Review Article

Invasive Fungal Infection

New Treatments to Meet New Challenges

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Summary

Background: The incidence of invasive fungal infection is approximately 6 cases per 100 000 persons per year. It is estimated that only half of such infections are detected during the patient's lifetime, making this one of the more common overlooked causes of death in intensive-care patients. The low detection rate is due in part to the complexity of the diagnostic work-up, in which the clinical, radiological, and microbiological findings must be considered. Fungi with resistance to antimycotic drugs have been found to be on the rise around the world.

Methods: This review is based on pertinent publications retrieved from a selective search in PubMed, with special attention to guidelines on the diagnosis and treatment of invasive fungal infections caused by *Candida* spp., *Aspergillus* spp., *Mucorales*, and *Fusarium* spp.

Results: The clinical risk factors for invasive fungal infection include, among others, congenital immune deficiency, protracted (>10 days) marked granulocytopenia ($<0.5 \times 10^9/L$), allogeneic stem-cell transplantation, and treatment with immunosuppressive drugs or corticosteroids. High-risk groups include patients in intensive care and those with structural pulmonary disease and/or complicated influenza. The first line of treatment, supported by the findings of randomized clinical trials, consists of echinocandins for infections with *Candida* spp. (candidemia response rates: 75.6% for anidulafungin vs. 60.2% for fluconazole) and azole antimycotic drugs for infections with *Aspergillus* spp. (response rates: 52.8% for voriconazole vs. 31.6% for conventional amphotericin B). The recommended first-line treatment also depends on the local epidemiology. This challenge should be met by interdisciplinary collaboration. Therapeutic decision-making should also take account of the often severe undesired effects of antimycotic drugs (including impairment of hepatic and/or renal function) and the numerous interactions that some of them have with other drugs.

Conclusion: Invasive fungal infections are often overlooked in routine hospital care. They should be incorporated into antimicrobial stewardship programs as an essential component. There is also a pressing need for the development of new classes of antimycotic drug.

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Since the start of the new millennium, fungal infections have drastically increased in different ecosystems (1). Bat populations in North America have undergone a 70% reduction as a result of fungal infections; several species of amphibians have become extinct (e1, e2). Overall no group of microorganisms causes species extinction as frequently as fungi (1). Fungal infections are also among the most important causes for crop failures (e3). In spite of this ecological relevance, invasive fungal infections in humans are rare.

Epidemiology

According to estimates, more than 10% of Germany's population is affected by fungal infections. Superficial skin and nail mycoses are most common in this setting. Data on life-threatening infections are lacking, and valid conclusions can therefore not be drawn (2). On the basis of discharge diagnoses, in France the total

incidence of invasive fungal infections has been found to be 5.9/100 000 cases/year, with a mortality of 27.6%. Both the incidence and mortality increased during the observation period (2001–2010) (3).

Yeasts of the *Candida* genus are the most common pathogens causing invasive fungal infections in Germany (2). They are responsible for a relevant proportion of all nosocomial bloodstream infections. According to data from the German nosocomial infection surveillance system (*Krankenhaus-Infektions-Surveillance-System*, KISS), 6.5% of bloodstream infections in intensive care wards are caused by this pathogen (4) (*Table 1*). Apart from *Candida albicans*, *Candida glabrata* is most commonly implicated (e4).

Infections with *Aspergillus* spp. are the most common mold infections in Germany. They mostly occur in patients with cell-mediated immune defects

(Table 1) (2). Review articles of autopsy studies showed that invasive aspergillosis is one of the most commonly overlooked diagnoses and that according to estimates, only about half of all invasive fungal infections are diagnosed pre-death (5, 6) (Table 1). In addition to *Aspergillus fumigatus* (>80%) other species have been found in locally varying but clearly lower numbers. Determining the species is relevant because of partly varying resistance profiles.

Different pathogens from the large group of Mucorales, as well as *Fusarium* spp., rarely cause invasive infections, but always present a therapeutic challenge because of numerous resistances. It is not possible to give data on case numbers as these infections are very rare. *Fusarium* spp. are also the most common pathogens causing fungal keratitis, which in about half of all affected patients has severe sequelae, including the loss of the affected eye (in 3 out of 15 cases in a German case series) (7). Furthermore, there are numerous descriptions of invasive fungal infections caused by rare or undescribed pathogens. In 2018, the National Reference Center for Invasive Fungal Infections (*Nationales Referenzzentrum für invasive Mykosen*, NRZMyk) documented some 80 different species obtained from clinical specimens. The present article focuses on invasive infections caused by *Candida* spp., aspergillosis, mucormycosis, and fusariosis as the most common invasive fungal infections in Germany. Because of the particularities of the treatment, we exempted *Pneumocystis jirovecii* from this study. The same holds true for *Cryptococcus neoformans*, a pathogen that is highly prevalent especially in Africa, but occurs only very rarely in Germany (e5).

