD score >30	To identify patients with high risk of IA	Consider prophylaxis	B	II_h	[210, 211, 217, 224, 308, 311, 607, 699-702]

SOT liver with one of the following characteristics: ICU admission or corticosteroid requirement previous 2-4 weeks to transplant OR >15 units of packed red blood cells during transplant surgery OR reoperation involving the intraabdominal cavity OR choledochojejunostomy			C	III	
SOT kidney with one of the following characteristics: Pre-transplant COPD OR delayed graft function OR post-transplant blood stream infection OR acute graft rejection	To identify patients with high risk of IA	Consider prophylaxis	A	II_h	[228]
COPD with one of the following characteristics: high (systemic) cumulative glucocorticosteroid dose OR refractory to antibiotic therapy OR admission to the intensive-care unit	To identify patients with high risk of IA	Consider prophylaxis	A	II_t	[232, 257, 703, 704]
HIV with CD4 count <100 cells/µl	To identify patients with high risk of IA	Consider prophylaxis	A	II_h	[232]
ICU patients with either COPD OR requiring glucocorticosteroids therapy	To identify patients with high risk of IA	Consider prophylaxis	A	II_h	[257, 703, 704]
ICU patients with either acute liver failure OR burns OR severe bacterial infection OR malnutrition			B	III	

ICU or SOT recipients with Increased environmental exposure	To identify patients with high risk of IA	Consider prophylaxis	A	II	[203, 204, 705, 706]
Liver insufficiency	To identify patients with high risk of IA	Consider prophylaxis	B	II_h	[244, 707]
Burn patients with positive fungal cultures	To identify patients with high risk of IA	Consider prophylaxis	A	II_h	[708, 709]
Percentage of total body surface area burn injury; length of stay			B	III	[706]
Patient receiving one of the following: TNF-α blockers, basiliximab, daclizumab, infliximab, etanercept, alemtuzumab, adalimumab, rituximab, abatacept	To identify populations at high risk of IA	Consider prophylaxis	C	III	No reference found.

763 SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis; CMV, cytomegalovirus; ICU, intensive care unit; COPD, chronic

764 obstructive pulmonary disease; BAL, bronchoalveolar lavage

765

766 **Table 31. Diagnosis-driven ("pre-emptive") approach in non-haematological patients**

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
COPD	To diagnose IA	Respiratory culture	A	II_u	Isolation of *Aspergillus* in culture from admitted patients with COPD represents IA in at least 22% of patients	[257, 281, 282, 710]
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%	[281]
Underlying respiratory disease	To diagnose IA	Lateral flow device BAL	C	II	Sensitivity / specificity 77% / 92% (Not commercially available at the time of writing)	[285]
HIV	To diagnose IA	Direct microscopy	A	II_h	50% positive	[232]
HIV	To diagnose IA	GM BAL	B	II_u	53% positive	[232]
HIV	To diagnose IA	GM serum	B	II_u	34% positive	[232]
HIV	To diagnose IA	Histology	A	II_u	75% positive	[232]
ICU	To diagnose IA	BDG serum	B	II_u	Autopsy study, non-haematological immunocompromised critically	[429]

					ill patients with lower respiratory tract infection. Using 140 pg/ml cut-off, sensitivity/specificity 100% / 70%	
ICU	To diagnose IA	BDG serum	B	II_u	BDG appeared a mean of 6.5 days before *Aspergillus* was grown	[711]
ICU	To diagnose IA	Respiratory culture	B	II_u		[89, 712, 713]
ICU	To diagnose IA	GM BAL	C	II_u	Using cut-off ODI 0.5 sensitivity/specificity 88-90% / 87-100%	[89, 712, 713]
ICU	To diagnose IA	SeptiFast®	C	II_h	Sensitivity/specificity 66% / 98%, PPV 93%, NPV 88%	[714, 715]
Non haematological	To diagnose IA	Culture	A	II_h	Very low PPV of *Aspergillus* spp. culture from respiratory samples	[197]
Non haematological	To diagnose IA	Culture	A	II_h	Sensitivity of BAL higher for non-neutropenic patients	[52]
Non-haematological	To diagnose IA	GM serum	C	II	Using cut-off of 0.5 ng/ml sensitivity/specificity 60% / 89%	[710]

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%	[278]
SOT, any	To diagnose IA	Respiratory culture	D	II	Low sensitivity and specificity	[87, 282]
SOT, any	To diagnose IA	GM BAL	B	II	Using cut-off ODI 1.0 sensitivity/specificity 100% / 91%	[716]
SOT, any	To diagnose IA	High-resolution chest 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%)	[214, 717]
SOT, any	To diagnose IA	Lateral flow device BAL	C	II	N=11 SOT	[284, 434, 718]
SOT Heart	To diagnose IA	Respiratory 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%	[271]
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%	[274]

		of the thorax				
SOT Lung	To diagnose IA	BDG serum	C	II_u	Sensitivity/specificity 64%, 9%, PPV 14%, NPV 50%	[719]
SOT Lung	To diagnose IA	GM BAL	B	II	Using cut-off ODI 1.5 sensitivity/specificity 100% / 90%	[87, 88, 720, 721]
SOT Lung	To diagnose IA	PCR of respiratory samples	B	II		[88]

767 SoR, Strength of recommendation; QoE, Quality of evidence; COPD, chronic obstructive pulmonary disease; BDG, ß-D-glucan; IA, invasive aspergillosis; ICU,
768 intensive care unit; SOT, solid organ transplantation; PPV, positive predictive value; GM, galactomannan; ODI, optical density index; NPV, negative predictive
769 value; BAL, bronchoalveolar lavage; PCR, polymerase chain reaction

770 **Table 32. Treatment 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.	[722]
SOT Heart	To treat IA	Itraconazole	C	III	6 patients cured with itraconazole 200-400 mg/d Erratic absorption and interaction with calcineurin inhibitors and other agents	[723]
SOT, any	To treat IA	Voriconazole	A	III	e.g. Herbrecht study 11 SOT; voriconazole increases the levels of anti-calcineurin immunesuppressors, TDM; monitor liver function tests especially in liver transplant recipients.	[170, 214, 287, 333, 607-609, 673, 724-726]
SOT, any	To treat IA	L-AmB	A	II		[678, 727, 728]
SOT, any	To treat IA	Voriconazole &	B	II	40 SOT voriconazole & caspofungin (n=40) vs amphotericin B (n=47).	[289]

		caspofungin			Survival 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	[621, 622, 686, 729]

771 SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis; SOT, solid organ transplantation; L-AmB, Liposomal amphotericin B; SOT,

772 solid organ transplantation; TDM, therapeutic drug monitoring

773

774 **Table 33. Prophylaxis 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	[304, 315, 730]
	Targeted* prophylaxis	To prevent IA	C	III		[315, 694, 731]
	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 Breakthrough IA in 7-10%	[732, 733]
	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	[724, 732-735]

	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	[303, 304, 315, 731, 736]
	Voriconazole pre-emptive, if colonized	To prevent IA	B	II_u	Breakthrough IA <2% at 6 months	[731]
	Voriconazole for three months	To prevent IA	C	II	No effect of voriconazole on the incidence of IA (45% vs 49%)	[303]
SOT Heart	Universal* prophylaxis with itraconazole or inhaled AmB	To prevent IA	C	I		[214, 737, 738]
	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	[214, 737, 738]
	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	[215]

					factors persistence	
SOT Liver	Targeted* prophylaxis with lipid AmB	To prevent IA	B	III	IA rate reduced, mortality unaffected	[607, 739-741]
	Targeted* prophylaxis with echinocandins	To prevent IA	A	I	Standard dosed echinocandins reduced IA rate; duration of prophylaxis usually 21 days post SOT	[217, 308, 311, 742]

775 SoR, Strength of recommendation; QoE, Quality of evidence; * targeted prophylaxis = only if additional risk factors; universal prophylaxis = to all patients in
776 population; IA, invasive aspergillosis; SOT, solid organ transplantation; AmB, Amphotericin B; cAmB, conventional amphotericin B deoxycholate
777

778 **Table 34. Prophylaxis in children at high risk**

Population	Intention	Intervention	SoR	QoE	Comment	Ref
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	TDM recommended; Approved indication; not approved EU < 18 years	[122, 559, 570-579]
		Posaconazole	A	II_t	TDM recommended; only supportive paediatric data for ≥ 13 years of age	[136, 137, 338, 553, 569, 580-586]
		Voriconazole	A	II_t	Not approved for <2 years; Inference from efficacy from HSCT trials and supportive studies; TDM recommended	[130, 131, 135, 546, 567, 568, 587-593]
		Liposomal amphotericin B	B	II_t/III*	Not approved for prophylaxis; Optimal dose of alternate administration unknown; Alternative if triazoles are not tolerated / contraindicated	[563, 594-599]

		Micafungin	B	II_t/III*	No definite evidence (trend only) for prophylactic efficacy against *Aspergillus* spp. Alternative if triazoles are not tolerated or contraindicated	[560, 600-604]
Chronic granulomatous disease (CGD) patients	Prevention of IA	Itraconazole	A	II	Approved indication; not approved in the EU for < 18 years; TDM recommended	[122, 575-578, 605, 606]
		Posaconazole	A	III	Not EU approved for children < 18 years; TDM recommended; PK and safety data for children ≥ 4 years	[136, 137, 582-585]

* 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

SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis; TDM, therapeutic drug monitoring; HSCT, haematopoietic stem cell transplantation

784 **Table 35. Treatment in children**

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.	[130, 131, 135, 170, 333, 546, 589-592, 607-613]
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	[171, 597, 599, 614-617]
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	[616, 618-628]
Neonates	Treatment proven/probable IA	L-AmB 3 mg/kg/d	A	III		[629-632]

785 SoR, Strength of recommendation; QoE, Quality of evidence; IA, invasive aspergillosis; TDM, therapeutic drug monitoring; L-AmB, liposomal amphotericin B

786 **Table 36. 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 proven to be effective in the actual patient	A	II	Results compared to historical data, mostly in allogeneic HSCT setting	[654-659]
		Voriconazole	A	II_h	IA: 31/45 pts, 1 year cumulative incidence of IFD 6.7±3.6%, TDM	[654]
		Caspofungin 70 mg day 1, followed by 50 mg/d IV until stable engraftment, followed by 400 mg itraconazole suspension PO	B	II_h		[658]
		L-AmB followed by voriconazole	C	II	Fungal infection related mortality 28% despite lipid-based AmB	[657, 660]
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.	[661-665]

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

787 SoR, Strength of recommendation; QoE, Quality of evidence; HSCT, haematopoietic stem cell transplantation; IA, invasive aspergillosis, IFD, invasive fungal

788 disease; TDM, therapeutic drug monitoring, PO, per os; L-AmB, liposomal amphotericin B

789 **Table 37. Antifungal drugs in refractory disease**

Population	Intention	Intervention	SoR	QoE	Comment	Ref
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	[671]
		Voriconazole	A	II		[333, 672-674]
		L-AmB 3-5 mg/kg	B	II	Majority voted for BII others for AII	[598, 675, 676]
		ABLC 5 mg/kg	C	II		[636, 676-678]
		ABCD			No longer commercially available	[679, 680]
		Caspofungin 70 mg qd day 1, followed by 50 mg qd (if body weight <80kg)	B	II	Very few data in case of voriconazole/posaconazole failure	[335, 674, 681-687]
		Micafungin 75-200 mg qd	C	II		[638, 688]

		Posaconazole 200 mg qid or 400 bid suspension or 300 mg tablet bid day 1, followed by 300 mg qd	B	II		[138, 336, 689, 690]
		Itraconazole	D	III	In case of refractoriness to voriconazole	
		Itraconazole oral forms	C	II	Poor bioavailability	[126]
		Itraconazole IV formulation			Commercially not available everywhere	[542, 691]

790 SoR, Strength of recommendation; QoE, Quality of evidence; L-AmB, Liposomal amphotericin B; ABLC, amphotericin B lipid complex; ABCD, amphotericin B

791 colloidal dispersion; IV, intravenous; TDM, therapeutic drug monitoring; qd, once daily; bid, twice daily; qid, four times daily

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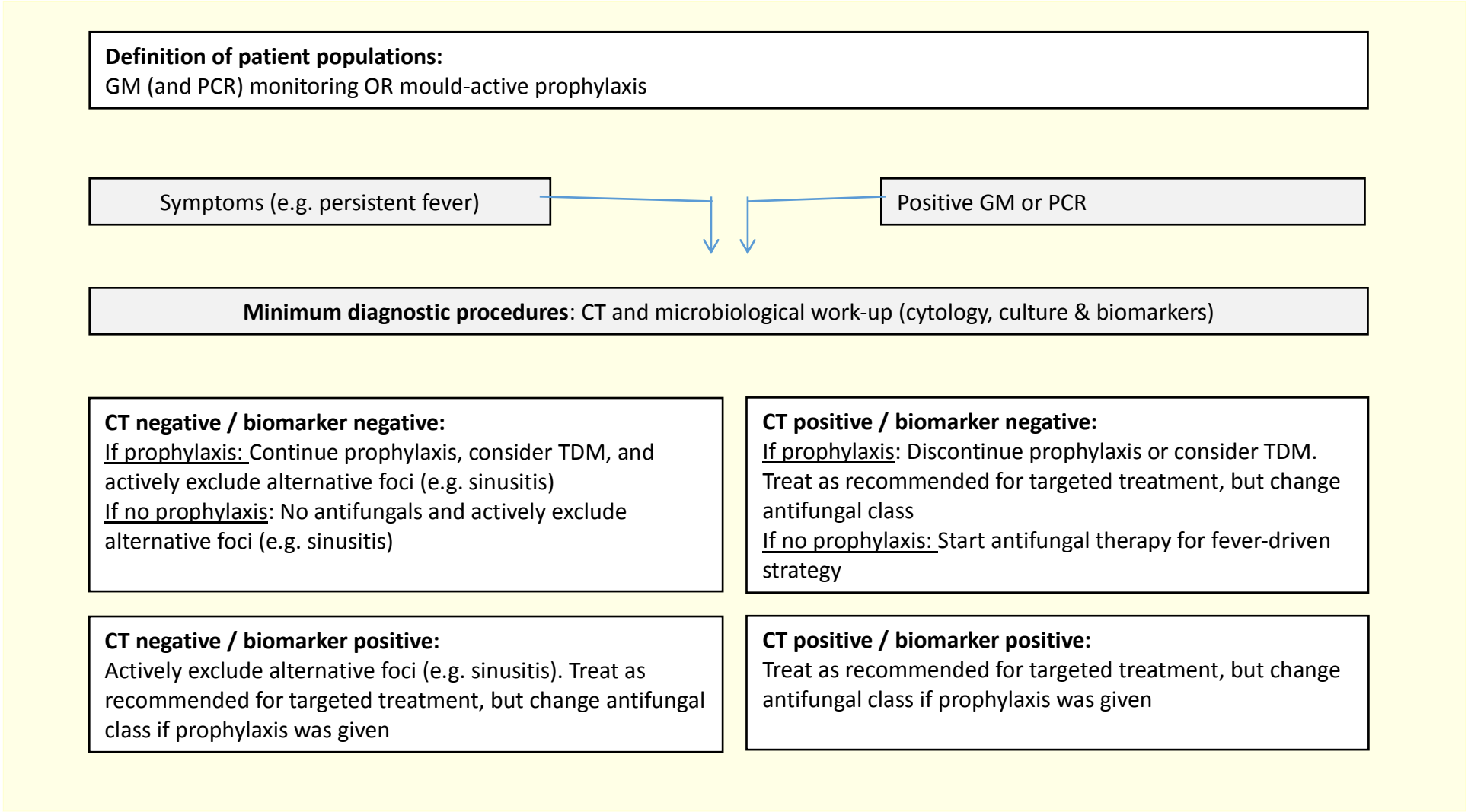
793 **Table 38. Chronic pulmonary aspergillosis**

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	[743]
		Histology	A	II	In CPA histology distinguishes between CNPA and CCPA	[744]
		Fungal culture (respiratory secretion)	A	III	Bacterial culture plates are less sensitive than fungal culture plates	[269]
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	[364]
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	[364, 745]

		Voriconazole Start 150-200 mg bid, adjust with TDM			Voriconazole preferred for CNPA and patients with fungal balls to minimize risk of resistance	[366, 746, 747]
		Posaconazole 400 mg bid (oral suspension) 300 mg qd (delayed release tablets)	B	II	Higher rate of adverse events, if some adverse events with itraconazole and voriconazole	[748]

SoR, Strength of recommendation; QoE, Quality of evidence; CPA, chronic pulmonary aspergillosis; ABPA, allergic bronchopulmonary aspergillosis; SAIA, subacute invasive aspergillosis; CNPA, chronic necrotising pulmonary aspergillosis; CCPA, chronic cavitary pulmonary aspergillosis; qd, once daily; bid, twice daily; TDM, therapeutic drug monitoring

798 **Figure 1. Management during neutropenia**



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References

1 Arendrup MC, Boekhout T, Akova M, et al. Escmid and ecmm joint clinical guidelines for the diagnosis and management of rare invasive yeast infections. *Clin Microbiol Infect*. 2014; **20 Suppl 3**: 76-98.

2 Chowdhary A, Meis JF, Guarro J, et al. Escmid and ecmm joint clinical guidelines for the diagnosis and management of systemic phaeohyphomycosis: Diseases caused by black fungi. *Clin Microbiol Infect*. 2014; **20 Suppl 3**: 47-75.

3 Cornely OA, Arikan-Akdagli S, Dannaoui E, et al. Escmid and ecmm joint clinical guidelines for the diagnosis and management of mucormycosis 2013. *Clin Microbiol Infect*. 2014; **20 Suppl 3**: 5-26.

4 Cornely OA, Bassetti M, Calandra T, et al. Escmid* guideline for the diagnosis and management of candida diseases 2012: Non-neutropenic adult patients. *Clin Microbiol Infect*. 2012; **18 Suppl 7**: 19-37.

5 Cuenca-Estrella M, Verweij PE, Arendrup MC, et al. Escmid* guideline for the diagnosis and management of candida diseases 2012: Diagnostic procedures. *Clin Microbiol Infect*. 2012; **18 Suppl 7**: 9-18.

6 Hope WW, Castagnola E, Groll AH, et al. Escmid* guideline for the diagnosis and management of candida diseases 2012: Prevention and management of invasive infections in neonates and children caused by candida spp. *Clin Microbiol Infect*. 2012; **18 Suppl 7**: 38-52.

7 Lortholary O, Petrikkos G, Akova M, et al. Escmid* guideline for the diagnosis and management of candida diseases 2012: Patients with hiv infection or aids. *Clin Microbiol Infect*. 2012; **18 Suppl 7**: 68-77.

8 Tortorano AM, Richardson M, Roilides E, et al. Escmid and ecmm joint guidelines on diagnosis and management of hyalohyphomycosis: Fusarium spp., scedosporium spp. And others. *Clin Microbiol Infect*. 2014; **20 Suppl 3**: 27-46.

9 Ullmann AJ, Akova M, Herbrecht R, et al. Escmid* guideline for the diagnosis and management of candida diseases 2012: Adults with haematological malignancies and after haematopoietic stem cell transplantation (hct). *Clin Microbiol Infect*. 2012; **18 Suppl 7**: 53-67.

10 Ullmann AJ, Cornely OA, Donnelly JP, et al. Escmid* guideline for the diagnosis and management of candida diseases 2012: Developing european guidelines in clinical microbiology and infectious diseases. *Clin Microbiol Infect*. 2012; **18 Suppl 7**: 1-8.

11 Denning DW, Cadranel J, Beigelman-Aubry C, et al. Chronic pulmonary aspergillosis: Rationale and clinical guidelines for diagnosis and management. *Eur Respir J*. 2016; **47**: 45-68.

12 Cornely OA, Cuenca-Estrella M, Meis JF, Ullmann AJ. European society of clinical microbiology and infectious diseases (escmid) fungal infection study group (efisg) and european confederation of medical mycology (ecmm) 2013 joint guidelines on diagnosis and management of rare and emerging fungal diseases. *Clin Microbiol Infect*. 2014; **20 Suppl 3**: 1-4.

13 Marchiori E, Irion KL. Commentary on: "Analysis of initial and follow-up ct findings in patients with invasive pulmonary aspergillosis after solid organ transplantation". *Clin Radiol*. 2012; **67**: 1153-1154.

14 Bergeron A, Porcher R, Sulahian A, et al. The strategy for the diagnosis of invasive pulmonary aspergillosis should depend on both the underlying condition and the leukocyte count of patients with hematologic malignancies. *Blood*. 2012; **119**: 1831-1837; quiz 1956.

15 Lim C, Seo JB, Park SY, et al. Analysis of initial and follow-up ct findings in patients with invasive pulmonary aspergillosis after solid organ transplantation. *Clin Radiol*. 2012; **67**: 1179-1186.

16 Wingard JR. New approaches to invasive fungal infections in acute leukemia and hematopoietic stem cell transplant patients. *Best practice & research Clinical haematology*. 2007; **20**: 99-107.

17 Greene RE, Schlamm HT, Oestmann JW, et al. Imaging findings in acute invasive pulmonary aspergillosis: Clinical significance of the halo sign. *Clin Infect Dis*. 2007; **44**: 373-379.

18 Greene R. The radiological spectrum of pulmonary aspergillosis. *Medical mycology*. 2005; **43 Suppl 1**: S147-154.

19 Heussel CP, Kauczor HU, Heussel G, Fischer B, Mildenberger P, Thelen M. Early detection of pneumonia in febrile neutropenic patients: Use of thin-section ct. *AJR American journal of roentgenology*. 1997; **169**: 1347-1353.

20 Heussel CP, Kauczor HU, Heussel GE, et al. Pneumonia in febrile neutropenic patients and in bone marrow and blood stem-cell transplant recipients: Use of high-resolution computed tomography. *J Clin Oncol*. 1999; **17**: 796-805.

21 Caillot D, Casasnovas O, Bernard A, et al. Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. *J Clin Oncol*. 1997; **15**: 139-147.

22 Caillot D, Mannone L, Cuisenier B, Couaillier JF. Role of early diagnosis and aggressive surgery in the management of invasive pulmonary aspergillosis in neutropenic patients. *Clin Microbiol Infect*. 2001; **7 Suppl 2**: 54-61.

23 Chamilos G, Marom EM, Lewis RE, Lionakis MS, Kontoyiannis DP. Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. *Clin Infect Dis*. 2005; **41**: 60-66.

24 Stanzani M, Battista G, Sassi C, et al. Computed tomographic pulmonary angiography for diagnosis of invasive mold diseases in patients with hematological malignancies. *Clin Infect Dis*. 2012; **54**: 610-616.

25 Stanzani M, Sassi C, Lewis RE, et al. High resolution computed tomography angiography improves the radiographic diagnosis of invasive mold disease in patients with hematological malignancies. *Clin Infect Dis*. 2015; **60**: 1603-1610.

26 Sonnet S, Buitrago-Tellez CH, Tamm M, Christen S, Steinbrich W. Direct detection of angioinvasive pulmonary aspergillosis in immunosuppressed patients: Preliminary results with high-resolution 16-mdct angiography. *AJR American journal of roentgenology*. 2005; **184**: 746-751.

27 Sodhi KS, Khandelwal N, Saxena AK, et al. Rapid lung mri in children with pulmonary infections: Time to change our diagnostic algorithms. *J Magn Reson Imaging*. 2016; **43**: 1196-1206.

28 Maschmeyer G, Carratala J, Buchheidt D, et al. Diagnosis and antimicrobial therapy of lung infiltrates in febrile neutropenic patients (allogeneic sct excluded): Updated guidelines of the infectious diseases working party (agiho) of the german society of hematology and medical oncology (dgho). *Ann Oncol*. 2015; **26**: 21-33.

29 Rieger C, Herzog P, Eibel R, Fiegl M, Ostermann H. Pulmonary mri--a new approach for the evaluation of febrile neutropenic patients with malignancies. *Support Care Cancer*. 2008; **16**: 599-606.

30 Araz O, Karaman A, Ucar EY, Bilen Y, Durur Subasi I. Dce-mri findings of invasive aspergillosis in patient with acute myeloid leukemia. *Clin Respir J*. 2014; **8**: 248-250.

31 Blum U, Windfuhr M, Buitrago-Tellez C, Sigmund G, Herbst EW, Langer M. Invasive pulmonary aspergillosis. Mri, ct, and plain radiographic findings and their contribution for early diagnosis. *Chest*. 1994; **106**: 1156-1161.

32 Yan C, Tan X, Wei Q, et al. Lung mri of invasive fungal infection at 3 tesla: Evaluation of five different pulse sequences and comparison with multidetector computed tomography (mdct). *Eur Radiol*. 2015; **25**: 550-557.

33 Hot A, Maunoury C, Poiree S, et al. Diagnostic contribution of positron emission tomography with [18f]fluorodeoxyglucose for invasive fungal infections. *Clin Microbiol Infect*. 2011; **17**: 409-417.

34 Camus V, Edet-Sanson A, Bubenheim M, et al. (1)(8)f-fdg-pet/ct imaging in patients with febrile neutropenia and haematological malignancies. *Anticancer research*. 2015; **35**: 2999-3005.

35 Desoubeaux G, Bailly E, Chandenier J. Diagnosis of invasive pulmonary aspergillosis: Updates and recommendations. *Med Mal Infect*. 2014; **44**: 89-101.

36 Bruno C, Minniti S, Vassanelli A, Pozzi-Mucelli R. Comparison of ct features of aspergillus and bacterial pneumonia in severely neutropenic patients. *Journal of thoracic imaging*. 2007; **22**: 160-165.

37 Nucci M, Nouer SA, Grazziutti M, Kumar NS, Barlogie B, Anaissie E. Probable invasive aspergillosis without prespecified radiologic findings: Proposal for inclusion of a new

category of aspergillosis and implications for studying novel therapies. *Clin Infect Dis*. 2010; **51**: 1273-1280.

38 Caillot D, Couaillier JF, Bernard A, et al. Increasing volume and changing characteristics of invasive pulmonary aspergillosis on sequential thoracic computed tomography scans in patients with neutropenia. *J Clin Oncol*. 2001; **19**: 253-259.

39 Kami M, Kishi Y, Hamaki T, et al. The value of the chest computed tomography halo sign in the diagnosis of invasive pulmonary aspergillosis. An autopsy-based retrospective study of 48 patients. *Mycoses*. 2002; **45**: 287-294.

40 Kuhlman JE, Fishman EK, Burch PA, Karp JE, Zerhouni EA, Siegelman SS. Invasive pulmonary aspergillosis in acute leukemia. The contribution of ct to early diagnosis and aggressive management. *Chest*. 1987; **92**: 95-99.

41 Franquet T, Gimenez A, Hidalgo A. Imaging of opportunistic fungal infections in immunocompromised patient. *Eur J Radiol*. 2004; **51**: 130-138.

42 Horger M, Hebart H, Einsele H, et al. Initial ct manifestations of invasive pulmonary aspergillosis in 45 non-hiv immunocompromised patients: Association with patient outcome? *Eur J Radiol*. 2005; **55**: 437-444.

43 Althoff Souza C, Muller NL, Marchiori E, Escuissato DL, Franquet T. Pulmonary invasive aspergillosis and candidiasis in immunocompromised patients: A comparative study of the high-resolution ct findings. *Journal of thoracic imaging*. 2006; **21**: 184-189.

44 Horger M, Einsele H, Schumacher U, et al. Invasive pulmonary aspergillosis: Frequency and meaning of the "hypodense sign" on unenhanced ct. *The British journal of radiology*. 2005; **78**: 697-703.

45 Marchiori E, Godoy MC, Zanetti G, Hochhegger B, Rodrigues RS. The reversed halo sign. Another ct finding useful for distinguish invasive pulmonary aspergillosis and pulmonary lymphoma. *Eur J Radiol*. 2011; **79**: e96-97.

46 Kojima R, Tateishi U, Kami M, et al. Chest computed tomography of late invasive aspergillosis after allogeneic hematopoietic stem cell transplantation. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2005; **11**: 506-511.

940 47 Logan PM, Primack SL, Miller RR, Muller NL. Invasive aspergillosis of the airways:
941 Radiographic, ct, and pathologic findings. *Radiology*. 1994; **193**: 383-388.

942 48 Liss B, Vehreschild JJ, Bangard C, et al. Our 2015 approach to invasive pulmonary
943 aspergillosis. *Mycoses*. 2015; **58**: 375-382.

944 49 Azoulay E, Mokart D, Lambert J, et al. Diagnostic strategy for hematology and oncology
945 patients with acute respiratory failure: Randomized controlled trial. *Am J Respir Crit Care*
946 *Med*. 2010; **182**: 1038-1046.

947 50 Hummel M, Rudert S, Hof H, Hehlmann R, Buchheidt D. Diagnostic yield of bronchoscopy
948 with bronchoalveolar lavage in febrile patients with hematologic malignancies and
949 pulmonary infiltrates. *Ann Hematol*. 2008; **87**: 291-297.

950 51 Boersma WG, Erjavec Z, van der Werf TS, de Vries-Hosper HG, Gouw AS, Manson WL.
951 Bronchoscopic diagnosis of pulmonary infiltrates in granulocytopenic patients with
952 hematologic malignancies: Bal versus psb and pbal. *Respiratory medicine*. 2007; **101**: 317-
953 325.

954 52 Cornillet A, Camus C, Nimubona S, et al. Comparison of epidemiological, clinical, and
955 biological features of invasive aspergillosis in neutropenic and nonneutropenic patients: A 6-
956 year survey. *Clin Infect Dis*. 2006; **43**: 577-584.

957 53 Jain P, Sandur S, Meli Y, Arroliga AC, Stoller JK, Mehta AC. Role of flexible bronchoscopy in
958 immunocompromised patients with lung infiltrates. *Chest*. 2004; **125**: 712-722.

959 54 Peikert T, Rana S, Edell ES. Safety, diagnostic yield, and therapeutic implications of flexible
960 bronchoscopy in patients with febrile neutropenia and pulmonary infiltrates. *Mayo Clinic*
961 *proceedings*. 2005; **80**: 1414-1420.

962 55 Ramila E, Sureda A, Martino R, et al. Bronchoscopy guided by high-resolution computed
963 tomography for the diagnosis of pulmonary infections in patients with hematologic
964 malignancies and normal plain chest x-ray. *Haematologica*. 2000; **85**: 961-966.

965 56 Becker MJ, Lugtenburg EJ, Cornelissen JJ, Van Der Schee C, Hoogsteden HC, De Marie S.
966 Galactomannan detection in computerized tomography-based broncho-alveolar lavage fluid
967 and serum in haematological patients at risk for invasive pulmonary aspergillosis. *Br J*
968 *Haematol*. 2003; **121**: 448-457.

57 de Bazelaire C, Coffin A, Cohen-Zarade S, et al. Ct-guided biopsies in lung infections in patients with haematological malignancies. *Diagnostic and interventional imaging*. 2013; **94**: 202-215.

58 Reinwald M, Spiess B, Heinz WJ, et al. Aspergillus pcr-based investigation of fresh tissue and effusion samples in patients with suspected invasive aspergillosis enhances diagnostic capabilities. *Journal of clinical microbiology*. 2013; **51**: 4178-4185.

59 Gupta S, Sultenfuss M, Romaguera JE, et al. Ct-guided percutaneous lung biopsies in patients with haematologic malignancies and undiagnosed pulmonary lesions. *Hematol Oncol*. 2010; **28**: 75-81.

60 Shi JM, Cai Z, Huang H, et al. Role of ct-guided percutaneous lung biopsy in diagnosis of pulmonary fungal infection in patients with hematologic diseases. *International journal of hematology*. 2009; **89**: 624-627.

61 Lass-Florl C, Resch G, Nachbaur D, et al. The value of computed tomography-guided percutaneous lung biopsy for diagnosis of invasive fungal infection in immunocompromised patients. *Clin Infect Dis*. 2007; **45**: e101-104.

62 Rickerts V, Mousset S, Lambrecht E, et al. Comparison of histopathological analysis, culture, and polymerase chain reaction assays to detect invasive mold infections from biopsy specimens. *Clin Infect Dis*. 2007; **44**: 1078-1083.

63 Carrafiello G, Lagana D, Nosari AM, et al. Utility of computed tomography (ct) and of fine needle aspiration biopsy (fnab) in early diagnosis of fungal pulmonary infections. Study of infections from filamentous fungi in haematologically immunodeficient patients. *La Radiologia medica*. 2006; **111**: 33-41.

64 Nosari A, Anghilieri M, Carrafiello G, et al. Utility of percutaneous lung biopsy for diagnosing filamentous fungal infections in hematologic malignancies. *Haematologica*. 2003; **88**: 1405-1409.

65 Manhire A, Charig M, Clelland C, et al. Guidelines for radiologically guided lung biopsy. *Thorax*. 2003; **58**: 920-936.

66 Georgiadou SP, Sampsonas FL, Rice D, Granger JM, Swisher S, Kontoyiannis DP. Open-lung biopsy in patients with undiagnosed lung lesions referred at a tertiary cancer center is safe

and reveals noncancerous, noninfectious entities as the most common diagnoses. *Eur J Clin Microbiol Infect Dis*. 2013; **32**: 101-105.

67 Armenian SH, Hoffman JA, Butturini AM, Kapoor N, Mascarenhas L. Invasive diagnostic procedures for pulmonary infiltrates in pediatric hematopoietic stem cell transplant recipients. *Pediatr Transplant*. 2007; **11**: 736-742.

68 Zihlif M, Khanchandani G, Ahmed HP, Soubani AO. Surgical lung biopsy in patients with hematological malignancy or hematopoietic stem cell transplantation and unexplained pulmonary infiltrates: Improved outcome with specific diagnosis. *Am J Hematol*. 2005; **78**: 94-99.

69 Wingard JR, Hiemenz JW, Jantz MA. How i manage pulmonary nodular lesions and nodular infiltrates in patients with hematologic malignancies or undergoing hematopoietic cell transplantation. *Blood*. 2012; **120**: 1791-1800.

70 Choi YR, An JY, Kim MK, et al. The diagnostic efficacy and safety of endobronchial ultrasound-guided transbronchial needle aspiration as an initial diagnostic tool. *Korean J Intern Med*. 2013; **28**: 660-667.

71 Casal RF, Adachi R, Jimenez CA, Sarkiss M, Morice RC, Eapen GA. Diagnosis of invasive aspergillus tracheobronchitis facilitated by endobronchial ultrasound-guided transbronchial needle aspiration: A case report. *Journal of medical case reports*. 2009; **3**: 9290.

72 Aragaki-Nakahodo A, Benzaquen S, Kirschner M. Coinfection by nocardia beijingensis and nocardia arthritidis in an immunocompromised patient diagnosed by endobronchial ultrasound guided transbronchial needle aspiration (ebus-tbna). *Respir Med Case Rep*. 2014; **12**: 22-23.

73 Thery A, Espitalier F, Cassagnau E, Durand N, Malard O. Clinical features and outcome of sphenoid sinus aspergillosis: A retrospective series of 15 cases. *European annals of otorhinolaryngology, head and neck diseases*. 2012; **129**: 179-184.

74 Miyamoto Y, Sakamoto Y, Ohuchi M, et al. Orbital apex syndrome caused by invasive aspergillosis as an adverse effect of systemic chemotherapy for metastatic colorectal cancer: A case report. *Anticancer research*. 2016; **36**: 821-823.

75 Yuan L, Prayson RA. Optic nerve aspergillosis. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia*. 2015; **22**: 1191-1193.

76 Marzolf G, Sabou M, Lannes B, et al. Magnetic resonance imaging of cerebral aspergillosis: Imaging and pathological correlations. *PLoS One*. 2016; **11**: e0152475.

77 Ashdown BC, Tien RD, Felsberg GJ. Aspergillosis of the brain and paranasal sinuses in immunocompromised patients: Ct and mr imaging findings. *AJR American journal of roentgenology*. 1994; **162**: 155-159.

78 DeLone DR, Goldstein RA, Petermann G, et al. Disseminated aspergillosis involving the brain: Distribution and imaging characteristics. *AJNR American journal of neuroradiology*. 1999; **20**: 1597-1604.

79 Guermazi A, Gluckman E, Tabti B, Miaux Y. Invasive central nervous system aspergillosis in bone marrow transplantation recipients: An overview. *Eur Radiol*. 2003; **13**: 377-388.

80 Rüchel R, Schaffrinski M. Versatile fluorescent staining of fungi in clinical specimens by using the optical brightener blankophor. *Journal of clinical microbiology*. 1999; **37**: 2694-2696.

81 Fraczek MG, Kirwan MB, Moore CB, Morris J, Denning DW, Richardson MD. Volume dependency for culture of fungi from respiratory secretions and increased sensitivity of aspergillus quantitative pcr. *Mycoses*. 2014; **57**: 69-78.

82 Maertens JA, Klont R, Masson C, et al. Optimization of the cutoff value for the aspergillus double-sandwich enzyme immunoassay. *Clin Infect Dis*. 2007; **44**: 1329-1336.

83 Duarte RF, Sanchez-Ortega I, Cuesta I, et al. Serum galactomannan-based early detection of invasive aspergillosis in hematology patients receiving effective antimold prophylaxis. *Clin Infect Dis*. 2014; **59**: 1696-1702.

84 Teering S, Verreth A, Peeters A, et al. Prognostic value of serum galactomannan in mixed icu patients: A retrospective observational study. *Anaesthesiol Intensive Ther*. 2014; **46**: 145-154.

85 Nouér SA, Nucci M, Kumar NS, Grazziutti M, Barlogie B, Anaissie E. Earlier response assessment in invasive aspergillosis based on the kinetics of serum aspergillus galactomannan: Proposal for a new definition. *Clin Infect Dis*. 2011; **53**: 671-676.

86 D'Haese J, Theunissen K, Vermeulen E, et al. Detection of galactomannan in bronchoalveolar lavage fluid samples of patients at risk for invasive pulmonary aspergillosis: Analytical and clinical validity. *Journal of clinical microbiology*. 2012; **50**: 1258-1263.

87 Pasqualotto AC, Xavier MO, Sanchez LB, et al. Diagnosis of invasive aspergillosis in lung transplant recipients by detection of galactomannan in the bronchoalveolar lavage fluid. *Transplantation*. 2010; **90**: 306-311.

88 Luong ML, Clancy CJ, Vadnerkar A, et al. Comparison of an aspergillus real-time polymerase chain reaction assay with galactomannan testing of bronchoalvelolar lavage fluid for the diagnosis of invasive pulmonary aspergillosis in lung transplant recipients. *Clin Infect Dis*. 2011; **52**: 1218-1226.

89 Meersseman W, Lagrou K, Maertens J, et al. Galactomannan in bronchoalveolar lavage fluid: A tool for diagnosing aspergillosis in intensive care unit patients. *Am J Respir Crit Care Med*. 2008; **177**: 27-34.

90 Karageorgopoulos DE, Vouloumanou EK, Ntziora F, Michalopoulos A, Rafailidis PI, Falagas ME. ß-d-glucan assay for the diagnosis of invasive fungal infections: A meta-analysis. *Clin Infect Dis*. 2011; **52**: 750-770.

91 Prattes J, Lackner M, Eigl S, et al. Diagnostic accuracy of the aspergillus -specific bronchoalveolar lavage lateral-flow assay in haematological malignancy patients. *Mycoses*. 2015; **58**: 461-469.

92 Boch T, Reinwald M, Postina P, et al. Identification of invasive fungal diseases in immunocompromised patients by combining an aspergillus specific pcr with a multifungal DNA-microarray from primary clinical samples. *Mycoses*. 2015; **58**: 735-745.

93 Boch T, Spiess B, Cornely OA, et al. Diagnosis of invasive fungal infections in haematological patients by combined use of galactomannan, 1,3-beta-d-glucan, aspergillus pcr, multifungal DNA-microarray, and aspergillus azole resistance pcrs in blood and bronchoalveolar lavage samples: Results of a prospective multicentre study. *Clin Microbiol Infect*. 2016.

94 Springer J, Morton CO, Perry M, et al. Multicenter comparison of serum and whole-blood specimens for detection of aspergillus DNA in high-risk hematological patients. *Journal of clinical microbiology*. 2013; **51**: 1445-1450.

95 Springer J, White PL, Hamilton S, et al. Comparison of performance characteristics of aspergillus pcr in testing a range of blood-based samples in accordance with international methodological recommendations. *Journal of clinical microbiology*. 2016; **54**: 705-711.

96 White PL, Wiederhold NP, Loeffler J, et al. Comparison of nonculture blood-based tests for diagnosing invasive aspergillosis in an animal model. *Journal of clinical microbiology*. 2016; **54**: 960-966.

97 White PL, Barnes RA, Springer J, et al. Clinical performance of aspergillus pcr for testing serum and plasma: A study by the european aspergillus pcr initiative. *Journal of clinical microbiology*. 2015; **53**: 2832-2837.

98 Rogers TR, Morton CO, Springer J, et al. Combined real-time pcr and galactomannan surveillance improves diagnosis of invasive aspergillosis in high risk patients with haematological malignancies. *Br J Haematol*. 2013; **161**: 517-524.

99 Aguado JM, Vazquez L, Fernandez-Ruiz M, et al. Serum galactomannan versus a combination of galactomannan and polymerase chain reaction-based aspergillus DNA detection for early therapy of invasive aspergillosis in high-risk hematological patients: A randomized controlled trial. *Clin Infect Dis*. 2015; **60**: 405-414.

100 Vermeulen E, Lagrou K, Verweij PE. Azole resistance in aspergillus fumigatus: A growing public health concern. *Curr Opin Infect Dis*. 2013; **26**: 493-500.

101 Chowdhary A, Kathuria S, Xu J, Meis JF. Emergence of azole-resistant aspergillus fumigatus strains due to agricultural azole use creates an increasing threat to human health. *PLoS pathogens*. 2013; **9**: e1003633.

102 Koehler P, Hamprecht A, Bader O, et al. Epidemiology of invasive aspergillosis and azole resistance in patients with acute leukaemia: The sepia study. *International journal of antimicrobial agents*. 2017; **49**: 218-223.

103 Van Der Linden JW, Warris A, Verweij PE. Aspergillus species intrinsically resistant to antifungal agents. *Medical mycology*. 2011; **49 Suppl 1**: S82-89.

104 Anderson JB. Evolution of antifungal-drug resistance: Mechanisms and pathogen fitness. *Nat Rev Microbiol*. 2005; **3**: 547-556.

105 van der Linden JW, Arendrup MC, Warris A, et al. Prospective multicenter international surveillance of azole resistance in aspergillus fumigatus. *Emerg Infect Dis*. 2015; **21**: 1041-1044.

106 Chowdhary A, Sharma C, van den Boom M, et al. Multi-azole-resistant aspergillus fumigatus in the environment in tanzania. *J Antimicrob Chemother*. 2014; **69**: 2979-2983.

107 Verweij PE, Chowdhary A, Melchers WJ, Meis JF. Azole resistance in aspergillus fumigatus: Can we retain the clinical use of mold-active antifungal azoles? *Clin Infect Dis*. 2016; **62**: 362-368.

108 Ozmerdiven GE, Ak S, Ener B, et al. First determination of azole resistance in aspergillus fumigatus strains carrying the tr34/l98h mutations in turkey. *J Infect Chemother*. 2015; **21**: 581-586.

109 Astvad KM, Jensen RH, Hassan TM, et al. First detection of tr46/y121f/t289a and tr34/l98h alterations in aspergillus fumigatus isolates from azole-naive patients in denmark despite negative findings in the environment. *Antimicrob Agents Chemother*. 2014; **58**: 5096-5101.

110 Verweij PE, Snelders E, Kema GH, Mellado E, Melchers WJ. Azole resistance in aspergillus fumigatus: A side-effect of environmental fungicide use? *Lancet Infect Dis*. 2009; **9**: 789-795.

111 Stensvold CR, Nistrup Jørgensen L, M CA. Azole-resistant invasive aspergillosis: Relationship to agriculture. *Curr Fungal Infect Rep*. 2012; **6**: 178-191.

112 Bowyer P, Denning DW. Environmental fungicides and triazole resistance in aspergillus. *Pest Manag Sci*. 2014; **70**: 173-178.

113 van der Linden JW, Snelders E, Kampinga GA, et al. Clinical implications of azole resistance in aspergillus fumigatus, the netherlands, 2007-2009. *Emerg Infect Dis*. 2011; **17**: 1846-1854.

114 van der Linden JW, Camps SM, Kampinga GA, et al. Aspergillosis due to voriconazole highly resistant aspergillus fumigatus and recovery of genetically related resistant isolates from domiciles. *Clin Infect Dis*. 2013; **57**: 513-520.

115 Howard SJ, Cerar D, Anderson MJ, et al. Frequency and evolution of azole resistance in aspergillus fumigatus associated with treatment failure. *Emerg Infect Dis*. 2009; **15**: 1068-1076.

116 Camps SM, van der Linden JW, Li Y, et al. Rapid induction of multiple resistance mechanisms in aspergillus fumigatus during azole therapy: A case study and review of the literature. *Antimicrob Agents Chemother*. 2012; **56**: 10-16.

117 Ahmad S, Joseph L, Hagen F, Meis JF, Khan Z. Concomitant occurrence of itraconazole-resistant and -susceptible strains of aspergillus fumigatus in routine cultures. *J Antimicrob Chemother*. 2015; **70**: 412-415.

118 Arendrup MC, Verweij PE, Mouton JW, Lagrou K, Meletiadis J. Multicentre validation of 4-well azole agar plates as a screening method for detection of clinically relevant azole-resistant aspergillus fumigatus. *J Antimicrob Chemother*. 2017; **72**: 3325-3333.

119 Andes D, Pascual A, Marchetti O. Antifungal therapeutic drug monitoring: Established and emerging indications. *Antimicrob Agents Chemother*. 2009; **53**: 24-34.

120 Tricot G, Joosten E, Boogaerts MA, Vande-Pitte J, Cauwenbergh G. Ketoconazole vs. Itraconazole for antifungal prophylaxis in patients with severe granulocytopenia: Preliminary results of two nonrandomized studies. *Rev Infect Diseases*. **9**: S94-S95.

121 Morgenstern GR, Prentice AG, Grant Prentice H, et al. A randomized controlled trial of itraconazole versus fluconazole for the prevention of fungal infections in patients with haematological malignancies. *Br J Haematol*. 1999; **105**: 901-911.

122 Glasmacher A, Hahn C, Molitor E, Marklein G, Sauerbruch T, Schmidt-Wolf I. Itraconazole trough concentrations in antifungal prophylaxis with six different dosing regimens using hydroxypropyl-ß-cyclodextrin oral solution or coated-pellet capsules. *Mycoses*. 1999; **42**: 591-600.

123 Glasmacher A, Hahn C, Leutner C, et al. Breakthrough invasive fungal infections in neutropenic patients after prophylaxis with itraconazole. *Mycoses*. 1999; **42**: 443-451.

124 Glasmacher A, Prentice A, Gorschlüter M, et al. Itraconazole prevents invasive fungal infections in neutropenic patients treated for hematologic malignancies: Evidence from a meta-analysis of 3,597 patients. *J Clin Oncol*. 2003; **21**: 4615-4626.

125 Boogaerts MA, Verhoef GE, Zachee P, Demuynck H, Verbist L, De Beule K. Antifungal prophylaxis with itraconazole in prolonged neutropenia: Correlation with plasma levels. *Mycoses*. 1989; **32 Suppl 1**: 103-108.

126 Denning DW, Lee JY, Hostetler JS, et al. Niaid mycoses study group multicenter trial of oral itraconazole therapy for invasive aspergillosis. *Am J Med*. 1994; **97**: 135-144.

127 Lestner JM, Roberts SA, Moore CB, Howard SJ, Denning DW, Hope WW. Toxicodynamics of itraconazole: Implications for therapeutic drug monitoring. *Clin Infect Dis*. 2009; **49**: 928-930.

128 Pascual A, Csajka C, Buclin T, et al. Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety: Population pharmacokinetics-based analysis of adult patients with invasive fungal infections. *Clin Infect Dis*. 2012; **55**: 381-390.

129 Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. *Clin Infect Dis*. 2008; **46**: 201-211.

130 Park WB, Kim N-H, Kim K-H, et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: A randomized controlled trial. *Clin Infect Dis*. 2012; **55**: 1080-1087.