The therapeutic challenges associated with invasive fungal infections have changed over the past 20 years (8):

- Since the mid-1990s, *Aspergillus fumigatus* isolates with resistance to azoles have been increasingly identified. Azole-resistant isolates have also been identified in Germany and at individual centers were responsible for a substantial proportion of invasive infections (9).
- With the increased use of echinocandins, resistant *Candida* isolates started to be seen worldwide (e6).
- Since 2009, the new species *Candida auris* has spread globally. Nosocomial transmissions of this pathogen have caused institutions of the public health-care system to issue warnings (e7).

New therapeutic options have become available to meet these challenges. Since the start of the new millennium, the portfolio of antimycotics has expanded (eFigure 2). For the fungal infections that are the subject of this review article, three main classes of substance are available: polyenes, azoles, and echinocandins (eFigure 3). In this article, the authors aim to provide—on the basis of the recent literature and guidelines—an overview of the diagnostic evaluation and therapy of invasive fungal infections.

Diagnostic evaluation

The safe and early diagnosis of invasive fungal infections is the central challenge in routine clinical practice and forms the crucial basis for targeted treatment (10–17). The diagnosis of an invasive fungal infection is based on three elements: the clinical examination, imaging, and confirmation/proof of the causative agent.

The clinical diagnostic criteria for invasive fungal infections were defined by an international working group (the EORTC/MSG Study Group). These criteria selectively apply to immunosuppressed patients and were conceived primarily for clinical studies (18). In addition to congenital immunodeficiencies (Table 1), the relevant clinical risk factors include:

- Prolonged (>10 days) deep granulocytopenia ($<0.55 \times 10^9/L$)
- Allogeneic stem cell transplantation
- Medication-induced immunosuppression, or
- Treatment with prednisone (the equivalent of at least 0.3 mg/kg/d for a minimum of 3 weeks).

This list is by no means complete and excludes important but less well-defined risk groups. Examples include patients in intensive care wards, patients with structural lung disease, and patients with severe influenza (Table 1) (19, 20).

Tomography imaging yields crucial clues (eFigure 1). Infections of the respiratory tract require computed tomography (CT), neurological infections require magnetic resonance imaging (MRI), and abdominal infections require CT or MRI scanning in order to identify abscesses that are characteristic for the special variety of hepatolienal candidiasis. Abdominal infections can also be visualized by using sonography.

Where a diagnosis is suspected, the next step will be confirmation of the pathogen (eTable 1). Bloodstream infections with *Candida* spp. are almost exclusively confirmed by blood cultures. The identification of *Candida* in specimens taken from the respiratory tract does not indicate an invasive infection (21); for other, non-sterile specimens, a decision always has to be made on the basis of the individual clinical situation as to whether it is a case of colonization or a clinically relevant situation. Because of their wide environmental spread, the confirmation of molds from physiologically non-sterile material should be interpreted with caution; this is also the case for all specimens from the respiratory tract.

For serological diagnostic evaluation, *Candida* antigen/antibody confirmation is not recommended in current guidelines because of the lack of pertinent studies. Beta D-glucan (BDG) is not specific for *Candida*, but it does indicate an invasive fungal infection. A patient's risk profile, symptoms, and imaging results will narrow down this differential diagnosis, however. The sensitivity and specificity of this marker vary substantially between different patient populations and depend on the test system used

TABLE 1

Epidemiology of the most important invasive fungal infections in Germany (Candida, Aspergillus)