131 Troke PF, Hockey HP, Hope WW. Observational study of the clinical efficacy of voriconazole and its relationship to plasma concentrations in patients. *Antimicrob Agents Chemother*. 2011; **55**: 4782-4788.

132 Trifilio S, Singhal S, Williams S, et al. Breakthrough fungal infections after allogeneic hematopoietic stem cell transplantation in patients on prophylactic voriconazole. *Bone Marrow Transplant*. 2007; **40**: 451-456.

133 Dolton MJ, Ray JE, Chen SCA, Ng K, Pont LG, McLachlan AJ. Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring. *Antimicrob Agents Chemother*. 2012; **56**: 4793-4799.

134 Neely M, Margol A, Fu X, et al. Achieving target voriconazole concentrations more accurately in children and adolescents. *Antimicrob Agents Chemother*. 2015; **59**: 3090-3097.

135 Friberg LE, Ravva P, Karlsson MO, Liu P. Integrated population pharmacokinetic analysis of voriconazole in children, adolescents and adults. *Antimicrob Agents Chemother*. 2012; **56**: 3032-3042.

136 Jang SH, Colangelo PM, Gobburu JVS. Exposure--response of posaconazole used for prophylaxis against invasive fungal infections: Evaluating the need to adjust doses based on drug concentrations in plasma. *Clinical Pharmacology & Therapeutics*. 2010; **88**: 115-119.

137 Cornely OA, Ullmann AJ. Lack of evidence for exposure-response relationship in the use of posaconazole as prophylaxis against invasive fungal infections. *Clinical pharmacology and therapeutics*. 2011; **89**: 351-352.

138 Walsh TJ, Raad I, Patterson TF, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: An externally controlled trial. *Clin Infect Dis*. 2007; **44**: 2-12.

139 European Medicine A. Assessment report: Noxafil. 2014.

140 Cornely OA, Robertson MN, Haider S, et al. Pharmacokinetics and safety results from the phase 3 randomized, open-label, study of intravenous posaconazole in patients at risk of invasive fungal disease *Journal of Antimicrobial Chemotherapy*. 2017.

141 Cornely OA, Duarte RF, Haider S, et al. Phase 3 pharmacokinetics and safety study of a posaconazole tablet formulation in patients at risk for invasive fungal disease. *J Antimicrob Chemother*. 2016; **71**: 1747.

142 Bowden R, Chandrasekar P, White MH, et al. A double-blind, randomized, controlled trial of amphotericin b colloidal dispersion versus amphotericin b for treatment of invasive aspergillosis in immunocompromised patients. *Clin Infect Dis*. 2002; **35**: 359-366.

143 Stamm AM, Diasio RB, Dismukes WE, et al. Toxicity of amphotericin b plus flucytosine in 194 patients with cryptococcal meningitis. *Am J Med*. 1987; **83**: 236-242.

144 Pasqualotto AC, Howard SJ, Moore CB, Denning DW. Flucytosine therapeutic monitoring: 15 years experience from the uk. *J Antimicrob Chemother*. 2007; **59**: 791-793.

145 Walsh TJ, Dixon DM. Nosocomial aspergillosis: Environmental microbiology, hospital epidemiology, diagnosis and treatment. *European journal of epidemiology*. 1989; **5**: 131-142.

146 Goodley JM, Clayton YM, Hay RJ. Environmental sampling for aspergilli during building construction on a hospital site. *The Journal of hospital infection*. 1994; **26**: 27-35.

147 Perraud M, Piens MA, Nicoloyannis N, Girard P, Sepetjan M, Garin JP. Invasive nosocomial pulmonary aspergillosis: Risk factors and hospital building works. *Epidemiol Infect*. 1987; **99**: 407-412.

148 Opal SM, Asp AA, Cannady PB, Jr., Morse PL, Burton LJ, Hammer PG, 2nd. Efficacy of infection control measures during a nosocomial outbreak of disseminated aspergillosis associated with hospital construction. *The Journal of infectious diseases*. 1986; **153**: 634-637.

149 Weems JJ, Jr., Davis BJ, Tablan OC, Kaufman L, Martone WJ. Construction activity: An independent risk factor for invasive aspergillosis and zygomycosis in patients with hematologic malignancy. *Infect Control*. 1987; **8**: 71-75.

150 Meheust D, Le Cann P, Reboux G, Millon L, Gangneux JP. Indoor fungal contamination: Health risks and measurement methods in hospitals, homes and workplaces. *Crit Rev Microbiol*. 2014; **40**: 248-260.

151 Sherertz RJ, Belani A, Kramer BS, et al. Impact of air filtration on nosocomial aspergillus infections. Unique risk of bone marrow transplant recipients. *The American journal of medicine*. 1987; **83**: 709-718.

152 Barnes RA, Rogers TR. Control of an outbreak of nosocomial aspergillosis by laminar air-flow isolation. *The Journal of hospital infection*. 1989; **14**: 89-94.

153 Thio CL, Smith D, Merz WG, et al. Refinements of environmental assessment during an outbreak investigation of invasive aspergillosis in a leukemia and bone marrow transplant unit. *Infect Control Hosp Epidemiol*. 2000; **21**: 18-23.

154 Hahn T, Cummings KM, Michalek AM, Lipman BJ, Segal BH, McCarthy PL, Jr. Efficacy of high-efficiency particulate air filtration in preventing aspergillosis in immunocompromised patients with hematologic malignancies. *Infect Control Hosp Epidemiol*. 2002; **23**: 525-531.

155 Maschmeyer G, Neuburger S, Fritz L, et al. A prospective, randomised study on the use of well-fitting masks for prevention of invasive aspergillosis in high-risk patients. *Ann Oncol*. 2009; **20**: 1560-1564.

156 Anaissie EJ, Stratton SL, Dignani MC, et al. Pathogenic aspergillus species recovered from a hospital water system: A 3-year prospective study. *Clin Infect Dis*. 2002; **34**: 780-789.

157 Anaissie EJ, Penzak SR, Dignani MC. The hospital water supply as a source of nosocomial infections: A plea for action. *Archives of internal medicine*. 2002; **162**: 1483-1492.

158 Anaissie EJ, Stratton SL, Dignani MC, et al. Cleaning patient shower facilities: A novel approach to reducing patient exposure to aerosolized aspergillus species and other opportunistic molds. *Clin Infect Dis*. 2002; **35**: E86-88.

159 Anaissie EJ, Stratton SL, Dignani MC, et al. Pathogenic molds (including aspergillus species) in hospital water distribution systems: A 3-year prospective study and clinical implications for patients with hematologic malignancies. *Blood*. 2003; **101**: 2542-2546.

160 Lee LD, Hachem RY, Berkheiser M, Hackett B, Jiang Y, Raad, II. Hospital environment and invasive aspergillosis in patients with hematologic malignancy. *Am J Infect Control*. 2012; **40**: 247-249.

161 Mahieu LM, De Dooy JJ, Van Laer FA, Jansens H, Ieven MM. A prospective study on factors influencing aspergillus spore load in the air during renovation works in a neonatal intensive care unit. *The Journal of hospital infection*. 2000; **45**: 191-197 [Record as supplied by publisher].

162 Rüping MJ, Gerlach S, Fischer G, et al. Environmental and clinical epidemiology of aspergillus terreus: Data from a prospective surveillance study. *The Journal of hospital infection*. 2011; **78**: 226-230.

163 Chamilos G, Luna M, Lewis RE, et al. Invasive fungal infections in patients with hematologic malignancies in a tertiary care cancer center: An autopsy study over a 15-year period (1989-2003). *Haematologica*. 2006; **91**: 986-989.

164 Sinko J, Csomor J, Nikolova R, et al. Invasive fungal disease in allogeneic hematopoietic stem cell transplant recipients: An autopsy-driven survey. *Transpl Infect Dis*. 2008; **10**: 106-109.

165 Lewis RE, Cahyame-Zuniga L, Leventakos K, et al. Epidemiology and sites of involvement of invasive fungal infections in patients with haematological malignancies: A 20-year autopsy study. *Mycoses*. 2013; **56**: 638-645.

166 Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 2002; **34**: 909-917.

167 Wald A, Leisenring W, van Burik JA, Bowden RA. Epidemiology of aspergillus infections in a large cohort of patients undergoing bone marrow transplantation. *The Journal of infectious diseases*. 1997; **175**: 1459-1466.

168 Neofytos D, Horn D, Anaissie E, et al. Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: Analysis of multicenter prospective antifungal therapy (path) alliance registry. *Clin Infect Dis*. 2009; **48**: 265-273.

169 De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the european organization for research and treatment of cancer/invasive fungal infections cooperative group and the national institute of allergy and infectious diseases mycoses study group (eortc/msg) consensus group. *Clin Infect Dis*. 2008; **46**: 1813-1821.

170 Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin b for primary therapy of invasive aspergillosis. *N Engl J Med*. 2002; **347**: 408-415.

171 Cornely OA, Maertens J, Bresnik M, et al. Liposomal amphotericin b as initial therapy for invasive mold infection: A randomized trial comparing a high-loading dose regimen with standard dosing (ambiload trial). *Clin Infect Dis*. 2007; **44**: 1289-1297.

172 Marr KA, Schlamm HT, Herbrecht R, et al. Combination antifungal therapy for invasive aspergillosis: A randomized trial. *Annals of internal medicine*. 2015; **162**: 81-89.

173 Maertens JA, Raad, II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by aspergillus and other filamentous fungi (secure): A phase 3, randomised-controlled, non-inferiority trial. *Lancet*. 2016; **387**: 760-769.

174 Ofran Y, Avivi I, Oliven A, et al. Granulocyte transfusions for neutropenic patients with life-threatening infections: A single centre experience in 47 patients, who received 348 granulocyte transfusions. *Vox Sang*. 2007; **93**: 363-369.

175 Safdar A, Rodriguez GH, Lichtiger B, et al. Recombinant interferon gamma1b immune enhancement in 20 patients with hematologic malignancies and systemic opportunistic infections treated with donor granulocyte transfusions. *Cancer*. 2006; **106**: 2664-2671.

176 Sachs UJ, Reiter A, Walter T, Bein G, Woessmann W. Safety and efficacy of therapeutic early onset granulocyte transfusions in pediatric patients with neutropenia and severe infections. *Transfusion*. 2006; **46**: 1909-1914.

177 Dignani MC, Rex JH, Chan KW, et al. Immunomodulation with interferon-gamma and colony-stimulating factors for refractory fungal infections in patients with leukemia. *Cancer*. 2005; **104**: 199-204.

178 Lee JJ, Chung IJ, Park MR, et al. Clinical efficacy of granulocyte transfusion therapy in patients with neutropenia-related infections. *Leukemia*. 2001; **15**: 203-207.

179 Dignani MC, Anaissie EJ, Hester JP, et al. Treatment of neutropenia-related fungal infections with granulocyte colony-stimulating factor-elicited white blood cell transfusions: A pilot study. *Leukemia*. 1997; **11**: 1621-1630.

180 Massey E, Paulus U, Doree C, Stanworth S. Granulocyte transfusions for preventing infections in patients with neutropenia or neutrophil dysfunction. *Cochrane Database Syst Rev*. 2009: CD005341.

181 Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG. Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. *The American journal of medicine*. 1982; **72**: 101-111.

182 Pizzo PA, Robichaud KJ, Wesley R, Commers JR. Fever in the pediatric and young adult patient with cancer. A prospective study of 1001 episodes. *Medicine (Baltimore)*. 1982; **61**: 153-165.

183 Empiric antifungal therapy in febrile granulocytopenic patients. Eortc international antimicrobial therapy cooperative group. *The American journal of medicine*. 1989; **86**: 668-672.

184 Goldberg E, Gafter-Gvili A, Robenshtok E, Leibovici L, Paul M. Empirical antifungal therapy for patients with neutropenia and persistent fever: Systematic review and meta-analysis. *Eur J Cancer*. 2008; **44**: 2192-2203.

185 Cordonnier C, Pautas C, Maury S, et al. Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: A randomized, controlled trial. *Clin Infect Dis*. 2009; **48**: 1042-1051.

186 Girmenia C, Micozzi A, Gentile G, et al. Clinically driven diagnostic antifungal approach in neutropenic patients: A prospective feasibility study. *J Clin Oncol*. 2010; **28**: 667-674.

187 Pagano L, Caira M, Nosari A, et al. The use and efficacy of empirical versus pre-emptive therapy in the management of fungal infections: The hema e-chart project. *Haematologica*. 2011; **96**: 1366-1370.

188 Walsh TJ, Teppler H, Donowitz GR, et al. Caspofungin versus liposomal amphotericin b for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med*. 2004; **351**: 1391-1402.

189 Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin b for empirical therapy in patients with persistent fever and neutropenia. National institute of allergy and infectious diseases mycoses study group. *N Engl J Med*. 1999; **340**: 764-771.

190 Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal amphotericin b for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med*. 2002; **346**: 225-234.

191 White PL, Parr C, Thornton C, Barnes RA. Evaluation of real-time pcr, galactomannan enzyme-linked immunosorbent assay (elisa), and a novel lateral-flow device for diagnosis of invasive aspergillosis. *Journal of clinical microbiology*. 2013; **51**: 1510-1516.

192 White PL, Wingard JR, Bretagne S, et al. Aspergillus polymerase chain reaction: Systematic review of evidence for clinical use in comparison with antigen testing. *Clin Infect Dis*. 2015; **61**: 1293-1303.

193 Liss B, Cornely OA, Hoffmann D, Dimitriou V, Wisplinghoff H. 1,3-beta-d-glucan contamination of common antimicrobials-authors' response. *J Antimicrob Chemother*. 2016; **71**: 2997-2999.

194 Liss B, Cornely OA, Hoffmann D, Dimitriou V, Wisplinghoff H. 1,3-beta-d-glucan contamination of common antimicrobials. *J Antimicrob Chemother*. 2016; **71**: 913-915.

195 Liss B, Cornely OA, Hoffmann D, Dimitriou V, Wisplinghoff H. 1,3-ß-d-glucan concentrations in blood products predict false positive post-transfusion results. *Mycoses*. 2016; **59**: 39-42.

196 Hammarstrom H, Kondori N, Friman V, Wenneras C. How to interpret serum levels of beta-glucan for the diagnosis of invasive fungal infections in adult high-risk hematology patients: Optimal cut-off levels and confounding factors. *Eur J Clin Microbiol Infect Dis*. 2015; **34**: 917-925.

197 Bouza E, Guinea J, Pelaez T, Perez-Molina J, Alcala L, Munoz P. Workload due to aspergillus fumigatus and significance of the organism in the microbiology laboratory of a general hospital. *Journal of clinical microbiology*. 2005; **43**: 2075-2079.

198 Montagna MT, Lovero G, Coretti C, et al. Simiff study: Italian fungal registry of mold infections in hematological and non-hematological patients. *Infection*. 2014; **42**: 141-151.

199 Garcia-Vidal C, Peghin M, Cervera C, et al. Causes of death in a contemporary cohort of patients with invasive aspergillosis. *PLoS One*. 2015; **10**: e0120370.

200 Vena A, Munoz P, Pelaez T, Guinea J, Valerio M, Bouza E. Non-construction related aspergillus outbreak in non-haematological patients related to high concentrations of airborne spores in non-hepa filtered areas. *ID week, San Diego, Ca*. 2015; **Octuber 7-11**.

201 Ruiz-Camps I, Aguado JM, Almirante B, et al. [recommendations of the spanish society of infectious diseases and clinical microbiology (seimc) on the prevention of invasive fungal infection due to filamentous fungi]. *Enferm Infecc Microbiol Clin*. 2010; **28**: 172 e171-172 e121.

202 Guinea J, Pelaez T, Alcala L, Bouza E. Outdoor environmental levels of aspergillus spp. Conidia over a wide geographical area. *Medical mycology*. 2006; **44**: 349-356.

203 Pelaez T, Munoz P, Guinea J, et al. Outbreak of invasive aspergillosis after major heart surgery caused by spores in the air of the intensive care unit. *Clin Infect Dis*. 2012; **54**: e24-31.

204 Munoz P, Guinea J, Pelaez T, Duran C, Blanco JL, Bouza E. Nosocomial invasive aspergillosis in a heart transplant patient acquired during a break in the hepa air filtration system. *Transpl Infect Dis*. 2004; **6**: 50-54.

205 Tang HJ, Liu WL, Chang TC, et al. Multiple brain abscesses due to aspergillus fumigatus in a patient with liver cirrhosis: A case report. *Medicine (Baltimore)*. 2016; **95**: e2813.

206 Pilmis B, Puel A, Lortholary O, Lanternier F. New clinical phenotypes of fungal infections in special hosts. *Clin Microbiol Infect*. 2016.

207 Falcone M, Concia E, Iori I, et al. Identification and management of invasive mycoses in internal medicine: A road-map for physicians. *Intern Emerg Med*. 2014; **9**: 501-511.

208 Peghin M, Ruiz-Camps I, Garcia-Vidal C, et al. Unusual forms of subacute invasive pulmonary aspergillosis in patients with solid tumors. *J Infect*. 2014; **69**: 387-395.

209 Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: Results of the transplant-associated infection surveillance network (transnet). *Clin Infect Dis*. 2010; **50**: 1101-1111.

210 Gavalda J, Len O, San Juan R, et al. Risk factors for invasive aspergillosis in solid-organ transplant recipients: A case-control study. *Clin Infect Dis*. 2005; **41**: 52-59.

211 Singh N, Husain S, Practice ASTIDCo. Aspergillosis in solid organ transplantation. *Am J Transplant*. 2013; **13 Suppl 4**: 228-241.

212 Singh N, Limaye AP, Forrest G, et al. Late-onset invasive aspergillosis in organ transplant recipients in the current era. *Medical mycology*. 2006; **44**: 445-449.

213 Gavalda J, Meije Y, Fortun J, et al. Invasive fungal infections in solid organ transplant recipients. *Clin Microbiol Infect*. 2014; **20 Suppl 7**: 27-48.

214 Munoz P, Ceron I, Valerio M, et al. Invasive aspergillosis among heart transplant recipients: A 24-year perspective. *J Heart Lung Transplant*. 2014; **33**: 278-288.

215 Munoz P, Valerio M, Palomo J, et al. Targeted antifungal prophylaxis in heart transplant recipients. *Transplantation*. 2013; **96**: 664-669.

216 Barchiesi F, Mazzocato S, Mazzanti S, et al. Invasive aspergillosis in liver transplant recipients: Epidemiology, clinical characteristics, treatment, and outcomes in 116 cases. *Liver Transpl*. 2015; **21**: 204-212.

217 Winston DJ, Limaye AP, Pelletier S, et al. Randomized, double-blind trial of anidulafungin versus fluconazole for prophylaxis of invasive fungal infections in high-risk liver transplant recipients. *Am J Transplant*. 2014; **14**: 2758-2764.

218 Lichtenstern C, Hochreiter M, Zehnter VD, et al. Pretransplant model for end stage liver disease score predicts posttransplant incidence of fungal infections after liver transplantation. *Mycoses*. 2013; **56**: 350-357.

219 Ohkubo T, Sugawara Y, Takayama T, Kokudo N, Makuuchi M. The risk factors of fungal infection in living-donor liver transplantations. *J Hepatobiliary Pancreat Sci*. 2012; **19**: 382-388.

220 San-Juan R, Aguado JM, Lumbreras C, et al. Universal prophylaxis with fluconazole for the prevention of early invasive fungal infection in low-risk liver transplant recipients. *Transplantation*. 2011; **92**: 346-350.

221 Singh N, Wagener MM, Cacciarelli TV, Levitsky J. Antifungal management practices in liver transplant recipients. *Am J Transplant*. 2008; **8**: 426-431.

222 Osawa M, Ito Y, Hirai T, et al. Risk factors for invasive aspergillosis in living donor liver transplant recipients. *Liver Transpl*. 2007; **13**: 566-570.

223 Pappas PG, Andes D, Schuster M, et al. Invasive fungal infections in low-risk liver transplant recipients: A multi-center prospective observational study. *Am J Transplant*. 2006; **6**: 386-391.

224 Fortun J, Martin-Davila P, Moreno S, et al. Risk factors for invasive aspergillosis in liver transplant recipients. *Liver Transpl*. 2002; **8**: 1065-1070.

225 Singh N, Husain S. Aspergillus infections after lung transplantation: Clinical differences in type of transplant and implications for management. *J Heart Lung Transplant*. 2003; **22**: 258-266.

226 Weigt SS, Elashoff RM, Huang C, et al. Aspergillus colonization of the lung allograft is a risk factor for bronchiolitis obliterans syndrome. *Am J Transplant*. 2009; **9**: 1903-1911.

227 Geltner C, Lass-Florl C. Invasive pulmonary aspergillosis in organ transplants--focus on lung transplants. *Respir Investig*. 2016; **54**: 76-84.

228 Lopez-Medrano F, Silva JT, Fernandez-Ruiz M, et al. Risk factors associated with early invasive pulmonary aspergillosis in kidney transplant recipients: Results from a multinational matched case-control study. *Am J Transplant*. 2016; **16**: 2148-2157.

229 Gustafson TL, Schaffner W, Lavely GB, Stratton CW, Johnson HK, Hutcheson RH, Jr. Invasive aspergillosis in renal transplant recipients: Correlation with corticosteroid therapy. *The Journal of infectious diseases*. 1983; **148**: 230-238.

230 Wojtowicz A, Gresnigt MS, Lecompte T, et al. Il1b and defb1 polymorphisms increase susceptibility to invasive mold infection after solid-organ transplantation. *The Journal of infectious diseases*. 2015; **211**: 1646-1657.

231 Wojtowicz A, Lecompte TD, Bibert S, et al. Ptx3 polymorphisms and invasive mold infections after solid organ transplant. *Clin Infect Dis*. 2015; **61**: 619-622.

232 Denis B, Guiguet M, de Castro N, et al. Relevance of eortc criteria for the diagnosis of invasive aspergillosis in hiv-infected patients, and survival trends over a 20-year period in france. *Clin Infect Dis*. 2015; **61**: 1273-1280.

233 Libanore M, Prini E, Mazzetti M, et al. Invasive aspergillosis in italian aids patients. *Infection*. 2002; **30**: 341-345.

234 Moreno A, Perez-Elias M, Casado J, et al. Role of antiretroviral therapy in long-term survival of patients with aids-related pulmonary aspergillosis. *Eur J Clin Microbiol Infect Dis*. 2000; **19**: 688-693.

235 Mylonakis E, Paliou M, Sax PE, Skolnik PR, Baron MJ, Rich JD. Central nervous system aspergillosis in patients with human immunodeficiency virus infection. Report of 6 cases and review. *Medicine (Baltimore)*. 2000; **79**: 269-280.

236 Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: Systematic review of the literature. *Clin Infect Dis*. 2001; **32**: 358-366.

237 Gastaca M, Aguero F, Rimola A, et al. Liver retransplantation in hiv-infected patients: A prospective cohort study. *Am J Transplant*. 2012; **12**: 2465-2476.

238 Moreno A, Cervera C, Fortun J, et al. Epidemiology and outcome of infections in human immunodeficiency virus/hepatitis c virus-coinfected liver transplant recipients: A fipse/gesida prospective cohort study. *Liver Transpl*. 2012; **18**: 70-81.

239 Woitas RP, Rockstroh JK, Theisen A, Leutner C, Sauerbruch T, Spengler U. Changing role of invasive aspergillosis in aids--a case control study. *J Infect*. 1998; **37**: 116-122.

240 Lortholary O, Meyohas MC, Dupont B, et al. Invasive aspergillosis in patients with acquired immunodeficiency syndrome: Report of 33 cases. French cooperative study group on aspergillosis in aids. *The American journal of medicine*. 1993; **95**: 177-187.

241 Denning DW, Follansbee SE, Scolaro M, Norris S, Edelstein H, Stevens DA. Pulmonary aspergillosis in the acquired immunodeficiency syndrome. *N Engl J Med*. 1991; **324**: 654-662.

242 Antinori S, Nebuloni M, Magni C, et al. Trends in the postmortem diagnosis of opportunistic invasive fungal infections in patients with aids: A retrospective study of 1,630 autopsies performed between 1984 and 2002. *Am J Clin Pathol*. 2009; **132**: 221-227.

243 Chen J, Yang Q, Huang J, Li L. Clinical findings in 19 cases of invasive pulmonary aspergillosis with liver cirrhosis. *Multidiscip Respir Med*. 2014; **9**: 1.

244 Jeurissen S, Vogelaers D, Sermijn E, et al. Invasive aspergillosis in patients with cirrhosis, a case report and review of the last 10 years. *Acta Clin Belg*. 2013; **68**: 368-375.

245 Vandewoude K, Blot S, Benoit D, Depuydt P, Vogelaers D, Colardyn F. Invasive aspergillosis in critically ill patients: Analysis of risk factors for acquisition and mortality. *Acta Clin Belg*. 2004; **59**: 251-257.

246 Cheruvattath R, Balan V. Infections in patients with end-stage liver disease. *J Clin Gastroenterol*. 2007; **41**: 403-411.

247 Falcone M, Massetti AP, Russo A, Vullo V, Venditti M. Invasive aspergillosis in patients with liver disease. *Medical mycology*. 2011; **49**: 406-413.

248 Russo A, Giuliano S, Vena A, et al. Predictors of mortality in non-neutropenic patients with invasive pulmonary aspergillosis: Does galactomannan have a role? *Diagn Microbiol Infect Dis*. 2014; **80**: 83-86.

249 Delsuc C, Cottereau A, Frealle E, et al. Putative invasive pulmonary aspergillosis in critically ill patients with chronic obstructive pulmonary disease: A matched cohort study. *Crit Care*. 2015; **19**: 421.

250 Tortorano AM, Dho G, Prigitano A, et al. Invasive fungal infections in the intensive care unit: A multicentre, prospective, observational study in italy (2006-2008). *Mycoses*. 2012; **55**: 73-79.

251 Jensen J, Guinea J, Torres-Narbona M, Munoz P, Pelaez T, Bouza E. Post-surgical invasive aspergillosis: An uncommon and under-appreciated entity. *J Infect*. 2010; **60**: 162-167.

252 Vehreschild JJ, Brockelmann PJ, Bangard C, et al. Pandemic 2009 influenza a(h1n1) virus infection coinciding with invasive pulmonary aspergillosis in neutropenic patients. *Epidemiol Infect*. 2012; **140**: 1848-1852.

253 Garnacho-Montero J, Amaya-Villar R, Ortiz-Leyba C, et al. Isolation of aspergillus spp. From the respiratory tract in critically ill patients: Risk factors, clinical presentation and outcome. *Crit Care*. 2005; **9**: R191-199.

254 Koulenti D, Garnacho-Montero J, Blot S. Approach to invasive pulmonary aspergillosis in critically ill patients. *Curr Opin Infect Dis*. 2014; **27**: 174-183.

255 Bassetti M, Righi E, De Pascale G, et al. How to manage aspergillosis in non-neutropenic intensive care unit patients. *Crit Care*. 2014; **18**: 458.

256 Dimopoulos G, Frantzeskaki F, Poulakou G, Armaganidis A. Invasive aspergillosis in the intensive care unit. *Ann N Y Acad Sci*. 2012; **1272**: 31-39.

257 Guinea J, Torres-Narbona M, Gijon P, et al. Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: Incidence, risk factors, and outcome. *Clin Microbiol Infect*. 2010; **16**: 870-877.

258 Tutar N, Metan G, Koc AN, et al. Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease. *Multidiscip Respir Med*. 2013; **8**: 59.

259 Giannella M, Munoz P, Guinea J, Escribano P, Rodriguez-Creixems M, Bouza E. Growth of aspergillus in blood cultures: Proof of invasive aspergillosis in patients with chronic obstructive pulmonary disease? *Mycoses*. 2013; **56**: 488-490.

260 Eworo A, Munoz P, Yanez JF, et al. [cardiac invasive aspergillosis in a heart transplant recipient]. *Rev Iberoam Micol*. 2011; **28**: 134-138.

261 El-Sayed Ahmed MM, Almanfi A, Aftab M, Singh SK, Mallidi HR, Frazier OH. Aspergillus mediastinitis after orthotopic heart transplantation: A case report. *Tex Heart Inst J*. 2015; **42**: 468-470.

262 Wiltberger G, Schmelzle M, Schubert S, et al. Invasive cardiac aspergillosis after orthotopic liver transplantation. *Z Gastroenterol*. 2014; **52**: 813-817.

263 Spapen H, Spapen J, Taccone FS, et al. Cerebral aspergillosis in adult critically ill patients: A descriptive report of 10 patients from the aspicu cohort. *Int J Antimicrob Agents*. 2014; **43**: 165-169.

264 Sole A, Ussetti P. [mold infections in lung transplants]. *Rev Iberoam Micol*. 2014; **31**: 229-236.

265 Fortun J, Meije Y, Fresco G, Moreno S. [aspergillosis. Clinical forms and treatment]. *Enferm Infecc Microbiol Clin*. 2012; **30**: 201-208.

266 Singh N, Sun HY. Iron overload and unique susceptibility of liver transplant recipients to disseminated disease due to opportunistic pathogens. *Liver Transpl*. 2008; **14**: 1249-1255.

267 Shields RK, Nguyen MH, Shullo MA, et al. Invasive aspergillosis among heart transplant recipients is rare but causes rapid death due to septic shock and multiple organ dysfunction syndrome. *Scand J Infect Dis*. 2012; **44**: 982-986.

268 Perfect JR, Cox GM, Lee JY, et al. The impact of culture isolation of aspergillus species: A hospital-based survey of aspergillosis. *Clin Infect Dis*. 2001; **33**: 1824-1833.

269 Horvath JA, Dummer S. The use of respiratory-tract cultures in the diagnosis of invasive pulmonary aspergillosis. *The American journal of medicine*. 1996; **100**: 171-178.

270 Escribano P, Marcos-Zambrano LJ, Pelaez T, et al. Sputum and bronchial secretion samples are equally useful as bronchoalveolar lavage samples for the diagnosis of invasive pulmonary aspergillosis in selected patients. *Medical mycology*. 2015; **53**: 235-240.

271 Munoz P, Alcala L, Sanchez Conde M, et al. The isolation of aspergillus fumigatus from respiratory tract specimens in heart transplant recipients is highly predictive of invasive aspergillosis. *Transplantation*. 2003; **75**: 326-329.

272 Barton RC, Hobson RP, McLoughlin H, Morris A, Datta B. Assessment of the significance of respiratory culture of aspergillus in the non-neutropenic patient. A critique of published diagnostic criteria. *Eur J Clin Microbiol Infect Dis*. 2013; **32**: 923-928.

273 Zaspel U, Denning DW, Lemke AJ, et al. Diagnosis of ipa in hiv: The role of the chest x-ray and radiologist. *Eur Radiol*. 2004; **14**: 2030-2037.

274 Munoz P, Vena A, Ceron I, et al. Invasive pulmonary aspergillosis in heart transplant recipients: Two radiologic patterns with a different prognosis. *J Heart Lung Transplant*. 2014; **33**: 1034-1040.

275 Blot SI, Taccone FS, Van den Abeele AM, et al. A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. *Am J Respir Crit Care Med*. 2012; **186**: 56-64.

276 Bulpa P, Dive A. Diagnosis of invasive bronchial-pulmonary aspergillosis in patients with chronic obstructive respiratory diseases. *Crit Care*. 2011; **15**: 420; author reply 420.

277 Singh N, Winston DJ, Limaye AP, et al. Performance characteristics of galactomannan and beta-d-glucan in high-risk liver transplant recipients. *Transplantation*. 2015; **99**: 2543-2550.

278 Guinea J, Padilla C, Escribano P, et al. Evaluation of mycassay aspergillus for diagnosis of invasive pulmonary aspergillosis in patients without hematological cancer. *PLoS One*. 2013; **8**: e61545.

279 Zarrinfar H, Makimura K, Satoh K, Khodadadi H, Mirhendi H. Incidence of pulmonary aspergillosis and correlation of conventional diagnostic methods with nested pcr and real-time pcr assay using bal fluid in intensive care unit patients. *J Clin Lab Anal*. 2013; **27**: 181-185.

280 Chong GL, van de Sande WW, Dingemans GJ, et al. Validation of a new aspergillus real-time pcr assay for direct detection of aspergillus and azole resistance of aspergillus fumigatus on bronchoalveolar lavage fluid. *Journal of clinical microbiology*. 2015; **53**: 868-874.

281 Fortun J, Martin-Davila P, Gomez Garcia de la Pedrosa E, et al. Galactomannan in bronchoalveolar lavage fluid for diagnosis of invasive aspergillosis in non-hematological patients. *J Infect*. 2016; **72**: 738-744.

282 Fortun J, Martin-Davila P, Alvarez ME, et al. False-positive results of aspergillus galactomannan antigenemia in liver transplant recipients. *Transplantation*. 2009; **87**: 256-260.

283 Cai X, Ni W, Wei C, Cui J. Diagnostic value of the serum galactomannan and (1, 3)-beta-d-glucan assays for invasive pulmonary aspergillosis in non-neutropenic patients. *Intern Med*. 2014; **53**: 2433-2437.

284 Eigl S, Prattes J, Lackner M, et al. Multicenter evaluation of a lateral-flow device test for diagnosing invasive pulmonary aspergillosis in icu patients. *Crit Care*. 2015; **19**: 178.

285 Prattes J, Flick H, Pruller F, et al. Novel tests for diagnosis of invasive aspergillosis in patients with underlying respiratory diseases. *Am J Respir Crit Care Med*. 2014; **190**: 922-929.

286 Lopez-Medrano F, Fernandez-Ruiz M, Silva JT, et al. Clinical presentation and determinants of mortality of invasive pulmonary aspergillosis in kidney transplant recipients: A multinational cohort study. *Am J Transplant*. 2016.

287 Cherian T, Giakoustidis A, Yokoyama S, et al. Treatment of refractory cerebral aspergillosis in a liver transplant recipient with voriconazole: Case report and review of the literature. *Exp Clin Transplant*. 2012; **10**: 482-486.

288 Patel DA, Gao X, Stephens JM, Forshag MS, Tarallo M. Us hospital database analysis of invasive aspergillosis in the chronic obstructive pulmonary disease non-traditional host. *J Med Econ*. 2011; **14**: 227-237.

289 Singh N, Limaye AP, Forrest G, et al. Combination of voriconazole and caspofungin as primary therapy for invasive aspergillosis in solid organ transplant recipients: A prospective, multicenter, observational study. *Transplantation*. 2006; **81**: 320-326.

290 Luong ML, Hosseini-Moghaddam SM, Singer LG, et al. Risk factors for voriconazole hepatotoxicity at 12 weeks in lung transplant recipients. *Am J Transplant*. 2012; **12**: 1929-1935.

291 Shoham S, Ostrander D, Marr K. Posaconazole liquid suspension in solid organ transplant recipients previously treated with voriconazole. *Transpl Infect Dis*. 2015; **17**: 493-496.

292 Hoenigl M, Duettmann W, Raggam RB, et al. Potential factors for inadequate voriconazole plasma concentrations in intensive care unit patients and patients with hematological malignancies. *Antimicrob Agents Chemother*. 2013; **57**: 3262-3267.

293 Kim SH, Kwon JC, Park C, et al. Therapeutic drug monitoring and safety of intravenous voriconazole formulated with sulfobutylether beta-cyclodextrin in haematological patients with renal impairment. *Mycoses*. 2016.

294 Guinea J, Escribano P, Marcos-Zambrano LJ, et al. Therapeutic drug monitoring of voriconazole helps to decrease the percentage of patients with off-target trough serum levels. *Medical mycology*. 2016; **54**: 353-360.

295 Vanstraelen K, Wauters J, Vercammen I, et al. Impact of hypoalbuminemia on voriconazole pharmacokinetics in critically ill adult patients. *Antimicrob Agents Chemother*. 2014; **58**: 6782-6789.

296 Shalhoub S, Luong ML, Howard SJ, et al. Rate of cyp51a mutation in aspergillus fumigatus among lung transplant recipients with targeted prophylaxis. *J Antimicrob Chemother*. 2015; **70**: 1064-1067.

297 Escribano P, Pelaez T, Munoz P, Bouza E, Guinea J. Is azole resistance in aspergillus fumigatus a problem in spain? *Antimicrob Agents Chemother*. 2013; **57**: 2815-2820.

298 Fuhren J, Voskuil WS, Boel CH, et al. High prevalence of azole resistance in aspergillus fumigatus isolates from high-risk patients. *J Antimicrob Chemother*. 2015; **70**: 2894-2898.

299 Egli A, Fuller J, Humar A, et al. Emergence of aspergillus calidoustus infection in the era of posttransplantation azole prophylaxis. *Transplantation*. 2012; **94**: 403-410.

300 Kuipers S, Bruggemann RJ, de Sevaux RG, et al. Failure of posaconazole therapy in a renal transplant patient with invasive aspergillosis due to aspergillus fumigatus with attenuated susceptibility to posaconazole. *Antimicrob Agents Chemother*. 2011; **55**: 3564-3566.

301 Singh N, Suarez JF, Avery R, et al. Immune reconstitution syndrome-like entity in lung transplant recipients with invasive aspergillosis. *Transpl Immunol*. 2013; **29**: 109-113.

302 Schaenman JM. Is universal antifungal prophylaxis mandatory in lung transplant patients? *Curr Opin Infect Dis*. 2013; **26**: 317-325.

303 Tofte N, Jensen C, Tvede M, Andersen CB, Carlsen J, Iversen M. Use of prophylactic voriconazole for three months after lung transplantation does not reduce infection with aspergillus: A retrospective study of 147 patients. *Scand J Infect Dis*. 2012; **44**: 835-841.

304 Bhaskaran A, Mumtaz K, Husain S. Anti-aspergillus prophylaxis in lung transplantation: A systematic review and meta-analysis. *Curr Infect Dis Rep*. 2013; **15**: 514-525.

305 Koo S, Kubiak DW, Issa NC, et al. A targeted peritransplant antifungal strategy for the prevention of invasive fungal disease after lung transplantation: A sequential cohort analysis. *Transplantation*. 2012; **94**: 281-286.

306 Munoz P, Rojas L, Cervera C, et al. Poor compliance with antifungal drug use guidelines by transplant physicians: A framework for educational guidelines and an international consensus on patient safety. *Clin Transplant*. 2012; **26**: 87-96.

307 He SY, Makhzoumi ZH, Singer JP, Chin-Hong PV, Arron ST. Practice variation in aspergillus prophylaxis and treatment among lung transplant centers: A national survey. *Transpl Infect Dis*. 2015; **17**: 14-20.

308 Saliba F, Pascher A, Cointault O, et al. Randomized trial of micafungin for the prevention of invasive fungal infection in high-risk liver transplant recipients. *Clin Infect Dis*. 2015; **60**: 997-1006.

309 Peghin M, Monforte V, Martin-Gomez MT, et al. 10 years of prophylaxis with nebulized liposomal amphotericin b and the changing epidemiology of aspergillus spp. Infection in lung transplantation. *Transpl Int*. 2016; **29**: 51-62.

310 Patel TS, Eschenauer GA, Stuckey LJ, Carver PL. Antifungal prophylaxis in lung transplant recipients. *Transplantation*. 2016.

311 Fortun J, Muriel A, Martin-Davila P, et al. Caspofungin versus fluconazole as prophylaxis of invasive fungal infection in high-risk liver transplantation recipients: A propensity score analysis. *Liver Transpl*. 2016; **22**: 427-435.

312 Kato K, Nagao M, Nakano S, et al. Itraconazole prophylaxis for invasive aspergillus infection in lung transplantation. *Transpl Infect Dis*. 2014; **16**: 340-343.

313 Balogh J, Gordon Burroughs S, Boktour M, et al. Efficacy and cost-effectiveness of voriconazole prophylaxis for prevention of invasive aspergillosis in high-risk liver transplant recipients. *Liver Transpl*. 2016; **22**: 163-170.

314 Aguado JM, Varo E, Usetti P, et al. Safety of anidulafungin in solid organ transplant recipients. *Liver Transpl*. 2012; **18**: 680-685.

315 Husain S, Zaldonis D, Kusne S, Kwak EJ, Paterson DL, McCurry KR. Variation in antifungal prophylaxis strategies in lung transplantation. *Transpl Infect Dis*. 2006; **8**: 213-218.

316 Taccone A, Occhi M, Garaventa A, Manfredini L, Viscoli C. Ct of invasive pulmonary aspergillosis in children with cancer. *Pediatr Radiol*. 1993; **23**: 177-180.

317 Archibald S, Park J, Geyer JR, Hawkins DS. Computed tomography in the evaluation of febrile neutropenic pediatric oncology patients. *Pediatr Infect Dis J*. 2001; **20**: 5-10.

318 Burgos A, Zaoutis TE, Dvorak CC, et al. Pediatric invasive aspergillosis: A multicenter retrospective analysis of 139 contemporary cases. *Pediatrics*. 2008; **121**: e1286-1294.

319 Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: A meta-analysis. *Clin Infect Dis*. 2006; **42**: 1417-1727.

320 Hovi L, Saxen H, Saarinen-Pihkala UM, Vettenranta K, Meri T, Richardson M. Prevention and monitoring of invasive fungal infections in pediatric patients with cancer and hematologic disorders. *Pediatric blood & cancer*. 2007; **48**: 28-34.

321 Steinbach WJ, Addison RM, McLaughlin L, et al. Prospective aspergillus galactomannan antigen testing in pediatric hematopoietic stem cell transplant recipients. *Pediatr Infect Dis J*. 2007; **26**: 558-564.

322 Hayden R, Pounds S, Knapp K, et al. Galactomannan antigenemia in pediatric oncology patients with invasive aspergillosis. *Pediatr Infect Dis J*. 2008; **27**: 815-819.

323 Castagnola E, Furfaro E, Caviglia I, et al. Performance of the galactomannan antigen detection test in the diagnosis of invasive aspergillosis in children with cancer or undergoing haemopoietic stem cell transplantation. *Clin Microbiol Infect*. 2010; **16**: 1197-1203.

324 Fisher BT, Zaoutis TE, Park JR, et al. Galactomannan antigen testing for diagnosis of invasive aspergillosis in pediatric hematology patients. *J Pediatric Infect Dis Soc*. 2012; **1**: 103-111.

325 Choi SH, Kang ES, Eo H, et al. Aspergillus galactomannan antigen assay and invasive aspergillosis in pediatric cancer patients and hematopoietic stem cell transplant recipients. *Pediatric blood & cancer*. 2013; **60**: 316-322.

326 Jha AK, Bansal D, Chakrabarti A, Shivaprakash MR, Trehan A, Marwaha RK. Serum galactomannan assay for the diagnosis of invasive aspergillosis in children with haematological malignancies. *Mycoses*. 2013; **56**: 442-448.

327 Dinand V, Anjan M, Oberoi JK, et al. Threshold of galactomannan antigenemia positivity for early diagnosis of invasive aspergillosis in neutropenic children. *J Microbiol Immunol Infect*. 2016; **49**: 66-73.

328 Smith PB, Benjamin DK, Jr., Alexander BD, Johnson MD, Finkelman MA, Steinbach WJ. Quantification of 1,3-beta-d-glucan levels in children: Preliminary data for diagnostic use of the beta-glucan assay in a pediatric setting. *Clin Vaccine Immunol*. 2007; **14**: 924-925.

329 Zhao L, Tang JY, Wang Y, et al. [value of plasma beta-glucan in early diagnosis of invasive fungal infection in children]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2009; **11**: 905-908.

330 Mularoni A, Furfaro E, Faraci M, et al. High levels of beta-d-glucan in immunocompromised children with proven invasive fungal disease. *Clin Vaccine Immunol*. 2010; **17**: 882-883.

331 Badiee P, Alborzi A, Karimi M, et al. Diagnostic potential of nested pcr, galactomannan eia, and beta-d-glucan for invasive aspergillosis in pediatric patients. *J Infect Dev Ctries*. 2012; **6**: 352-357.

332 Koltze A, Rath P, Schoning S, et al. Beta-d-glucan screening for detection of invasive fungal disease in children undergoing allogeneic hematopoietic stem cell transplantation. *Journal of clinical microbiology*. 2015; **53**: 2605-2610.

333 Denning DW, Ribaud P, Milpied N, et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clin Infect Dis*. 2002; **34**: 563-571.

334 Walsh TJ, Lutsar I, Driscoll T, et al. Voriconazole in the treatment of aspergillosis, scedosporiosis and other invasive fungal infections in children. *Pediatr Infect Dis J*. 2002; **21**: 240-248.

335 Maertens J, Raad I, Petrikkos G, et al. Efficacy and safety of caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy. *Clin Infect Dis*. 2004; **39**: 1563-1571.

336 Raad, II, Hanna HA, Boktour M, et al. Novel antifungal agents as salvage therapy for invasive aspergillosis in patients with hematologic malignancies: Posaconazole compared with high-dose lipid formulations of amphotericin b alone or in combination with caspofungin. *Leukemia*. 2008; **22**: 496-503.

337 Cornely OA, Maertens J, Bresnik M, Ullmann AJ, Ebrahimi R, Herbrecht R. Treatment outcome of invasive mould disease after sequential exposure to azoles and liposomal amphotericin b. *J Antimicrob Chemother*. 2010; **65**: 114-117.

338 Winston DJ, Bartoni K, Territo MC, Schiller GJ. Efficacy, safety, and breakthrough infections associated with standard long-term posaconazole antifungal prophylaxis in allogeneic stem cell transplantation recipients. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2011; **17**: 507-515.

339 De la Serna J, Jarque I, Lopez-Jimenez J, et al. Treatment of invasive fungal infections in high risk hematological patients. The outcome with liposomal amphotericin b is not negatively affected by prior administration of mold-active azoles. *Rev Esp Quimioter*. 2013; **26**: 64-69.

340 Auberger J, Lass-Florl C, Aigner M, Clausen J, Gastl G, Nachbaur D. Invasive fungal breakthrough infections, fungal colonization and emergence of resistant strains in high-risk patients receiving antifungal prophylaxis with posaconazole: Real-life data from a single-centre institutional retrospective observational study. *J Antimicrob Chemother*. 2012; **67**: 2268-2273.

341 Lehrnbecher T, Kalkum M, Champer J, Tramsen L, Schmidt S, Klingebiel T. Immunotherapy in invasive fungal infection--focus on invasive aspergillosis. *Current pharmaceutical design*. 2013; **19**: 3689-3712.

342 Prentice HG, Hann IM, Herbrecht R, et al. A randomized comparison of liposomal versus conventional amphotericin b for the treatment of pyrexia of unknown origin in neutropenic patients. *Br J Haematol*. 1997; **98**: 711-718.

343 Maertens JA, Madero L, Reilly AF, et al. A randomized, double-blind, multicenter study of caspofungin versus liposomal amphotericin b for empiric antifungal therapy in pediatric patients with persistent fever and neutropenia. *Pediatr Infect Dis J*. 2010; **29**: 415-420.

344 Caselli D, Paolicchi O. Empiric antibiotic therapy in a child with cancer and suspected septicemia. *Pediatr Rep*. 2012; **4**: e2.

345 Tan BH, Low JG, Chlebicka NL, et al. Galactomannan-guided preemptive vs. Empirical antifungals in the persistently febrile neutropenic patient: A prospective randomized study. *Int J Infect Dis*. 2011; **15**: e350-356.

346 Castagnola E, Bagnasco F, Amoroso L, et al. Role of management strategies in reducing mortality from invasive fungal disease in children with cancer or receiving hemopoietic stem cell transplant: A single center 30-year experience. *Pediatr Infect Dis J*. 2014; **33**: 233-237.

347 Borjesson J, Latifi A, Friman O, Beckman MO, Oldner A, Labruto F. Accuracy of low-dose chest ct in intensive care patients. *Emerg Radiol*. 2011; **18**: 17-21.

348 Yamamura J, Tornquist K, Buchert R, et al. Simulated low-dose computed tomography in oncological patients: A feasibility study. *Journal of computer assisted tomography*. 2010; **34**: 302-308.

349 Segal BH, Herbrecht R, Stevens DA, et al. Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses study group and european organization for research and treatment of cancer consensus criteria. *Clin Infect Dis*. 2008; **47**: 674-683.

350 Vehreschild JJ, Heussel CP, Groll AH, et al. Serial assessment of pulmonary lesion volume by computed tomography allows survival prediction in invasive pulmonary aspergillosis. *Eur Radiol*. 2017.

351 Nouer SA, Nucci M, Kumar NS, Grazziutti M, Barlogie B, Anaissie E. Earlier response assessment in invasive aspergillosis based on the kinetics of serum aspergillus galactomannan: Proposal for a new definition. *Clin Infect Dis*. 2011; **53**: 671-676.

352 Nucci M, Perfect JR. When primary antifungal therapy fails. *Clin Infect Dis*. 2008; **46**: 1426-1433.

353 Bennett JE. Salvage therapy for aspergillosis. *Clin Infect Dis*. 2005; **41 Suppl 6**: S387-388.

354 Bergeron A, Porcher R, Menotti J, et al. Prospective evaluation of clinical and biological markers to predict the outcome of invasive pulmonary aspergillosis in hematological patients. *Journal of clinical microbiology*. 2012; **50**: 823-830.

355 Maertens J, Buve K, Theunissen K, et al. Galactomannan serves as a surrogate endpoint for outcome of pulmonary invasive aspergillosis in neutropenic hematology patients. *Cancer*. 2009; **115**: 355-362.

356 Boutboul F, Alberti C, Leblanc T, et al. Invasive aspergillosis in allogeneic stem cell transplant recipients: Increasing antigenemia is associated with progressive disease. *Clin Infect Dis*. 2002; **34**: 939-943.

357 Miceli MH, Maertens J, Buve K, et al. Immune reconstitution inflammatory syndrome in cancer patients with pulmonary aspergillosis recovering from neutropenia: Proof of principle, description, and clinical and research implications. *Cancer*. 2007; **110**: 112-120.

358 Almyroudis NG, Kontoyiannis DP, Sepkowitz KA, DePauw BE, Walsh TJ, Segal BH. Issues related to the design and interpretation of clinical trials of salvage therapy for invasive mold infection. *Clin Infect Dis*. 2006; **43**: 1449-1455.

359 Bergeron A, Porcher R, Menotti J, et al. Prospective evaluation of clinical and biological markers to predict the outcome of invasive pulmonary aspergillosis in hematological patients. *Journal of clinical microbiology*. 2012; **50**: 823-830.

360 Smith NL, Denning DW. Underlying conditions in chronic pulmonary aspergillosis including simple aspergilloma. *Eur Respir J*. 2011; **37**: 865-872.

361 Salzer HJ, Cornely OA. Awareness of predictors of mortality may help improve outcome in chronic pulmonary aspergillosis. *Eur Respir J*. 2017; **49**.

362 Muldoon EG, Sharman A, Page I, Bishop P, Denning DW. Aspergillus nodules; another presentation of chronic pulmonary aspergillosis. *BMC Pulm Med*. 2016; **16**: 123.

363 Salzer HJ, Heyckendorf J, Kalsdorf B, Rolling T, Lange C. Characterization of patients with chronic pulmonary aspergillosis according to the new escmid/ers/ecmm and idsa guidelines. *Mycoses*. 2017; **60**: 136-142.

364 Dumollard C, Bailly S, Perriot S, et al. Prospective evaluation of a new aspergillus igg enzyme immunoassay kit for diagnosis of chronic and allergic pulmonary aspergillosis. *Journal of clinical microbiology*. 2016; **54**: 1236-1242.

365 Farid S, Mohamed S, Devbhandari M, et al. Results of surgery for chronic pulmonary aspergillosis, optimal antifungal therapy and proposed high risk factors for recurrence--a national centre's experience. *J Cardiothorac Surg*. 2013; **8**: 180.

366 Cadranel J, Philippe B, Hennequin C, et al. Voriconazole for chronic pulmonary aspergillosis: A prospective multicenter trial. *Eur J Clin Microbiol Infect Dis*. 2012; **31**: 3231-3239.

367 Al-Shair K, Atherton GT, Harris C, Ratcliffe L, Newton PJ, Denning DW. Long-term antifungal treatment improves health status in patients with chronic pulmonary aspergillosis: A longitudinal analysis. *Clin Infect Dis*. 2013; **57**: 828-835.

368 Pasmans HL, Loosveld OJ, Schouten HC, Thunnissen F, van Engelshoven JM. Invasive aspergillosis in immunocompromised patients: Findings on plain film and (hr)ct. *Eur J Radiol*. 1992; **14**: 37-40.

369 Heussel CP, Kauczor HU, Heussel G, Mildenberger P, Dueber C. Aneurysms complicating inflammatory diseases in immunocompromised hosts: Value of contrast-enhanced ct. *European radiology*. 1997; **7**: 316-319.

370 Didier M, Guedin P, Staub F, et al. Pulmonary arterial mycotic pseudoaneurysms in a patient with invasive pulmonary aspergillosis. Successful occlusion by coils. *American journal of respiratory and critical care medicine*. 2014; **190**: 112-113.

371 Denning DW, Kibbler CC, Barnes RA, British Society for Medical M. British society for medical mycology proposed standards of care for patients with invasive fungal infections. *Lancet Infect Dis*. 2003; **3**: 230-240.

372 Vyzantiadis TA, Johnson EM, Kibbler CC. From the patient to the clinical mycology laboratory: How can we optimise microscopy and culture methods for mould identification? *J Clin Pathol*. 2012; **65**: 475-483.

373 Lass-Flörl C, Resch G, Nachbaur D, et al. The value of computed tomography-guided percutaneous lung biopsy for diagnosis of invasive fungal infection in immunocompromised patients. *Clin Infect Dis*. 2007; **45**: e101-e104.

374 Choi JK, Mauger J, McGowan KL. Immunohistochemical detection of aspergillus species in pediatric tissue samples. *Am J Clin Pathol*. 2004; **121**: 18-25.

375 Kaufman L, Standard PG, Jalbert M, Kraft DE. Immunohistologic identification of aspergillus spp. And other hyaline fungi by using polyclonal fluorescent antibodies. *Journal of clinical microbiology*. 1997; **35**: 2206-2209.

376 Verweij PE, Smedts F, Poot T, Bult P, Hoogkamp-Korstanje JA, Meis JF. Immunoperoxidase staining for identification of aspergillus species in routinely processed tissue sections. *J Clin Pathol*. 1996; **49**: 798-801.

377 Hayden RT, Isotalo PA, Parrett T, et al. In situ hybridization for the differentiation of aspergillus, fusarium , and pseudallescheria species in tissue section. *Diagn Mol Pathol*. 2003; **12**: 21-26.

1835 378 Sundaram C, Umabala P, Laxmi V, et al. Pathology of fungal infections of the central nervous
1836 system: 17 years' experience from southern india. *Histopathology*. 2006; **49**: 396-405.

1837 379 Chander J, Chakrabarti A, Sharma A, Saini JS, Panigarhi D. Evaluation of calcofluor staining in
1838 the diagnosis of fungal corneal ulcer. *Mycoses*. 1993; **36**: 243-245.

1839 380 Baxter CG, Jones AM, Webb K, Denning DW. Homogenisation of cystic fibrosis sputum by
1840 sonication--an essential step for aspergillus pcr. *J Microbiol Methods*. 2011; **85**: 75-81.

1841 381 Cuenca-Estrella M, Bassetti M, Lass-Flîrl C, R†cil Z, Richardson M, Rogers TR. Detection and
1842 investigation of invasive mould disease. *J Antimicrob Chemother*. 2011; **66**: i15-i24.

1843 382 Richardson M, Ellis M. Clinical and laboratory diagnosis. *Hosp Med*. 2000; **61**: 610-614.

1844 383 Alanio A, Beretti JL, Dauphin B, et al. Matrix-assisted laser desorption ionization time-of-flight
1845 mass spectrometry for fast and accurate identification of clinically relevant aspergillus
1846 species. *Clin Microbiol Infect*. 2011; **17**: 750-755.

1847 384 Bille E, Dauphin B, Leto J, et al. Maldi-tof ms andromas strategy for the routine identification
1848 of bacteria, mycobacteria, yeasts, aspergillus spp. And positive blood cultures. *Clin Microbiol*
1849 *Infect*. 2012; **18**: 1117-1125.

1850 385 De Carolis E, Vella A, Florio AR, et al. Use of matrix-assisted laser desorption ionization-time
1851 of flight mass spectrometry for caspofungin susceptibility testing of candida and aspergillus
1852 species. *Journal of clinical microbiology*. 2012; **50**: 2479-2483.

1853 386 Lau AF, Drake SK, Calhoun LB, Henderson CM, Zelazny AM. Development of a clinically
1854 comprehensive database and a simple procedure for identification of molds from solid media
1855 by matrix-assisted laser desorption ionization-time of flight mass spectrometry. *Journal of*
1856 *clinical microbiology*. 2013; **51**: 828-834.

1857 387 Balajee SA, Borman AM, Brandt ME, et al. Sequence-based identification of aspergillus ,
1858 fusarium , and mucorales species in the clinical mycology laboratory: Where are we and
1859 where should we go from here? *Journal of clinical microbiology*. 2009; **47**: 877-884.

1860 388 Samson RA, Hong S, Peterson SW, Frisvad JC, Varga J. Polyphasic taxonomy of aspergillus
1861 section fumigati and its teleomorph neosartorya. *Stud Mycol*. 2007; **59**: 147-203.

389 Caramalho R, GusmΔo L, Lackner M, Amorim A, Araujo R. Snapafu: A novel single nucleotide polymorphism multiplex assay for aspergillus fumigatus direct detection, identification and genotyping in clinical specimens. *PLoS One*. 2013; **8**: e75968.

390 Hurst SF, Kidd SE, Morrissey CO, et al. Interlaboratory reproducibility of a single-locus sequence-based method for strain typing of aspergillus fumigatus *Journal of clinical microbiology*. 2009; **47**: 1562-1564.

391 Guinea J, García de Viedma D, Peláez T, et al. Molecular epidemiology of aspergillus fumigatus : An in-depth genotypic analysis of isolates involved in an outbreak of invasive aspergillosis. *Journal of clinical microbiology*. 2011; **49**: 3498-3503.

392 Rougeron A, Giraud S, Razafimandimby B, Meis JF, Bouchara JP, Klaassen CH. Different colonization patterns of aspergillus terreus in patients with cystic fibrosis. *Clin Microbiol Infect*. 2014; **20**: 327-333.

393 Maertens J, Van Eldere J, Verhaegen J, Verbeken E, Verschakelen J, Boogaerts M. Use of circulating galactomannan screening for early diagnosis of invasive aspergillosis in allogeneic stem cell transplant recipients. *The Journal of infectious diseases*. 2002; **186**: 1297-1306.

394 Leeflang MM, Debets-Ossenkopp YJ, Visser CE, et al. Galactomannan detection for invasive aspergillosis in immunocompromised patients. *The Cochraen Collaboration*. 2008; **4**: CD007394.

395 Furfaro E, Mikulska M, Miletich F, Viscoli C. Galactomannan: Testing the same sample twice? *Transpl Infect Dis*. 2012; **14**: E38-E39.

396 Morrissey CO, Chen SC, Sorrell TC, et al. Galactomannan and pcr versus culture and histology for directing use of antifungal treatment for invasive aspergillosis in high-risk haematology patients: A randomised controlled trial. *Lancet Infect Dis*. 2013; **13**: 519-528.

397 Maertens J, Verhaegen J, Lagrou K, Van Eldere J, Boogaerts M. Screening for circulating galactomannan as a noninvasive diagnostic tool for invasive aspergillosis in prolonged neutropenic patients and stem cell transplantation recipients: A prospective validation. *Blood*. 2001; **97**: 1604-1610.

398 Hoenigl M, Seeber K, Koidl C, et al. Sensitivity of galactomannan enzyme immunoassay for diagnosing breakthrough invasive aspergillosis under antifungal prophylaxis and empirical therapy. *Mycoses*. 2013; **56**: 471-476.

399 Marr KA, Laverdiere M, Gugel A, Leisenring W. Antifungal therapy decreases sensitivity of the aspergillus galactomannan enzyme immunoassay. *Clin Infect Dis*. 2005; **40**: 1762-1769.

400 Cordonnier C, Botterel F, Ben Amor R, et al. Correlation between galactomannan antigen levels in serum and neutrophil counts in haematological patients with invasive aspergillosis. *Clin Microbiol Infect*. 2009; **15**: 81-86.

401 Maertens J, Theunissen K, Verhoef G, et al. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: A prospective feasibility study. *Clin Infect Dis*. 2005; **41**: 1242-1250.

402 Guinea J, Jensen J, Peláez T, et al. Value of a single galactomannan determination (platelia) for the diagnosis of invasive aspergillosis in non-hematological patients with clinical isolation of aspergillus spp. *Medical mycology*. 2008; **46**: 575-579.

403 Husain S, Kwak EJ, Obman A, et al. Prospective assessment of platelia aspergillus galactomannan antigen for the diagnosis of invasive aspergillosis in lung transplant recipients. *Am J Transplant*. 2004; **4**: 796-802.

404 Tabarsi P, Soraghi A, Marjani M, et al. Comparison of serum and bronchoalveolar lavage galactomannan in diagnosing invasive aspergillosis in solid-organ transplant recipients. *Exp Clin Transplant*. 2012; **10**: 278-281.

405 Guigue N, Menotti J, Ribaud P. False positive galactomannan test after ice-pop ingestion. *N Engl J Med*. 2013; **369**: 97-98.

406 Petraitiene R, Petraitis V, Witt JR, 3rd, et al. Galactomannan antigenemia after infusion of gluconate-containing plasma-lyte. *Journal of clinical microbiology*. 2011; **49**: 4330-4332.

407 Martin-Rabadan P, Gijon P, Alonso Fernandez R, Ballesteros M, Anguita J, Bouza E. False-positive aspergillus antigenemia due to blood product conditioning fluids. *Clin Infect Dis*. 2012; **55**: e22-27.

408 Mikulska M, Furfaro E, Del Bono V, et al. Piperacillin/tazobactam (tazocintm) seems to be no longer responsible for false-positive results of the galactomannan assay. *J Antimicrob Chemother*. 2012; **67**: 1746-1748.

409 Vergidis P, Walker RC, Kaul DR, et al. False-positive aspergillus galactomannan assay in solid organ transplant recipients with histoplasmosis. *Transpl Infect Dis*. 2012; **14**: 213-217.

410 Huang YT, Hung CC, Liao CH, Sun HY, Chang SC, Chen YC. Detection of circulating galactomannan in serum samples for diagnosis of penicillium marneffei infection and cryptococcosis among patients infected with human immunodeficiency virus. *Journal of clinical microbiology*. 2007; **45**: 2858-2862.

411 Nucci M, Carlesse F, Cappellano P, et al. Earlier diagnosis of invasive fusariosis with aspergillus serum galactomannan testing. *PLoS One*. 2014; **9**: e87784.

412 King ST, Stover KR. Considering confounders of the galactomannan index: The role of piperacillin-tazobactam. *Clin Infect Dis*. 2014; **58**: 751-752.

413 Chai LY, Kullberg BJ, Johnson EM, et al. Early serum galactomannan trend as a predictor of outcome of invasive aspergillosis. *Journal of clinical microbiology*. 2012; **50**: 2330-2336.

414 Luong ML, Clancy CJ, Vadnerkar A, et al. Comparison of an aspergillus real-time polymerase chain reaction assay with galactomannan testing of bronchoalvelolar lavage fluid for the diagnosis of invasive pulmonary aspergillosis in lung transplant recipients. *Clin Infect Dis*. 2011; **52**: 1218-1226.

415 Reinwald M, Spiess B, Heinz WJ, et al. Diagnosing pulmonary aspergillosis in patients with hematological malignancies: A multicenter prospective evaluation of an aspergillus pcr assay and a galactomannan elisa in bronchoalveolar lavage sample. *Eur J Haematol*. 2012; **89**: 120-127.

416 Heng SC, Morrissey O, Chen SC, et al. Utility of bronchoalveolar lavage fluid galactomannan alone or in combination with pcr for the diagnosis of invasive aspergillosis in adult hematology patients: A systematic review and meta-analysis. *Crit Rev Microbiol*. 2015; **41**: 124-134.

417 Zou M, Tang L, Zhao S, et al. Systematic review and meta-analysis of detecting galactomannan in bronchoalveolar lavage fluid for diagnosing invasive aspergillosis. *PLoS One*. 2012; **7**: e43347.

418 Fisher CE, Stevens AM, Leisenring W, Pergam SA, Boeckh M, Hohl TM. The serum galactomannan index predicts mortality in hematopoietic stem cell transplant recipients with invasive aspergillosis. *Clin Infect Dis*. 2013; **57**: 1001-1004.

419 Verweij PE, Brinkman K, Kremer HP, Kullberg BJ, Meis JF. Aspergillus meningitis: Diagnosis by non-culture-based microbiological methods and management. *Journal of clinical microbiology*. 1999; **37**: 1186-1189.

420 Viscoli C, Machetti M, Gazzola P, et al. Aspergillus galactomannan antigen in the cerebrospinal fluid of bone marrow transplant recipients with probable cerebral aspergillosis. *Journal of clinical microbiology*. 2002; **40**: 1496-1499.

421 Klont RR, Mennink-Kersten MA, Verweij PE. Utility of aspergillus antigen detection in specimens other than serum specimens. *Clin Infect Dis*. 2004; **39**: 1467-1474.

422 Lu Y, Chen YQ, Guo YL, Qin SM, Wu C, Wang K. Diagnosis of invasive fungal disease using serum (1-3)-ß-d-glucan: A bivariate meta-analysis. *Intern Med*. 2011; **50**: 2783-2791.

423 Lamoth F, Cruciani M, Mengoli C, et al. ß-glucan antigenemia assay for the diagnosis of invasive fungal infections in patients with hematological malignancies: A systematic review and meta-analysis of cohort studies from the third european conference on infections in leukemia (ecil-3). *Clin Infect Dis*. 2012; **54**: 633-643.

424 Senn L, Robinson JO, Schmidt S, et al. 1,3-beta-d-glucan antigenemia for early diagnosis of invasive fungal infections in neutropenic patients with acute leukemia. *Clin Infect Dis*. 2008; **46**: 878-885.

425 Ellis M, Al-Ramadi B, Finkelman M, et al. Assessment of the clinical utility of serial beta-d-glucan concentrations in patients with persistent neutropenic fever. *J Med Microbiol*. 2008; **57**: 287-295.

426 Kawazu M, Kanda Y, Nannya Y, et al. Prospective comparison of the diagnostic potential of real-time pcr, double-sandwich enzyme-linked immunosorbent assay for galactomannan,

and a (1-->3)-beta-d-glucan test in weekly screening for invasive aspergillosis in patients with hematological disorders. *Journal of clinical microbiology*. 2004; **42**: 2733-2741.

427 Odabasi Z, Mattiuzzi G, Estey E, et al. Beta-d-glucan as a diagnostic adjunct for invasive fungal infections: Validation, cutoff development, and performance in patients with acute myelogenous leukemia and myelodysplastic syndrome. *Clin Infect Dis*. 2004; **39**: 199-205.

428 Ostrosky-Zeichner L, Alexander BD, Kett DH, et al. Multicenter clinical evaluation of the (1-->3) beta-d-glucan assay as an aid to diagnosis of fungal infections in humans. *Clin Infect Dis*. 2005; **41**: 654-659.

429 De Vlieger G, Lagrou K, Maertens J, Verbeken E, Meersseman W, Van Wijngaerden E. Beta-d-glucan detection as a diagnostic test for invasive aspergillosis in immunocompromised critically ill patients with symptoms of respiratory infection: An autopsy-based study. *Journal of clinical microbiology*. 2011; **49**: 3783-3787.

430 Del Bono V, Delfino E, Furfaro E, et al. Clinical performance of the (1,3)-beta-d-glucan assay in early diagnosis of nosocomial candida bloodstream infections. *Clin Vaccine Immunol*. 2011; **18**: 2113-2117.

431 Acosta J, Catalan M, del Palacio-Pérez-Medel A, et al. Prospective study in critically ill non-neutropenic patients: Diagnostic potential of (1,3)-ß-d-glucan assay and circulating galactomannan for the diagnosis of invasive fungal disease. *Eur J Clin Microbiol Infect Dis*. 2012; **31**: 721-731.

432 Hoenigl M, Koidl C, Duettmann W, et al. Bronchoalveolar lavage lateral-flow device test for invasive pulmonary aspergillosis diagnosis in haematological malignancy and solid organ transplant patients. *J Infect*. 2012; **65**: 588-591.

433 Held J, Schmidt T, Thornton CR, Kotter E, Bertz H. Comparison of a novel aspergillus lateral-flow device and the platelia© galactomannan assay for the diagnosis of invasive aspergillosis following haematopoietic stem cell transplantation. *Infection*. 2013; **41**: 1163-1169.

434 Hoenigl M, Prattes J, Spiess B, et al. Performance of galactomannan, beta-d-glucan, aspergillus lateral-flow device, conventional culture, and pcr tests with bronchoalveolar lavage fluid for diagnosis of invasive pulmonary aspergillosis. *Journal of clinical microbiology*. 2014; **52**: 2039-2045.

435 Einsele H, Quabeck K, Müller KD, et al. Prediction of invasive pulmonary aspergillosis from colonisation of lower respiratory tract before marrow transplantation. *Lancet*. 1998; **352**: 1443.

436 Tang CM, Holden DW, Aufauvre-Brown A, Cohen J. The detection of aspergillus spp. By the polymerase chain reaction and its evaluation in bronchoalveolar lavage fluid. *Am Rev Respir Dis*. 1993; **148**: 1313-1317.

437 Verweij PE, Latge JP, Rijs AJ, et al. Comparison of antigen detection and pcr assay using bronchoalveolar lavage fluid for diagnosing invasive pulmonary aspergillosis in patients receiving treatment for hematological malignancies. *Journal of clinical microbiology*. 1995; **33**: 3150-3153.

438 Bretagne S, Costa JM, Marmorat-Khuong A, et al. Detection of aspergillus species DNA in bronchoalveolar lavage samples by competitive pcr. *Journal of clinical microbiology*. 1995; **33**: 1164-1168.

439 Jones ME, Fox AJ, Barnes AJ, et al. Pcr-elisa for the early diagnosis of invasive pulmonary aspergillus infection in neutropenic patients. *J Clin Pathol*. 1998; **51**: 652-656.

440 Skladny H, Buchheidt D, Baust C, et al. Specific detection of aspergillus species in blood and bronchoalveolar lavage samples of immunocompromised patients by two-step pcr. *Journal of clinical microbiology*. 1999; **37**: 3865-3871.

441 Buchheidt D, Baust C, Skladny H, et al. Detection of aspergillus species in blood and bronchoalveolar lavage samples from immunocompromised patients by means of 2-step polymerase chain reaction: Clinical results. *Clin Infect Dis*. 2001; **33**: 428-435.

442 Hayette MP, Vaira D, Susin F, et al. Detection of aspergillus species DNA by pcr in bronchoalveolar lavage fluid. *Journal of clinical microbiology*. 2001; **39**: 2338-2340.

443 Melchers WJ, Verweij PE, van den Hurk P, et al. General primer-mediated pcr for detection of aspergillus species. *Journal of clinical microbiology*. 1994; **32**: 1710-1717.

444 Buchheidt D, Baust C, Skladny H, Baldus M, Bräuninger S, Hehlmann R. Clinical evaluation of a polymerase chain reaction assay to detect aspergillus species in bronchoalveolar lavage samples of neutropenic patients. *Br J Haematol*. 2002; **116**: 803-811.

445 Raad I, Hanna H, Huaringa A, Sumoza D, Hachem R, Albitar M. Diagnosis of invasive pulmonary aspergillosis using polymerase chain reaction-based detection of aspergillus in bal. *Chest*. 2002; **121**: 1171-1176.

446 Spiess B, Buchheidt D, Baust C, et al. Development of a lightcycler pcr assay for detection and quantification of aspergillus fumigatus DNA in clinical samples from neutropenic patients. *Journal of clinical microbiology*. 2003; **41**: 1811-1818.

447 Meltiadis J, Melchers WJ, Meis JF, van den Hurk P, Jannes G, Verweij PE. Evaluation of a polymerase chain reaction reverse hybridization line probe assay for the detection and identification of medically important fungi in bronchoalveolar lavage fluids. *Medical mycology*. 2003; **41**: 65-74.

448 Sanguinetti M, Posteraro B, Pagano L, et al. Comparison of real-time pcr, conventional pcr, and galactomannan antigen detection by enzyme-linked immunosorbent assay using bronchoalveolar lavage fluid samples from hematology patients for diagnosis of invasive pulmonary aspergillosis. *Journal of clinical microbiology*. 2003; **41**: 3922-3925.

449 Rantakokko-Jalava K, Laaksonen S, Issakainen J, et al. Semiquantitative detection by real-time pcr of aspergillus fumigatus in bronchoalveolar lavage fluids and tissue biopsy specimens from patients with invasive aspergillosis. *Journal of clinical microbiology*. 2003; **41**: 4304-4311.

450 Lass-Flörl C, Gunsilius E, Gastl G, et al. Diagnosing invasive aspergillosis during antifungal therapy by pcr analysis of blood samples. *Journal of clinical microbiology*. 2004; **42**: 4154-4157.

451 Musher B, Fredricks D, Leisenring W, Balajee SA, Smith C, Marr KA. Aspergillus galactomannan enzyme immunoassay and quantitative pcr for diagnosis of invasive aspergillosis with bronchoalveolar lavage fluid. *Journal of clinical microbiology*. 2004; **42**: 5517-5522.

452 Khot PD, Ko DL, Hackman RC, Fredricks DN. Development and optimization of quantitative pcr for the diagnosis of invasive aspergillosis with bronchoalveolar lavage fluid. *BMC Infect Dis*. 2008; **8**: 73.

453 Fréalle E, Decrucq K, Botterel F, et al. Diagnosis of invasive aspergillosis using bronchoalveolar lavage in haematology patients: Influence of bronchoalveolar lavage human DNA content on real-time pcr performance. *Eur J Clin Microbiol Infect Dis*. 2009; **28**: 223-232.

454 Torelli R, Sanguinetti M, Moody A, et al. Diagnosis of invasive aspergillosis by a commercial real-time pcr assay for aspergillus DNA in bronchoalveolar lavage fluid samples from high-risk patients compared to a galactomannan enzyme immunoassay. *Journal of clinical microbiology*. 2011; **49**: 4273-4278.

455 Buess M, Cathomas G, Halter J, et al. Aspergillus- pcr in bronchoalveolar lavage for detection of invasive pulmonary aspergillosis in immunocompromised patients. *BMC Infect Dis*. 2012; **12**: 237.

456 Reinwald M, Hummel M, Kovalevskaya E, et al. Therapy with antifungals decreases the diagnostic performance of pcr for diagnosing invasive aspergillosis in bronchoalveolar lavage samples of patients with haematological malignancies. *J Antimicrob Chemother*. 2012; **67**: 2260-2267.

457 Orsi CF, Gennari W, Venturelli C, et al. Performance of 2 commercial real-time polymerase chain reaction assays for the detection of aspergillus and pneumocystis DNA in bronchoalveolar lavage fluid samples from critical care patients. *Diagn Microbiol Infect Dis*. 2012; **73**: 138-143.

458 Guinea J, Padilla C, Escribano P, et al. Evaluation of mycassayt aspergillus for diagnosis of invasive pulmonary aspergillosis in patients without hematological cancer. *PLoS One*. 2013; **8**: e61545.

459 Steinmann J, Buer J, Rath PM, Paul A, Saner F. Invasive aspergillosis in two liver transplant recipients: Diagnosis by septifast. *Transpl Infect Dis*. 2009; **11**: 175-178.

460 Komatsu H, Fujisawa T, Inui A, et al. Molecular diagnosis of cerebral aspergillosis by sequence analysis with panfungal polymerase chain reaction. *J Pediatr Hematol Oncol*. 2004; **26**: 40-44.

461 Kami M, Shirouzu I, Mitani K, et al. Early diagnosis of central nervous system aspergillosis with combination use of cerebral diffusion-weighted echo-planar magnetic resonance image and polymerase chain reaction of cerebrospinal fluid. *Intern Med*. 1999; **38**: 45-48.

462 Hummel M, Spiess B, Kentouche K, et al. Detection of aspergillus DNA in cerebrospinal fluid from patients with cerebral aspergillosis by a nested pcr assay. *Journal of clinical microbiology*. 2006; **44**: 3989-3993.

463 Badiee P, Alborzi A. Assessment of a real-time pcr method to detect human non-cryptococcal fungal meningitis. *Arch Iran Med*. 2011; **14**: 381-384.

464 Mengoli C, Cruciani M, Barnes RA, Loeffler J, Donnely JP. Use of pcr for diagnosis of invasive aspergillosis: Systematic review and meta-analysis. *Lancet Infect Dis*. 2009; **9**: 89-96.

465 White PL, Mengoli C, Bretagne S, et al. Evaluation of aspergillus pcr protocols for testing serum specimens. *Journal of clinical microbiology*. 2011; **49**: 3842-3848.

466 White PL, Linton CJ, Perry MD, Johnson EM, Barnes RA. The evolution and evaluation of a whole blood polymerase chain reaction assay for the detection of invasive aspergillosis in hematology patients in a routine clinical setting. *Clin Infect Dis*. 2006; **42**: 479-486.

467 Lass-Flörl C, Mutschlechner W, Aigner M, et al. Utility of pcr in diagnosis of invasive fungal infections: Real-life data from a multicenter study. *Journal of clinical microbiology*. 2013; **51**: 863-868.

468 Paterson PJ, Seaton S, McLaughlin J, Kibbler CC. Development of molecular methods for the identification of aspergillus and emerging moulds in paraffin wax embedded tissue sections. *Mol Pathol*. 2003; **56**: 368-370.

469 Paterson PJ, Seaton S, McHugh TD, et al. Validation and clinical application of molecular methods for the identification of molds in tissue. *Clin Infect Dis*. 2006; **42**: 51-56.

470 von Eiff M, Roos N, Schulten R, Hesse M, ZÅhlsdorf M, van de Loo J. Pulmonary aspergillosis: Early diagnosis improves survival. *Respiration*. 1995; **62**: 341-347.

471 Kappe R, Rimek D. Antibody detection in patients with invasive aspergillosis. *Mycoses*. 2004; **47**: 59.

472 Cornillet A, Camus C, Nimubona S, et al. Comparison of epidemiological, clinical, and biological features of invasive aspergillosis in neutropenic and nonneutropenic patients: A 6-year survey. *Clin Infect Dis*. 2006; **43**: 577-584.

473 Weig M, Frosch M, Tintelnot K, et al. Use of recombinant mitogillin for improved serodiagnosis of aspergillus fumigatus -associated diseases. *Journal of clinical microbiology*. 2001; **39**: 1721-1730.

474 Du C, Wingard JR, Cheng S, Nguyen MH, Clancy C. Serum igg responses against aspergillus proteins before hematopoietic stem cell transplantation or chemotherapy identify patients who develop invasive aspergillosis. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2012; **18**: 1927-1934.

475 Holmberg K, Berdischewsky M, Young LS. Serologic immunodiagnosis of of invasive aspergillosis. *The Journal of infectious diseases*. 1980; **141**: 656-664.

476 Manso E, Montillo M, De Sio G, D'Amico S, Discepoli G, Leoni P. Value of antigen and antibody detection in the serological diagnosis of invasive aspergillosis in patients with hematological malignancies. *Eur J Clin Microbiol Infect Dis*. 1994; **13**: 756-760.

477 Mishra SK, Falkenberg S, Masihi KN. Efficacy of enzyme-linked immunosorbent assay in serodiagnosis of aspergillosis. *Journal of clinical microbiology*. 1983; **17**: 708-710.

478 Kappe R, Schulze-Berge A, Sonntag HG. Evaluation of eight antibody tests and one antigen test for the diagnosis of invasive aspergillosis. *Mycoses*. 1996; **39**: 13-23.

479 Fraczek MG, Bromley M, Buied A, et al. The cdr1b efflux transporter is associated with non-cyp51a-mediated itraconazole resistance in aspergillus fumigatus. *J Antimicrob Chemother*. 2013; **68**: 1486-1496.

480 Bueid A, Howard SJ, Moore CB, et al. Azole antifungal resistance in aspergillus fumigatus: 2008 and 2009. *J Antimicrob Chemother*. 2010; **65**: 2116-2118.

481 Arendrup MC, Mavridou E, Mortensen KL, et al. Development of azole resistance in aspergillus fumigatus during azole therapy associated with change in virulence. *PLoS ONE*. 2010; **5**: e10080.

482 van der Linden JW, Jansen RR, Bresters D, et al. Azole-resistant central nervous system aspergillosis. *Clin Infect Dis*. 2009; **48**: 1111-1113.

483 Badali H, Vaezi A, Haghani I, et al. Environmental study of azole-resistant aspergillus fumigatus with tr34/l98h mutations in the cyp51a gene in iran. *Mycoses*. 2013; **56**: 659-663.

484 Chowdhary A, Kathuria S, Xu J, et al. Clonal expansion and emergence of environmental multiple-triazole-resistant aspergillus fumigatus strains carrying the tr(3)(4)/l98h mutations in the cyp51a gene in india. *PLoS ONE*. 2012; **7**: e52871.

485 Mortensen KL, Mellado E, Lass-Florl C, Rodriguez-Tudela JL, Johansen HK, Arendrup MC. Environmental study of azole-resistant aspergillus fumigatus and other aspergilli in austria, denmark, and spain. *Antimicrob Agents Chemother*. 2010; **54**: 4545-4549.

486 Arendrup MC, Cuenca-Estrella M, Lass-Florl C, Hope WW. Breakpoints for antifungal agents: An update from eucast focussing on echinocandins against candida spp. And triazoles against aspergillus spp. *Drug Resist Updat*. 2013; **16**: 81-95.

487 Vermeulen E, Maertens J, Schoemans H, Lagrou K. Azole-resistant aspergillus fumigatus due to tr46/y121f/t289a mutation emerging in belgium, july 2012. *Euro Surveill*. 2012; **17**.

488 Chowdhary A, Kathuria S, Randhawa HS, Gaur SN, Klaassen CH, Meis JF. Isolation of multiple-triazole-resistant aspergillus fumigatus strains carrying the tr/l98h mutations in the cyp51a gene in india. *J Antimicrob Chemother*. 2012; **67**: 362-366.

489 Rath PM, Buchheidt D, Spiess B, Arfanis E, Buer J, Steinmann J. First reported case of azole-resistant aspergillus fumigatus due to the tr/l98h mutation in germany. *Antimicrob Agents Chemother*. 2012; **56**: 6060-6061.

490 Balajee SA, Baddley JW, Peterson SW, et al. Aspergillus alabamensis, a new clinically relevant species in the section terrei. *Eukaryot Cell*. 2009; **8**: 713-722.

491 Buil JB, van der Lee HAL, Rijs A, et al. Single-center evaluation of an agar-based screening for azole resistance in aspergillus fumigatus by using vipcheck. *Antimicrob Agents Chemother*. 2017; **61**.

492 van Leer-Buter C, Takes RP, Hebeda KM, Melchers WJ, Verweij PE. Aspergillosis--and a misleading sensitivity result. *Lancet*. 2007; **370**: 102.

493 Howard SJ, Pasqualotto AC, Anderson MJ, et al. Major variations in aspergillus fumigatus arising within aspergillomas in chronic pulmonary aspergillosis. *Mycoses*. 2013; **56**: 434-441.

494 Hope WW, Cuenca-Estrella M, Lass-Florl C, Arendrup MC, European Committee on Antimicrobial Susceptibility Testing-Subcommittee on Antifungal Susceptibility T. Eucast technical note on voriconazole and aspergillus spp. *Clin Microbiol Infect*. 2013; **19**: E278-280.

495 Arendrup MC, Meletiadis J, Mouton JW, et al. Eucast technical note on isavuconazole breakpoints for aspergillus, itraconazole breakpoints for candida and updates for the antifungal susceptibility testing method documents. *Clin Microbiol Infect*. 2016; **22**: 571 e571-574.

496 Rex JH, Clinical, Institute LS. *Reference method for broth dilution antifungal susceptibility testing of filamentous fungi: Approved standard*: Clinical and Laboratory Standards Institute, 2008.

497 Burgel PR, Baixench MT, Amsellem M, et al. High prevalence of azole-resistant aspergillus fumigatus in adults with cystic fibrosis exposed to itraconazole. *Antimicrob Agents Chemother*. 2012; **56**: 869-874.

498 Araujo R, Espinel-Ingroff A. Comparison of assessment of oxygen consumption, etest, and clsi m38-a2 broth microdilution methods for evaluation of the susceptibility of aspergillus fumigatus to posaconazole. *Antimicrob Agents Chemother*. 2009; **53**: 4921-4923.

499 Arikan S, Sancak B, Alp S, Hascelik G, McNicholas P. Comparative in vitro activities of posaconazole, voriconazole, itraconazole, and amphotericin b against *aspergillus* and *rhizopus*, and synergy testing for *rhizopus*. *Medical mycology*. 2008; **46**: 567-573.

500 Guinea J, Pelaez T, Recio S, Torres-Narbona M, Bouza E. In vitro antifungal activities of isavuconazole (bal4815), voriconazole, and fluconazole against 1,007 isolates of zygomycete, candida, aspergillus, fusarium, and scedosporium species. *Antimicrob Agents Chemother*. 2008; **52**: 1396-1400.

501 Howard SJ, Harrison E, Bowyer P, Varga J, Denning DW. Cryptic species and azole resistance in the aspergillus niger complex. *Antimicrob Agents Chemother*. 2011; **55**: 4802-4809.

502 Denning DW, Radford SA, Oakley KL, Hall L, Johnson EM, Warnock DW. Correlation between in-vitro susceptibility testing to itraconazole and in-vivo outcome of aspergillus fumigatus infection. *J Antimicrob Chemother*. 1997; **40**: 401-414.

503 Denning DW, Venkateswarlu K, Oakley KL, et al. Itraconazole resistance in aspergillus fumigatus. *Antimicrob Agents Chemother*. 1997; **41**: 1364-1368.

504 Rudramurthy SM, Chakrabarti A, Geertsen E, Mouton JW, Meis JF. In vitro activity of isavuconazole against 208 aspergillus flavus isolates in comparison with 7 other antifungal

agents: Assessment according to the methodology of the european committee on antimicrobial susceptibility testing. *Diagn Microbiol Infect Dis*. 2011; **71**: 370-377.

505 Pfaller MA, Messer SA, Woosley LN, Jones RN, Castanheira M. Echinocandin and triazole antifungal susceptibility profiles for clinical opportunistic yeast and mold isolates collected from 2010 to 2011: Application of new clsi clinical breakpoints and epidemiological cutoff values for characterization of geographic and temporal trends of antifungal resistance. *Journal of clinical microbiology*. 2013; **51**: 2571-2581.

506 Snelders E, van der Lee HA, Kuijpers J, et al. Emergence of azole resistance in aspergillus fumigatus and spread of a single resistance mechanism. *PLoS Med*. 2008; **5**: e219.

507 Perkhofer S, Lechner V, Lass-Florl C, European Committee on Antimicrobial Susceptibility T. In vitro activity of isavuconazole against aspergillus species and zygomycetes according to the methodology of the european committee on antimicrobial susceptibility testing. *Antimicrob Agents Chemother*. 2009; **53**: 1645-1647.

508 Hodiamont CJ, Dolman KM, Ten Berge IJ, Melchers WJ, Verweij PE, Pajkrt D. Multiple-azole-resistant aspergillus fumigatus osteomyelitis in a patient with chronic granulomatous disease successfully treated with long-term oral posaconazole and surgery. *Medical mycology*. 2009; **47**: 217-220.

509 Mavridou E, Bruggemann RJ, Melchers WJ, Mouton JW, Verweij PE. Efficacy of posaconazole against three clinical aspergillus fumigatus isolates with mutations in the cyp51a gene. *Antimicrob Agents Chemother*. 2010; **54**: 860-865.

510 Espinel-Ingroff A, Chowdhary A, Gonzalez GM, et al. Multicenter study of isavuconazole mic distributions and epidemiological cutoff values for aspergillus spp. For the clsi m38-a2 broth microdilution method. *Antimicrob Agents Chemother*. 2013; **57**: 3823-3828.

511 Howard SJ, Lass-Florl C, Cuenca-Estrella M, Gomez-Lopez A, Arendrup MC. Determination of isavuconazole susceptibility of aspergillus and candida species by the eucast method. *Antimicrob Agents Chemother*. 2013; **57**: 5426-5431.

512 Gregson L, Goodwin J, Johnson A, et al. In vitro susceptibility of aspergillus fumigatus to isavuconazole: Correlation with itraconazole, voriconazole, and posaconazole. *Antimicrob Agents Chemother*. 2013; **57**: 5778-5780.

513 Lionakis MS, Lewis RE, Chamilos G, Kontoyiannis DP. Aspergillus susceptibility testing in patients with cancer and invasive aspergillosis: Difficulties in establishing correlation between in vitro susceptibility data and the outcome of initial amphotericin b therapy. *Pharmacotherapy*. 2005; **25**: 1174-1180.

514 Mosquera J, Warn PA, Morrissey J, Moore CB, Gil-Lamaignere C, Denning DW. Susceptibility testing of aspergillus flavus: Inoculum dependence with itraconazole and lack of correlation between susceptibility to amphotericin b in vitro and outcome in vivo. *Antimicrob Agents Chemother*. 2001; **45**: 1456-1462.

515 Barchiesi F, Spreghini E, Sanguinetti M, et al. Effects of amphotericin b on aspergillus flavus clinical isolates with variable susceptibilities to the polyene in an experimental model of systemic aspergillosis. *J Antimicrob Chemother*. 2013; **68**: 2587-2591.

516 Hadrich I, Makni F, Neji S, et al. Amphotericin b in vitro resistance is associated with fatal aspergillus flavus infection. *Medical mycology*. 2012; **50**: 829-834.

517 Arendrup MC, Cuenca-Estrella M, Lass-Florl C, Hope WW, European Committee on Antimicrobial Susceptibility Testing Subcommittee on Antifungal Susceptibility T. Eucast technical note on aspergillus and amphotericin b, itraconazole, and posaconazole. *Clin Microbiol Infect*. 2012; **18**: E248-250.

518 *European committee on antimicrobial susceptibility testing.* http://www.eucast.org

519 Espinel-Ingroff A, Diekema DJ, Fothergill A, et al. Wild-type mic distributions and epidemiological cutoff values for the triazoles and six aspergillus spp. For the clsi broth microdilution method (m38-a2 document). *Journal of clinical microbiology*. 2010; **48**: 3251-3257.

520 Nivoix Y, Velten M, Letscher-Bru V, et al. Factors associated with overall and attributable mortality in invasive aspergillosis. *Clin Infect Dis*. 2008; **47**: 1176-1184.

521 Upton A, Kirby KA, Carpenter P, Boeckh M, Marr KA. Invasive aspergillosis following hematopoietic cell transplantation: Outcomes and prognostic factors associated with mortality. *Clin Infect Dis*. 2007; **44**: 531-540.

522 Pagano L, Caira M, Candoni A, et al. Invasive aspergillosis in patients with acute myeloid leukemia: A seifem-2008 registry study. *Haematologica*. 2010; **95**: 644-650.

523 Baddley JW, Andes DR, Marr KA, et al. Factors associated with mortality in transplant patients with invasive aspergillosis. *Clin Infect Dis*. 2010; **50**: 1559-1567.

524 Lortholary O, Gangneux JP, Sitbon K, et al. Epidemiological trends in invasive aspergillosis in france: The saif network (2005-2007). *Clin Microbiol Infect*. 2011; **17**: 1882-1889.

525 Perkhofer S, Lass-Florl C, Hell M, et al. The nationwide austrian aspergillus registry: A prospective data collection on epidemiology, therapy and outcome of invasive mould infections in immunocompromised and/or immunosuppressed patients. *Int J Antimicrob Agents*. 2010; **36**: 531-536.

526 Lass-Florl C, Alastruey-Izquierdo A, Cuenca-Estrella M, Perkhofer S, Rodriguez-Tudela JL. In vitro activities of various antifungal drugs against aspergillus terreus: Global assessment using the methodology of the european committee on antimicrobial susceptibility testing. *Antimicrob Agents Chemother*. 2009; **53**: 794-795.

527 Kathuria S, Sharma C, Singh PK, et al. Molecular epidemiology and in-vitro antifungal susceptibility of aspergillus terreus species complex isolates in delhi, india: Evidence of genetic diversity by amplified fragment length polymorphism and microsatellite typing. *PLoS One*. 2015; **10**: e0118997.

528 Alastruey-Izquierdo A, Cuesta I, Houbraken J, Cuenca-Estrella M, Monzon A, Rodriguez-Tudela JL. In vitro activity of nine antifungal agents against clinical isolates of aspergillus calidoustus. *Medical mycology*. 2010; **48**: 97-102.

529 Alcazar-Fuoli L, Mellado E, Alastruey-Izquierdo A, Cuenca-Estrella M, Rodriguez-Tudela JL. Aspergillus section fumigati: Antifungal susceptibility patterns and sequence-based identification. *Antimicrob Agents Chemother*. 2008; **52**: 1244-1251.

530 Datta K, Rhee P, Byrnes E, 3rd, et al. Isavuconazole activity against aspergillus lentulus, neosartorya udagawae, and cryptococcus gattii, emerging fungal pathogens with reduced azole susceptibility. *Journal of clinical microbiology*. 2013; **51**: 3090-3093.

531 Howard SJ. Multi-resistant aspergillosis due to cryptic species. *Mycopathologia*. 2014; **178**: 435-439.

532 Falcone EL, Holland SM. Invasive fungal infection in chronic granulomatous disease: Insights into pathogenesis and management. *Curr Opin Infect Dis*. 2012; **25**: 658-669.

533 Segal BH, DeCarlo ES, Kwon-Chung KJ, Malech HL, Gallin JI, Holland SM. Aspergillus nidulans infection in chronic granulomatous disease. *Medicine (Baltimore)*. 1998; **77**: 345-354.

534 Seyedmousavi S, Bruggemann RJ, Melchers WJ, Rijs AJ, Verweij PE, Mouton JW. Efficacy and pharmacodynamics of voriconazole combined with anidulafungin in azole-resistant invasive aspergillosis. *J Antimicrob Chemother*. 2013; **68**: 385-393.

535 Seyedmousavi S, Mouton JW, Melchers WJ, Bruggemann RJ, Verweij PE. The role of azoles in the management of azole-resistant aspergillosis: From the bench to the bedside. *Drug Resist Updat*. 2014; **17**: 37-50.

536 Newton PJ, Harris C, Morris J, Denning DW. Impact of liposomal amphotericin b therapy on chronic pulmonary aspergillosis. *J Infect*. 2016.

537 Verweij PE, Howard SJ, Melchers WJ, Denning DW. Azole-resistance in aspergillus: Proposed nomenclature and breakpoints. *Drug Resist Updat*. 2009; **12**: 141-147.

538 Seyedmousavi S, Melchers WJ, Mouton JW, Verweij PE. Pharmacodynamics and dose-response relationships of liposomal amphotericin b against different azole-resistant aspergillus fumigatus isolates in a murine model of disseminated aspergillosis. *Antimicrob Agents Chemother*. 2013; **57**: 1866-1871.

539 Lepak AJ, Marchillo K, VanHecker J, Andes DR. Impact of in vivo triazole and echinocandin combination therapy for invasive pulmonary aspergillosis: Enhanced efficacy against cyp51 mutant isolates. *Antimicrob Agents Chemother*. 2013; **57**: 5438-5447.

540 Denning DW. Treatment of invasive aspergillosis. *J Infect*. 1994; **28 Suppl 1**: 25-33.

541 Denning DW, Tucker RM, Hanson LH, Stevens DA. Treatment of invasive aspergillosis with itraconazole. *The American journal of medicine*. 1989; **86**: 791-800.

542 Caillot D, Bassaris H, McGeer A, et al. Intravenous itraconazole followed by oral itraconazole in the treatment of invasive pulmonary aspergillosis in patients with hematologic malignancies, chronic granulomatous disease, or aids. *Clin Infect Dis*. 2001; **33**: e83-90.

543 Kim SH, Yim DS, Choi SM, et al. Voriconazole-related severe adverse events: Clinical application of therapeutic drug monitoring in korean patients. *Int J Infect Dis*. 2011; **15**: e753-758.

544 Ueda K, Nannya Y, Kumano K, et al. Monitoring trough concentration of voriconazole is important to ensure successful antifungal therapy and to avoid hepatic damage in patients with hematological disorders. *International journal of hematology*. 2009; **89**: 592-599.

545 Smith J, Safdar N, Knasinski V, et al. Voriconazole therapeutic drug monitoring. *Antimicrob Agents Chemother*. 2006; **50**: 1570-1572.

546 Pieper S, Kolve H, Gumbinger HG, Goletz G, Wurthwein G, Groll AH. Monitoring of voriconazole plasma concentrations in immunocompromised paediatric patients. *J Antimicrob Chemother*. 2012; **67**: 2717-2724.

547 Mitsani D, Nguyen MH, Shields RK, et al. Prospective, observational study of voriconazole therapeutic drug monitoring among lung transplant recipients receiving prophylaxis: Factors impacting levels of and associations between serum troughs, efficacy, and toxicity. *Antimicrob Agents Chemother*. 2012; **56**: 2371-2377.

548 Siopi M, Mavridou E, Mouton JW, Verweij PE, Zerva L, Meletiadis J. Susceptibility breakpoints and target values for therapeutic drug monitoring of voriconazole and aspergillus fumigatus in an in vitro pharmacokinetic/pharmacodynamic model. *J Antimicrob Chemother*. 2014; **69**: 1611-1619.

549 Conte JE, Jr., Golden JA, Krishna G, McIver M, Little E, Zurlinden E. Intrapulmonary pharmacokinetics and pharmacodynamics of posaconazole at steady state in healthy subjects. *Antimicrob Agents Chemother*. 2009; **53**: 703-707.

550 Campoli P, Perlin DS, Kristof AS, White TC, Filler SG, Sheppard DC. Pharmacokinetics of posaconazole within epithelial cells and fungi: Insights into potential mechanisms of action during treatment and prophylaxis. *The Journal of infectious diseases*. 2013; **208**: 1717-1728.

551 Campoli P, Al Abdallah Q, Robitaille R, et al. Concentration of antifungal agents within host cell membranes: A new paradigm governing the efficacy of prophylaxis. *Antimicrob Agents Chemother*. 2011; **55**: 5732-5739.

552 Blennow O, Eliasson E, Pettersson T, et al. Posaconazole concentrations in human tissues after allogeneic stem cell transplantation. *Antimicrob Agents Chemother*. 2014; **58**: 4941-4943.

553 Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. Fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. 2007; **356**: 348-359.

554 Rijnders BJ, Cornelissen JJ, Slobbe L, et al. Aerosolized liposomal amphotericin b for the prevention of invasive pulmonary aspergillosis during prolonged neutropenia: A randomized, placebo-controlled trial. *Clin Infect Dis*. 2008; **46**: 1401-1408.

555 Slobbe L, Boersma E, Rijnders BJ. Tolerability of prophylactic aerosolized liposomal amphotericin-b and impact on pulmonary function: Data from a randomized placebo-controlled trial. *Pulm Pharmacol Ther*. 2008; **21**: 855-859.

556 Mattiuzzi GN, Kantarjian H, Faderl S, et al. Amphotericin b lipid complex as prophylaxis of invasive fungal infections in patients with acute myelogenous leukemia and myelodysplastic syndrome undergoing induction chemotherapy. *Cancer*. 2004; **100**: 581-589.

557 Oren I, Rowe JM, Sprecher H, et al. A prospective randomized trial of itraconazole vs fluconazole for the prevention of fungal infections in patients with acute leukemia and hematopoietic stem cell transplant recipients. *Bone Marrow Transplant*. 2006; **38**: 127-134.

558 Glasmacher A, Cornely O, Ullmann AJ, et al. An open-label randomized trial comparing itraconazole oral solution with fluconazole oral solution for primary prophylaxis of fungal infections in patients with haematological malignancy and profound neutropenia. *J Antimicrob Chemother*. 2006; **57**: 317-325.

559 Marr KA, Crippa F, Leisenring W, et al. Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants. *Blood*. 2004; **103**: 1527-1533.

560 van Burik JA, Ratanatharathorn V, Stepan DE, et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. *Clin Infect Dis*. 2004; **39**: 1407-1416.

561 Park S, Kim K, Jang JH, et al. Randomized trial of micafungin versus fluconazole as prophylaxis against invasive fungal infections in hematopoietic stem cell transplant recipients. *J Infect*. 2016; **73**: 496-505.

562 Cordonnier C, Mohty M, Faucher C, et al. Safety of a weekly high dose of liposomal amphotericin b for prophylaxis of invasive fungal infection in immunocompromised patients: Prophysome study. *Int J Antimicrob Agents*. 2008; **31**: 135-141.

563 Penack O, Schwartz S, Martus P, et al. Low-dose liposomal amphotericin b in the prevention of invasive fungal infections in patients with prolonged neutropenia: Results from a randomized, single-center trial. *Ann Oncol*. 2006; **17**: 1306-1312.

564 Annino L, Chierichini A, Anaclerico B, et al. Prospective phase ii single-center study of the safety of a single very high dose of liposomal amphotericin b for antifungal prophylaxis in patients with acute myeloid leukemia. *Antimicrob Agents Chemother*. 2013; **57**: 2596-2602.

565 Wingard JR, Carter SL, Walsh TJ, et al. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. *Blood*. 2010; **116**: 5111-5118.

566 Cornely OA, Leguay T, Maertens J, et al. Randomized comparison of liposomal amphotericin b versus placebo to prevent invasive mycoses in acute lymphoblastic leukaemia. *J Antimicrob Chemother*. 2017; **72**: 2359-2367.

567 Wingard JR, Carter SL, Walsh TJ, et al. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. *Blood*. 2010; **116**: 5111-5118.

568 Marks DI, Pagliuca A, Kibbler CC, et al. Voriconazole versus itraconazole for antifungal prophylaxis following allogeneic haematopoietic stem-cell transplantation. *Br J Haematol*. 2011; **155**: 318-327.

569 Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med*. 2007; **356**: 335-347.

570 Winston DJ, Maziarz RT, Chandrasekar PH, et al. Intravenous and oral itraconazole versus intravenous and oral fluconazole for long-term antifungal prophylaxis in allogeneic hematopoietic stem-cell transplant recipients. A multicenter, randomized trial. *Annals of internal medicine*. 2003; **138**: 705-713.

571 Marr KA, Leisenring W, Crippa F, et al. Cyclophosphamide metabolism is affected by azole antifungals. *Blood*. 2004; **103**: 1557-1559.

572 Menichetti F, Del Favero A, Martino P, et al. Itraconazole oral solution as prophylaxis for fungal infections in neutropenic patients with hematologic malignancies: A randomized, placebo-controlled, double-blind, multicenter trial. Gimema infection program. Gruppo italiano malattie ematologiche dell' adulto. *Clin Infect Dis*. 1999; **28**: 250-255.

573 Prentice HG, Caillot D, Dupont B, Menichetti F, Schuler U. Oral and intravenous itraconazole for systemic fungal infections in neutropenic haematological patients: Meeting report. London, united kingdom, 20 june 1998. *Acta Haematol*. 1999; **101**: 56-62.

574 Harousseau JL, Dekker AW, Stamatoullas-Bastard A, et al. Itraconazole oral solution for primary prophylaxis of fungal infections in patients with hematological malignancy and profound neutropenia: A randomized, double-blind, double-placebo, multicenter trial comparing itraconazole and amphotericin b. *Antimicrob Agents Chemother*. 2000; **44**: 1887-1893.

575 Gallin JI, Alling DW, Malech HL, et al. Itraconazole to prevent fungal infections in chronic granulomatous disease. *N Engl J Med*. 2003; **348**: 2416-2422.

576 de Repentigny L, Ratelle J, Leclerc JM, et al. Repeated-dose pharmacokinetics of an oral solution of itraconazole in infants and children. *Antimicrob Agents Chemother*. 1998; **42**: 404-408.

577 Groll AH, Wood L, Roden M, et al. Safety, pharmacokinetics, and pharmacodynamics of cyclodextrin itraconazole in pediatric patients with oropharyngeal candidiasis. *Antimicrob Agents Chemother*. 2002; **46**: 2554-2563.

578 Foot AB, Veys PA, Gibson BE. Itraconazole oral solution as antifungal prophylaxis in children undergoing stem cell transplantation or intensive chemotherapy for haematological disorders. *Bone Marrow Transplant*. 1999; **24**: 1089-1093.

579 Simon A, Besuden M, Vezmar S, et al. Itraconazole prophylaxis in pediatric cancer patients receiving conventional chemotherapy or autologous stem cell transplants. *Support Care Cancer*. 2007; **15**: 213-220.

580 Ananda-Rajah MR, Grigg A, Downey MT, et al. Comparative clinical effectiveness of prophylactic voriconazole/posaconazole to fluconazole/itraconazole in patients with acute myeloid leukemia/myelodysplastic syndrome undergoing cytotoxic chemotherapy over a 12-year period. *Haematologica*. 2012; **97**: 459-463.

581 Ananda-Rajah MR, Grigg A, Slavin MA. Making sense of posaconazole therapeutic drug monitoring: A practical approach. *Curr Opin Infect Dis*. 2012; **25**: 605-611.

582 Krishna G, Martinho M, Chandrasekar P, Ullmann AJ, Patino H. Pharmacokinetics of oral posaconazole in allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease. *Pharmacotherapy*. 2007; **27**: 1627-1636.

583 Welzen ME, Bruggemann RJ, Van Den Berg JM, et al. A twice daily posaconazole dosing algorithm for children with chronic granulomatous disease. *Pediatr Infect Dis J*. 2011; **30**: 794-797.

584 Döring M, Müller C, Johann PD, et al. Analysis of posaconazole as oral antifungal prophylaxis in pediatric patients under 12 years of age following allogeneic stem cell transplantation. *BMC Infect Dis*. 2012; **12**: 263.

585 Lehrnbecher T, Attarbaschi A, Duerken M, et al. Posaconazole salvage treatment in paediatric patients: A multicentre survey. *Eur J Clin Microbiol Infect Dis*. 2010; **29**: 1043-1045.

586 Vanstraelen K, Colita A, Bica AM, et al. Pharmacokinetics of posaconazole oral suspension in children dosed according to body surface area. *Pediatr Infect Dis J*. 2016; **35**: 183-188.

587 Mattiuzzi GN, Cortes J, Alvarado G, et al. Efficacy and safety of intravenous voriconazole and intravenous itraconazole for antifungal prophylaxis in patients with acute myelogenous leukemia or high-risk myelodysplastic syndrome. *Support Care Cancer*. 2011; **19**: 19-26.

588 Barreto JN, Beach CL, Wolf RC, et al. The incidence of invasive fungal infections in neutropenic patients with acute leukemia and myelodysplastic syndromes receiving primary antifungal prophylaxis with voriconazole. *Am J Hematol*. 2013; **88**: 283-288.

589 Walsh TJ, Karlsson MO, Driscoll T, et al. Pharmacokinetics and safety of intravenous voriconazole in children after single- or multiple-dose administration. *Antimicrob Agents Chemother*. 2004; **48**: 2166-2172.

590 Karlsson MO, Lutsar I, Milligan PA. Population pharmacokinetic analysis of voriconazole plasma concentration data from pediatric studies. *Antimicrob Agents Chemother*. 2009; **53**: 935-944.

591 Driscoll TA, Frangoul H, Nemecek ER, et al. Comparison of pharmacokinetics and safety of voriconazole intravenous-to-oral switch in immunocompromised adolescents and healthy adults. *Antimicrob Agents Chemother*. 2011; **55**: 5780-5789.

592 Driscoll TA, Yu LC, Frangoul H, et al. Comparison of pharmacokinetics and safety of voriconazole intravenous-to-oral switch in immunocompromised children and healthy adults. *Antimicrob Agents Chemother*. 2011; **55**: 5770-5779.

593 Molina JR, Serrano J, Sanchez-Garcia J, et al. Voriconazole as primary antifungal prophylaxis in children undergoing allo-sct. *Bone Marrow Transplant*. 2012; **47**: 562-567.

594 Tollemar J, Ringden O, Andersson S, et al. Prophylactic use of liposomal amphotericin b (ambisome) against fungal infections: A randomized trial in bone marrow transplant recipients. *Transplant Proc*. 1993; **25**: 1495-1497.

595 Tollemar J, Ringden O, Andersson S, Sundberg B, Ljungman P, Tyden G. Randomized double-blind study of liposomal amphotericin b (ambisome) prophylaxis of invasive fungal infections in bone marrow transplant recipients. *Bone Marrow Transplant*. 1993; **12**: 577-582.

596 Kelsey SM, Goldman JM, McCann S, et al. Liposomal amphotericin (ambisome) in the prophylaxis of fungal infections in neutropenic patients: A randomised, double-blind, placebo-controlled study. *Bone Marrow Transplant*. 1999; **23**: 163-168.

597 Hong Y, Shaw PJ, Nath CE, et al. Population pharmacokinetics of liposomal amphotericin b in pediatric patients with malignant diseases. *Antimicrob Agents Chemother*. 2006; **50**: 935-942.

598 Ringden O, Meunier F, Tollemar J, et al. Efficacy of amphotericin b encapsulated in liposomes (ambisome) in the treatment of invasive fungal infections in immunocompromised patients. *J Antimicrob Chemother*. 1991; **28 Suppl B**: 73-82.

599 Kolve H, Ahlke E, Fegeler W, Ritter J, Jurgens H, Groll AH. Safety, tolerance and outcome of treatment with liposomal amphotericin b in paediatric patients with cancer or undergoing haematopoietic stem cell transplantation. *J Antimicrob Chemother*. 2009; **64**: 383-387.

600 Huang X, Chen H, Han M, et al. Multicenter, randomized, open-label study comparing the efficacy and safety of micafungin versus itraconazole for prophylaxis of invasive fungal infections in patients undergoing hematopoietic stem cell transplant. *Biology of blood and*

marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2012; **18**: 1509-1516.

601 Seibel NL, Schwartz C, Arrieta A, et al. Safety, tolerability, and pharmacokinetics of micafungin (fk463) in febrile neutropenic pediatric patients. *Antimicrob Agents Chemother*. 2005; **49**: 3317-3324.

602 Hope WW, Seibel NL, Schwartz CL, et al. Population pharmacokinetics of micafungin in pediatric patients and implications for antifungal dosing. *Antimicrob Agents Chemother*. 2007; **51**: 3714-3719.

603 Arrieta AC, Maddison P, Groll AH. Safety of micafungin in pediatric clinical trials. *Pediatr Infect Dis J*. 2011; **30**: e97-e102.

604 Mehta PA, Vinks AA, Filipovich A, et al. Alternate-day micafungin antifungal prophylaxis in pediatric patients undergoing hematopoietic stem cell transplantation: A pharmacokinetic study. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2010; **16**: 1458-1462.

605 Beaute J, Obenga G, Le Mignot L, et al. Epidemiology and outcome of invasive fungal diseases in patients with chronic granulomatous disease: A multicenter study in france. *Pediatr Infect Dis J*. 2011; **30**: 57-62.

606 Mouy R, Veber F, Blanche S, et al. Long-term itraconazole prophylaxis against aspergillus infections in thirty-two patients with chronic granulomatous disease. *J Pediatr*. 1994; **125**: 998-1003.

607 Fortun J, Martin-Davila P, Sanchez MA, et al. Voriconazole in the treatment of invasive mold infections in transplant recipients. *Eur J Clin Microbiol Infect Dis*. 2003; **22**: 408-413.

608 Wieland T, Liebold A, Jagiello M, Retzl G, Birnbaum DE. Superiority of voriconazole over amphotericin b in the treatment of invasive aspergillosis after heart transplantation. *J Heart Lung Transplant*. 2005; **24**: 102-104.

609 Veroux M, Corona D, Gagliano M, et al. Voriconazole in the treatment of invasive aspergillosis in kidney transplant recipients. *Transplant Proc*. 2007; **39**: 1838-1840.

610 Walsh TJ, Driscoll T, Milligan PA, et al. Pharmacokinetics, safety, and tolerability of voriconazole in immunocompromised children. *Antimicrob Agents Chemother*. 2010; **54**: 4116-4123.

611 Doby EH, Benjamin DK, Jr., Blaschke AJ, et al. Therapeutic monitoring of voriconazole in children less than three years of age: A case report and summary of voriconazole concentrations for ten children. *Pediatr Infect Dis J*. 2012; **31**: 632-635.

612 Soler-Palacin P, Frick MA, Martin-Nalda A, et al. Voriconazole drug monitoring in the management of invasive fungal infection in immunocompromised children: A prospective study. *J Antimicrob Chemother*. 2012; **67**: 700-706.

613 Bartelink IH, Wolfs T, Jonker M, et al. Highly variable plasma concentrations of voriconazole in pediatric hematopoietic stem cell transplantation patients. *Antimicrob Agents Chemother*. 2013; **57**: 235-240.

614 Kotwani RN, Gokhale PC, Bodhe PV, Kirodian BG, Kshirsagar NA, Pandya SK. A comparative study of plasma concentrations of liposomal amphotericin b (l-amp-lrc-1) in adults, children and neonates. *Int J Pharm*. 2002; **238**: 11-15.

615 Bochennek K, Tramsen L, Schedler N, et al. Liposomal amphotericin b twice weekly as antifungal prophylaxis in paediatric haematological malignancy patients. *Clin Microbiol Infect*. 2011; **17**: 1868-1874.

616 Groll AH, Silling G, Young C, et al. Randomized comparison of safety and pharmacokinetics of caspofungin, liposomal amphotericin b, and the combination of both in allogeneic hematopoietic stem cell recipients. *Antimicrob Agents Chemother*. 2010; **54**: 4143-4149.

617 Sunakawa K, Tsukimoto I, Tsunematsu Y, et al. Evaluation of the safety and efficacy of liposomal amphotericin b (l-amb) in children. *J Infect Chemother*. 2012; **18**: 456-465.

618 Herbrecht R, Maertens J, Baila L, et al. Caspofungin first-line therapy for invasive aspergillosis in allogeneic hematopoietic stem cell transplant patients: An european organisation for research and treatment of cancer study. *Bone Marrow Transplant*. 2010; **45**: 1227-1233.

619 Viscoli C, Herbrecht R, Akan H, et al. An eortc phase ii study of caspofungin as first-line therapy of invasive aspergillosis in haematological patients. *J Antimicrob Chemother*. 2009; **64**: 1274-1281.

620 Cornely OA, Vehreschild JJ, Vehreschild MJ, et al. Phase ii dose escalation study of caspofungin for invasive aspergillosis. *Antimicrob Agents Chemother*. 2011; **55**: 5798-5803.

621 Groetzner J, Kaczmarek I, Wittwer T, et al. Caspofungin as first-line therapy for the treatment of invasive aspergillosis after thoracic organ transplantation. *J Heart Lung Transplant*. 2008; **27**: 1-6.

622 Winkler M, Pratschke J, Schulz U, et al. Caspofungin for post solid organ transplant invasive fungal disease: Results of a retrospective observational study. *Transpl Infect Dis*. 2010; **12**: 230-237.

623 Walsh TJ, Adamson PC, Seibel NL, et al. Pharmacokinetics, safety, and tolerability of caspofungin in children and adolescents. *Antimicrob Agents Chemother*. 2005; **49**: 4536-4545.

624 Neely M, Jafri HS, Seibel N, et al. Pharmacokinetics and safety of caspofungin in older infants and toddlers. *Antimicrob Agents Chemother*. 2009; **53**: 1450-1456.

625 Cesaro S, Giacchino M, Locatelli F, et al. Safety and efficacy of a caspofungin-based combination therapy for treatment of proven or probable aspergillosis in pediatric hematological patients. *BMC Infect Dis*. 2007; **7**: 28.

626 Zaoutis T, Lehrnbecher T, Groll AH, et al. Safety experience with caspofungin in pediatric patients. *Pediatr Infect Dis J*. 2009; **28**: 1132-1135.

627 Zaoutis TE, Jafri HS, Huang LM, et al. A prospective, multicenter study of caspofungin for the treatment of documented candida or aspergillus infections in pediatric patients. *Pediatrics*. 2009; **123**: 877-884.

628 Ngai AL, Bourque MR, Lupinacci RJ, Strohmaier KM, Kartsonis NA. Overview of safety experience with caspofungin in clinical trials conducted over the first 15 years: A brief report. *Int J Antimicrob Agents*. 2011; **38**: 540-544.

629 Manzoni P, Rizzollo S, Farina D. Response to "is liposomal amphotericin b really safety in neonates?". *Early Hum Dev*. 2013; **89**: 37.

630 Karadag-Oncel E, Ozsurekci Y, Yurdakok M, Kara A. Is liposomal amphotericin b really safety in neonates? *Early Hum Dev*. 2013; **89**: 35-36.

631 Scarcella A, Pasquariello MB, Giugliano B, Vendemmia M, de Lucia A. Liposomal amphotericin b treatment for neonatal fungal infections. *Pediatr Infect Dis J*. 1998; **17**: 146-148.

632 Juster-Reicher A, Flidel-Rimon O, Amitay M, Even-Tov S, Shinwell E, Leibovitz E. High-dose liposomal amphotericin b in the therapy of systemic candidiasis in neonates. *Eur J Clin Microbiol Infect Dis*. 2003; **22**: 603-607.

633 Mellinghoff SC, Bassetti M, Dorfel D, et al. Isavuconazole shortens the qtc interval. *Mycoses*. 2017.

634 Cornely OA. Isavuconazole: Is there a need for a new antifungal? *J Antimicrob Chemother*. 2017; **72**: i2-i4.

635 Neofytos D, Ostrander D, Shoham S, et al. Voriconazole therapeutic drug monitoring: Results of a prematurely discontinued randomized multicenter trial. *Transpl Infect Dis*. 2015; **17**: 831-837.

636 Ito JI, Chandrasekar PH, Hooshmand-Rad R. Effectiveness of amphotericin b lipid complex (ablc) treatment in allogeneic hematopoietic cell transplant (hct) recipients with invasive aspergillosis (ia). *Bone Marrow Transplant*. 2005; **36**: 873-877.

637 Kohno S, Masaoka T, Yamaguchi H, et al. A multicenter, open-label clinical study of micafungin (fk463) in the treatment of deep-seated mycosis in japan. *Scand J Infect Dis*. 2004; **36**: 372-379.

638 Denning DW, Marr KA, Lau WM, et al. Micafungin (fk463), alone or in combination with other systemic antifungal agents, for the treatment of acute invasive aspergillosis. *J Infect*. 2006; **53**: 337-349.

639 Kontoyiannis DP, Ratanatharathorn V, Young JA, et al. Micafungin alone or in combination with other systemic antifungal therapies in hematopoietic stem cell transplant recipients with invasive aspergillosis. *Transpl Infect Dis*. 2009; **11**: 89-93.

640 Caillot D, Thiebaut A, Herbrecht R, et al. Liposomal amphotericin b in combination with caspofungin for invasive aspergillosis in patients with hematologic malignancies: A randomized pilot study (combistrat trial). *Cancer*. 2007; **110**: 2740-2746.

641 Dohen-Becue F, Salez F, Ramon P, et al. [management of hemoptysis in invasive pulmonary aspergillosis]. *Revue des maladies respiratoires*. 1998; **15**: 791-796.

642 Schwartz S, Ruhnke M, Ribaud P, et al. Improved outcome in central nervous system aspergillosis, using voriconazole treatment. *Blood*. 2005; **106**: 2641-2645.

643 Kourkoumpetis TK, Desalermos A, Muhammed M, Mylonakis E. Central nervous system aspergillosis: A series of 14 cases from a general hospital and review of 123 cases from the literature. *Medicine (Baltimore)*. 2012; **91**: 328-336.

644 Rüping MJ, Albermann N, Ebinger F, et al. Posaconazole concentrations in the central nervous system. *J Antimicrob Chemother*. 2008; **62**: 1468-1470.

645 Coleman JM, Hogg GG, Rosenfeld JV, Waters KD. Invasive central nervous system aspergillosis: Cure with liposomal amphotericin b, itraconazole, and radical surgery--case report and review of the literature. *Neurosurgery*. 1995; **36**: 858-863.

646 Clemons KV, Espiritu M, Parmar R, Stevens DA. Comparative efficacies of conventional amphotericin b, liposomal amphotericin b (ambisome), caspofungin, micafungin, and voriconazole alone and in combination against experimental murine central nervous system aspergillosis. *Antimicrob Agents Chemother*. 2005; **49**: 4867-4875.

647 Ellis M, Spence D, de Pauw B, et al. An eortc international multicenter randomized trial (eortc number 19923) comparing two dosages of liposomal amphotericin b for treatment of invasive aspergillosis. *Clin Infect Dis*. 1998; **27**: 1406-1412.

648 Schwartz S, Ruhnke M, Ribaud P, Reed E, Troke P, Thiel E. Poor efficacy of amphotericin b-based therapy in cns aspergillosis. *Mycoses*. 2007; **50**: 196-200.

649 Ullmann AJ, Sanz MA, Tramarin A, et al. Prospective study of amphotericin b formulations in immunocompromised patients in 4 european countries. *Clin Infect Dis*. 2006; **43**: e29-38.

650 Wingard JR, Kubilis P, Lee L, et al. Clinical significance of nephrotoxicity in patients treated with amphotericin b for suspected or proven aspergillosis. *Clin Infect Dis*. 1999; **29**: 1402-1407.

651 Girmenia C, Pizzarelli G, Pozzi E, Cimino G, Gentile G, Martino P. Improving outcomes of acute invasive aspergillus rhinosinusitis in patients with hematologic malignancies or aplastic anemia: The role of voriconazole. *Haematologica*. 2008; **93**: 159-160.

652 Thurtell MJ, Chiu AL, Goold LA, et al. Neuro-ophthalmology of invasive fungal sinusitis: 14 consecutive patients and a review of the literature. *Clin Experiment Ophthalmol*. 2013; **41**: 567-576.

653 Daudia A, Jones NS. Advances in management of paranasal sinus aspergillosis. *J Laryngol Otol*. 2008; **122**: 331-335.

654 Cordonnier C, Rovira M, Maertens J, et al. Voriconazole for secondary prophylaxis of invasive fungal infections in allogeneic stem cell transplant recipients: Results of the vosifi study. *Haematologica*. 2010; **95**: 1762-1768.

655 Liu F, Wu T, Wang JB, et al. Risk factors for recurrence of invasive fungal infection during secondary antifungal prophylaxis in allogeneic hematopoietic stem cell transplant recipients. *Transpl Infect Dis*. 2013; **15**: 243-250.

656 Gerlach S, Vehreschild JJ, Ruping MJTG, Fischer G, Cornely OA. Epidemiology of aspergillus spp. At the university hospital of cologne: Molecular typing of environmental and clinical isolates. In: *Gemeinsame Jahrestagung der Deutschen, Österreichischen und Schweizerichen GHO.* Wien, Österreich: Onkologie, 2008.

657 Allinson K, Kolve H, Gumbinger HG, Vormoor HJ, Ehlert K, Groll AH. Secondary antifungal prophylaxis in paediatric allogeneic haematopoietic stem cell recipients. *J Antimicrob Chemother*. 2008; **61**: 734-742.

658 de Fabritiis P, Spagnoli A, Di Bartolomeo P, et al. Efficacy of caspofungin as secondary prophylaxis in patients undergoing allogeneic stem cell transplantation with prior pulmonary and/or systemic fungal infection. *Bone Marrow Transplant*. 2007; **40**: 245-249.

659 Martino R, Parody R, Fukuda T, et al. Impact of the intensity of the pretransplantation conditioning regimen in patients with prior invasive aspergillosis undergoing allogeneic hematopoietic stem cell transplantation: A retrospective survey of the infectious diseases working party of the european group for blood and marrow transplantation. *Blood*. 2006; **108**: 2928-2936.

660 Kruger WH, Russmann B, de Wit M, et al. Haemopoietic cell transplantation of patients with a history of deep or invasive fungal infection during prophylaxis with liposomal amphotericin b. *Acta Haematol*. 2005; **113**: 104-108.

661 Nosari A, Ravini M, Cairoli R, et al. Surgical resection of persistent pulmonary fungus nodules and secondary prophylaxis are effective in preventing fungal relapse in patients receiving chemotherapy or bone marrow transplantation for leukemia. *Bone Marrow Transplant*. 2007; **39**: 631-635.

662 Eliashar R, Resnick IB, Goldfarb A, Wohlgelernter J, Gross M. Endoscopic surgery for sinonasal invasive aspergillosis in bone marrow transplantation patients. *The Laryngoscope*. 2007; **117**: 78-81.

663 Cesaro S, Cecchetto G, De Corti F, et al. Results of a multicenter retrospective study of a combined medical and surgical approach to pulmonary aspergillosis in pediatric neutropenic patients. *Pediatric blood & cancer*. 2007; **49**: 909-913.

664 Matt P, Bernet F, Habicht J, et al. Predicting outcome after lung resection for invasive pulmonary aspergillosis in patients with neutropenia. *Chest*. 2004; **126**: 1783-1788.

665 Reichenberger F, Habicht J, Kaim A, et al. Lung resection for invasive pulmonary aspergillosis in neutropenic patients with hematologic diseases. *Am J Respir Crit Care Med*. 1998; **158**: 885-890.

666 Boogaerts M, Winston DJ, Bow EJ, et al. Intravenous and oral itraconazole versus intravenous amphotericin b deoxycholate as empirical antifungal therapy for persistent fever in neutropenic patients with cancer who are receiving broad-spectrum antibacterial therapy. A randomized, controlled trial. *Annals of internal medicine*. 2001; **135**: 412-422.

667 Wingard JR, White MH, Anaissie E, et al. A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin b versus amphotericin b lipid complex in the empirical treatment of febrile neutropenia. L amph/ablc collaborative study group. *Clin Infect Dis*. 2000; **31**: 1155-1163.

668 White MH, Bowden RA, Sandler ES, et al. Randomized, double-blind clinical trial of amphotericin b colloidal dispersion vs. Amphotericin b in the empirical treatment of fever and neutropenia. *Clin Infect Dis*. 1998; **27**: 296-302.

669 Tamura K, Urabe A, Yoshida M, et al. Efficacy and safety of micafungin, an echinocandin antifungal agent, on invasive fungal infections in patients with hematological disorders. *Leuk Lymphoma*. 2009; **50**: 92-100.

670 Lass-Florl C. Triazole antifungal agents in invasive fungal infections: A comparative review. *Drugs*. 2011; **71**: 2405-2419.

671 Marr KA, Boeckh M, Carter RA, Kim HW, Corey L. Combination antifungal therapy for invasive aspergillosis. *Clin Infect Dis*. 2004; **39**: 797-802.

672 Perfect JR, Marr KA, Walsh TJ, et al. Voriconazole treatment for less-common, emerging, or refractory fungal infections. *Clin Infect Dis*. 2003; **36**: 1122-1131.

673 Baden LR, Katz JT, Fishman JA, et al. Salvage therapy with voriconazole for invasive fungal infections in patients failing or intolerant to standard antifungal therapy. *Transplantation*. 2003; **76**: 1632-1637.

674 Candoni A, Mestroni R, Damiani D, et al. Caspofungin as first line therapy of pulmonary invasive fungal infections in 32 immunocompromised patients with hematologic malignancies. *Eur J Haematol*. 2005; **75**: 227-233.

675 Ng TT, Denning DW. Liposomal amphotericin b (ambisome) therapy in invasive fungal infections. Evaluation of united kingdom compassionate use data. *Archives of internal medicine*. 1995; **155**: 1093-1098.

676 Hachem RY, Boktour MR, Hanna HA, et al. Amphotericin b lipid complex versus liposomal amphotericin b monotherapy for invasive aspergillosis in patients with hematologic malignancy. *Cancer*. 2008; **112**: 1282-1287.

677 Walsh TJ, Hiemenz JW, Seibel NL, et al. Amphotericin b lipid complex for invasive fungal infections: Analysis of safety and efficacy in 556 cases. *Clin Infect Dis*. 1998; **26**: 1383-1396.

678 Chandrasekar PH, Ito JI. Amphotericin b lipid complex in the management of invasive aspergillosis in immunocompromised patients. *Clin Infect Dis*. 2005; **40 Suppl 6**: S392-400.

679 Oppenheim BA, Herbrecht R, Kusne S. The safety and efficacy of amphotericin b colloidal dispersion in the treatment of invasive mycoses. *Clin Infect Dis*. 1995; **21**: 1145-1153.

680 Herbrecht R, Letscher V, Andres E, Cavalier A. Safety and efficacy of amphotericin b colloidal dispersion. An overview. *Chemotherapy*. 1999; **45 Suppl 1**: 67-76.

681 Betts R, Glasmacher A, Maertens J, et al. Efficacy of caspofungin against invasive candida or invasive aspergillus infections in neutropenic patients. *Cancer*. 2006; **106**: 466-473.

682 Egerer G, Reichert D, Pletz MW, Kaskel P, Krobot KJ, Maertens J. Caspofungin for treatment of invasive aspergillosis in germany: Results of a pre-planned subanalysis of an international registry. *Eur J Med Res*. 2012; **17**: 7.

683 Hiemenz JW, Raad, II, Maertens JA, et al. Efficacy of caspofungin as salvage therapy for invasive aspergillosis compared to standard therapy in a historical cohort. *Eur J Clin Microbiol Infect Dis*. 2010; **29**: 1387-1394.

684 Kartsonis NA, Saah AJ, Joy Lipka C, Taylor AF, Sable CA. Salvage therapy with caspofungin for invasive aspergillosis: Results from the caspofungin compassionate use study. *J Infect*. 2005; **50**: 196-205.

685 Morrissey CO, Slavin MA, O'Reilly MA, et al. Caspofungin as salvage monotherapy for invasive aspergillosis in patients with haematological malignancies or following allogeneic stem cell transplantation: Efficacy and concomitant cyclosporin a. *Mycoses*. 2007; **50 Suppl 1**: 24-37.

686 Maertens J, Egerer G, Shin WS, et al. Caspofungin use in daily clinical practice for treatment of invasive aspergillosis: Results of a prospective observational registry. *BMC Infect Dis*. 2010; **10**: 182.

687 Leon-Gil C, Ubeda-Iglesias A, Loza-Vazquez A, et al. Efficacy and safety of caspofungin in critically ill patients. Procas study. *Rev Esp Quimioter*. 2012; **25**: 274-282.

688 Enoch DA, Idris SF, Aliyu SH, Micallef C, Sule O, Karas JA. Micafungin for the treatment of invasive aspergillosis. *J Infect*. 2014; **68**: 507-526.

689 Hachem RY, Langston AA, Graybill JR, et al. Posaconazole as salvage treatment of invasive fungal infections in patients with underlying renal impairment. *J Antimicrob Chemother*. 2008; **62**: 1386-1391.

690 Heinz WJ, Egerer G, Lellek H, Boehme A, Greiner J. Posaconazole after previous antifungal therapy with voriconazole for therapy of invasive aspergillus disease, a retrospective analysis. *Mycoses*. 2013; **56**: 304-310.

691 Caillot D. Intravenous itraconazole followed by oral itraconazole for the treatment of amphotericin-b-refractory invasive pulmonary aspergillosis. *Acta Haematol*. 2003; **109**: 111-118.

692 Luong ML, Chaparro C, Stephenson A, et al. Pretransplant aspergillus colonization of cystic fibrosis patients and the incidence of post-lung transplant invasive aspergillosis. *Transplantation*. 2014; **97**: 351-357.

693 Monforte V, Roman A, Gavalda J, et al. Nebulized amphotericin b prophylaxis for aspergillus infection in lung transplantation: Study of risk factors. *J Heart Lung Transplant*. 2001; **20**: 1274-1281.

694 Iversen M, Burton CM, Vand S, et al. Aspergillus infection in lung transplant patients: Incidence and prognosis. *Eur J Clin Microbiol Infect Dis*. 2007; **26**: 879-886.

695 Hsu JL, Khan MA, Sobel RA, et al. Aspergillus fumigatus invasion increases with progressive airway ischemia. *PLoS One*. 2013; **8**: e77136.

696 Sole A, Morant P, Salavert M, Peman J, Morales P, Valencia Lung Transplant G. Aspergillus infections in lung transplant recipients: Risk factors and outcome. *Clin Microbiol Infect*. 2005; **11**: 359-365.

697 Danziger-Isakov LA, Worley S, Arrigain S, et al. Increased mortality after pulmonary fungal infection within the first year after pediatric lung transplantation. *J Heart Lung Transplant*. 2008; **27**: 655-661.

698 Sarmiento E, Rodriguez-Molina JJ, Fernandez-Yanez J, et al. Igg monitoring to identify the risk for development of infection in heart transplant recipients. *Transpl Infect Dis*. 2006; **8**: 49-53.

699 Collins LA, Samore MH, Roberts MS, et al. Risk factors for invasive fungal infections complicating orthotopic liver transplantation. *The Journal of infectious diseases*. 1994; **170**: 644-652.

700 Singh N, Husain S, Practice ASTIDCo. Invasive aspergillosis in solid organ transplant recipients. *Am J Transplant*. 2009; **9 Suppl 4**: S180-191.

701 Singh N, Pruett TL, Houston S, et al. Invasive aspergillosis in the recipients of liver retransplantation. *Liver Transpl*. 2006; **12**: 1205-1209.

702 Saliba F, Delvart V, Ichai P, et al. Fungal infections after liver transplantation: Outcomes and risk factors revisited in the meld era. *Clin Transplant*. 2013; **27**: E454-461.

703 He H, Ding L, Li F, Zhan Q. Clinical features of invasive bronchial-pulmonary aspergillosis in critically ill patients with chronic obstructive respiratory diseases: A prospective study. *Crit Care*. 2011; **15**: R5.

704 Bulpa P, Dive A, Sibille Y. Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease. *Eur Respir J*. 2007; **30**: 782-800.

705 Kistemann T, Huneburg H, Exner M, Vacata V, Engelhart S. Role of increased environmental aspergillus exposure for patients with chronic obstructive pulmonary disease (copd) treated with corticosteroids in an intensive care unit. *Int J Hyg Environ Health*. 2002; **204**: 347-351.

706 Murray CK, Loo FL, Hospenthal DR, et al. Incidence of systemic fungal infection and related mortality following severe burns. *Burns*. 2008; **34**: 1108-1112.

707 Lahmer T, Messer M, Schwerdtfeger C, et al. Invasive mycosis in medical intensive care unit patients with severe alcoholic hepatitis. *Mycopathologia*. 2014; **177**: 193-197.

708 Ballard J, Edelman L, Saffle J, et al. Positive fungal cultures in burn patients: A multicenter review. *J Burn Care Res*. 2008; **29**: 213-221.

709 Horvath EE, Murray CK, Vaughan GM, et al. Fungal wound infection (not colonization) is independently associated with mortality in burn patients. *Annals of surgery*. 2007; **245**: 978-985.

710 Guinea J, Jensen J, Pelaez T, et al. Value of a single galactomannan determination (platelia) for the diagnosis of invasive aspergillosis in non-hematological patients with clinical isolation of aspergillus spp. *Medical mycology*. 2008; **46**: 575-579.

711 Acosta J, Catalan M, del Palacio-Perez-Medel A, et al. Prospective study in critically ill non-neutropenic patients: Diagnostic potential of (1,3)-beta-d-glucan assay and circulating galactomannan for the diagnosis of invasive fungal disease. *Eur J Clin Microbiol Infect Dis*. 2012; **31**: 721-731.

712 He H, Ding L, Sun B, Li F, Zhan Q. Role of galactomannan determinations in bronchoalveolar lavage fluid samples from critically ill patients with chronic obstructive pulmonary disease for the diagnosis of invasive pulmonary aspergillosis: A prospective study. *Crit Care*. 2012; **16**: R138.

713 Khorvash F, Meidani M, Babaei L, Abbasi S, Ataei B, Yaran M. Galactomannan antigen assay from bronchoalveolar lavage fluid in diagnosis of invasive pulmonary aspergillosis in intensive care units patients. *Adv Biomed Res*. 2014; **3**: 68.

714 Steinmann J, Buer J, Rath PM. Detection of aspergillus fumigatus in blood samples from critically ill patients in intensive care units by use of the septifast assay. *Journal of clinical microbiology*. 2016; **54**: 1918-1921.

715 Westh H, Lisby G, Breysse F, et al. Multiplex real-time pcr and blood culture for identification of bloodstream pathogens in patients with suspected sepsis. *Clin Microbiol Infect*. 2009; **15**: 544-551.

716 Clancy CJ, Jaber RA, Leather HL, et al. Bronchoalveolar lavage galactomannan in diagnosis of invasive pulmonary aspergillosis among solid-organ transplant recipients. *Journal of clinical microbiology*. 2007; **45**: 1759-1765.

717 Gazzoni FF, Hochhegger B, Severo LC, et al. High-resolution computed tomographic findings of aspergillus infection in lung transplant patients. *Eur J Radiol*. 2014; **83**: 79-83.

718 Hoenigl M, Koidl C, Duettmann W, et al. Bronchoalveolar lavage lateral-flow device test for invasive pulmonary aspergillosis diagnosis in haematological malignancy and solid organ transplant patients. *J Infect*. 2012; **65**: 588-591.

719 Alexander BD, Smith PB, Davis RD, Perfect JR, Reller LB. The (1,3){beta}-d-glucan test as an aid to early diagnosis of invasive fungal infections following lung transplantation. *Journal of clinical microbiology*. 2010; **48**: 4083-4088.

720 Husain S, Kwak EJ, Obman A, et al. Prospective assessment of platelia aspergillus galactomannan antigen for the diagnosis of invasive aspergillosis in lung transplant recipients. *Am J Transplant*. 2004; **4**: 796-802.

721 Husain S, Paterson DL, Studer SM, et al. Aspergillus galactomannan antigen in the bronchoalveolar lavage fluid for the diagnosis of invasive aspergillosis in lung transplant recipients. *Transplantation*. 2007; **83**: 1330-1336.

722 Ambrosioni J, Coll S, Manzardo C, et al. Voriconazole and cobicistat-boosted antiretroviral salvage regimen co-administration to treat invasive aspergillosis in an hiv-infected patient. *J Antimicrob Chemother*. 2016; **71**: 1125-1127.

723 Utili R, Zampino R, De Vivo F, et al. Improved outcome of pulmonary aspergillosis in heart transplant recipients with early diagnosis and itraconazole treatment. *Clin Transplant*. 2000; **14**: 282-286.

724 Husain S, Capitano B, Corcoran T, et al. Intrapulmonary disposition of amphotericin b after aerosolized delivery of amphotericin b lipid complex (abelcet; ablc) in lung transplant recipients. *Transplantation*. 2010; **90**: 1215-1219.

725 Mucha K, Foroncewicz B, Orlowski T, et al. Atypical presentation of invasive pulmonary aspergillosis in a liver transplant recipient. *Ann Transplant*. 2013; **18**: 238-242.

726 Lopez-Medrano F, Fernandez-Ruiz M, Silva JT, et al. Clinical presentation and determinants of mortality of invasive pulmonary aspergillosis in kidney transplant recipients: A multinational cohort study. *Am J Transplant*. 2016; **16**: 3220-3234.

727 Kleinberg M. Aspergillosis in the clear outcomes trial: Working toward a real-world clinical perspective. *Medical mycology*. 2005; **43 Suppl 1**: S289-294.

728 Linden PK, Coley K, Fontes P, Fung JJ, Kusne S. Invasive aspergillosis in liver transplant recipients: Outcome comparison of therapy with amphotericin b lipid complex and a historical cohort treated with conventional amphotericin b. *Clin Infect Dis*. 2003; **37**: 17-25.

729 Walter J, Sobottka I, Rogiers X, Broering D, Fischer L. Invasive aspergillosis caused by aspergillus terreus in a living donor liver transplant recipient successfully treated by caspofungin. *Mycoses*. 2011; **54**: e220-222.

730 Aguilar-Guisado M, Givalda J, Ussetti P, et al. Pneumonia after lung transplantation in the resitra cohort: A multicenter prospective study. *Am J Transplant*. 2007; **7**: 1989-1996.

731 Neoh CF, Snell GI, Levvey B, et al. Preemptive treatment with voriconazole in lung transplant recipients. *Transpl Infect Dis*. 2013; **15**: 344-353.

732 Drew RH, Dodds Ashley E, Benjamin DK, Jr., Duane Davis R, Palmer SM, Perfect JR. Comparative safety of amphotericin b lipid complex and amphotericin b deoxycholate as aerosolized antifungal prophylaxis in lung-transplant recipients. *Transplantation*. 2004; **77**: 232-237.

733 Monforte V, Ussetti P, Gavalda J, et al. Feasibility, tolerability, and outcomes of nebulized liposomal amphotericin b for aspergillus infection prevention in lung transplantation. *J Heart Lung Transplant*. 2010; **29**: 523-530.

734 Monforte V, Lopez-Sanchez A, Zurbano F, et al. Prophylaxis with nebulized liposomal amphotericin b for aspergillus infection in lung transplant patients does not cause changes in the lipid content of pulmonary surfactant. *J Heart Lung Transplant*. 2013; **32**: 313-319.

735 Borro JM, Sole A, de la Torre M, et al. Efficiency and safety of inhaled amphotericin b lipid complex (abelcet) in the prophylaxis of invasive fungal infections following lung transplantation. *Transplant Proc*. 2008; **40**: 3090-3093.

736 Williams K, Mansh M, Chin-Hong P, Singer J, Arron ST. Voriconazole-associated cutaneous malignancy: A literature review on photocarcinogenesis in organ transplant recipients. *Clin Infect Dis*. 2014; **58**: 997-1002.

737 Montoya JG, Chaparro SV, Celis D, et al. Invasive aspergillosis in the setting of cardiac transplantation. *Clin Infect Dis*. 2003; **37 Suppl 3**: S281-292.

738 Paniagua Martin MJ, Marzoa Rivas R, Barge Caballero E, et al. Efficacy and tolerance of different types of prophylaxis for prevention of early aspergillosis after heart transplantation. *Transplant Proc*. 2010; **42**: 3014-3016.

739 Singh N, Paterson DL, Gayowski T, Wagener MM, Marino IR. Preemptive prophylaxis with a lipid preparation of amphotericin b for invasive fungal infections in liver transplant recipients requiring renal replacement therapy. *Transplantation*. 2001; **71**: 910-913.

740 Castroagudin JF, Ponton C, Bustamante M, et al. Prospective interventional study to evaluate the efficacy and safety of liposomal amphotericin b as prophylaxis of fungal infections in high-risk liver transplant recipients. *Transplant Proc*. 2005; **37**: 3965-3967.

741 Reed A, Herndon JB, Ersoz N, et al. Effect of prophylaxis on fungal infection and costs for high-risk liver transplant recipients. *Liver Transpl*. 2007; **13**: 1743-1750.

742 Fortun J, Martin-Davila P, Montejo M, et al. Prophylaxis with caspofungin for invasive fungal infections in high-risk liver transplant recipients. *Transplantation*. 2009; **87**: 424-435.

743 Chakrabarti A, Sethi S, Raman DS, Behera D. Eight-year study of allergic bronchopulmonary aspergillosis in an indian teaching hospital. *Mycoses*. 2002; **45**: 295-299.

744 Tashiro T, Izumikawa K, Tashiro M, et al. A case series of chronic necrotizing pulmonary aspergillosis and a new proposal. *Jpn J Infect Dis*. 2013; **66**: 312-316.

745 Dupont B. Itraconazole therapy in aspergillosis: Study in 49 patients. *J Am Acad Dermatol*. 1990; **23**: 607-614.

746 Sambatakou H, Dupont B, Lode H, Denning DW. Voriconazole treatment for subacute invasive and chronic pulmonary aspergillosis. *The American journal of medicine*. 2006; **119**: 527 e517-524.

747 Saito T, Fujiuchi S, Tao Y, et al. Efficacy and safety of voriconazole in the treatment of chronic pulmonary aspergillosis: Experience in japan. *Infection*. 2012; **40**: 661-667.

748 Felton TW, Baxter C, Moore CB, Roberts SA, Hope WW, Denning DW. Efficacy and safety of posaconazole for chronic pulmonary aspergillosis. *Clin Infect Dis*. 2010; **51**: 1383-1391.

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