	Invasive candidosis/candidiasis	Invasive aspergillosis
Pathogen	Candida spp. (<i>C. albicans</i> , <i>C. glabrata</i> , <i>C. parapsilosis</i> , <i>C. dubliniensis</i> , <i>C. krusei</i> , and others)	Aspergillus spp. (<i>A. fumigatus</i> , <i>A. flavus</i> , <i>A. terreus</i> , and others)
Invasive infections in Germany	2000–12 000 p. a.* ¹	1000–5000 p. a.* ¹
Infection source	Endogenous infection, triggered by (e.g. gastrointestinal) colonization, biofilms	Exogenous infection, inhalation of conidia from the environment
Person to person transmission	Very rare, except for <i>Candida auris</i> (e7)	No person to person transmission* ²
Risk factors		
Underlying condition/illness	• Hematological neoplasm (38) • Intensive care patients after abdominal surgery (especially after failed anastomosis) (38) • Acute necrotizing pancreatitis (38) • Organ transplantation (liver, heart, kidney, and others) (e25) • HIV (not adequately treated) (14)	• Acute myeloid leukemia (e26) • Acute lymphatic leukemia (e26) • Allogeneic stem cell transplantation (18) • Organ transplantation (lung, heart, liver) (e25, e27)
Performance status*³	–	• Poor performance status (e28)
Comorbidity	• Premature birth (38) • Esophagitis in chemotherapy patients (e28) • Requiring dialysis (38)	• Chronic obstructive pulmonary disease (COPD) (20) • Esophagitis after chemotherapy (e28) • Severe influenza/pneumonia (19)
Environmental factors	• Colonization with <i>Candida</i> spp. (e29)	• Building/renovating works (e26, e28) • Smoking (e26) • Increased exposure (e26)
Iatrogenic	• Central venous catheter, parenteral nutrition (38) • Steroid therapy (prednisone equivalent of at least 0.3 mg/kg/d for at least 3 weeks) (18) • Long-term stay in intensive care ward (38) • Broad spectrum antibiotic pre-treatment (38)	• Neutropenia $<0.5 \times 10^9/L$ over >10 days (18) • Steroid therapy (prednisone equivalent of at least 0.3 mg/kg/d over at least 3 weeks) (18)
Congenital immunodeficiencies/genetic risk factors	• Defects in the Th17-T-cell response (e30) • Defects in the Dectin-1 signaling pathway (e30) • Risk genotypes described for toll-like receptors TLR1, TLR4, interleukin IL-4, interferon IFN-gamma signaling pathway, CD58, LCE4A-C1orf68, TAGAP (e30–e31)	• Chronic granulomatosis (e32) • MonoMAC syndrome (e29) • Risk genotypes described for toll-like receptors TLR4, interleukins IL-1, IL-10, chemokine CXCL10, pentraxin PTX3, Dectin-1, plasminogen (39) (e30, e33)

*¹ The number of invasive fungal infections per year (p. a.) was estimated as follows: as the lower limit we determined the case numbers for Germany on the basis of the incidence found by Bitar et al 2014 (3) (population 2017: 82 790 000) (rounded down to 1000). The reported upper limits are based on the case numbers established in (2) and were rounded up to 1000.

*² Individual cases of potential transmission have been described. These occurred in atypical infections with *A. fumigatus*, in which conidia developed owing to exposure of the pathogen to environmental air (eg, cutaneous aspergillosis) (e34–35)

*³ As the measure for patients' impairment in terms of daily routine tasks defined according to the Eastern Cooperative Oncology Group (e36)

(e8–e10). To confirm *A. fumigatus*, galactomannan (“aspergillus antigen”) is available—in addition to BDG—which can be determined from serum and bronchial secretions (and, if applicable, cerebrospinal fluid). The sensitivity for serum is about 78%, the specificity is 85%, depending on the cut-off value and the patient population (22). To confirm invasive aspergillosis, furthermore, reference protocols for molecular diagnostics have been developed that function as examples for molecular diagnostic evaluation of infections and, in combination with other methods, contribute to improved diagnostics (23–25).

Resistances and testing for resistance

In recent years, increasing rates of resistant pathogens have been confirmed worldwide. In *Candida* spp., acquired echinocandin resistance now occurs, in addi-

tion to the long familiar fluconazole resistance (at least in *Candida glabrata*). In Denmark, the rates of resistant *C. glabrata* from blood cultures rose from 0.9% (2008/2009) to 3.1% (2012/2013) (e6). In the US, resistant *C. glabrata* is already much more common; one center posted a rise in the resistance rate from 4.9% in 2001 to 12.3% in 2010 (e11). In Germany, such strains are currently still rare. Because of lacking data, concrete resistance rates cannot be reliably determined. Most guidelines, meanwhile, are recommending testing all “clinically relevant” isolates of *Candida* spp. for sensitivity/susceptibility to azoles. For echinocandins, EUC-AST recommends because of the lacking reproducibility of the caspofungin test to test only for anidulafungin or micafungin. If the isolate proves susceptible to these two substances on testing, treatment can also consist of administering caspofungin.

TABLE 2

Antimycotics used in the therapy of invasive fungal infections

Class	Substance	Candida				Aspergillus			Mucorales			Application			Interactions/ *†	Common adverse effects*†	Treatment of neurological infections	Dosage (i. v.)	Licensed/recommended indications								
		albicans	dubliniensis	glabrata	krusei	parapsilosis	fumigatus	flavus	terreus	Lichtheimia spp.	Mucor spp.	Rhizopus spp.	Fusarium spp.	i. v.					p.o.	Other	Prophylaxis Aspergillus	Prophylaxis Candida	Therapy Aspergillus	Therapy Candida	Therapy: other fungal species	Empirical treatment	
Azoles	Fluconazole	R	R	R	R	R	R	R	R	R	R	R	+	+	Local	Common, CYP450 inhibition (2C9, 2C19, 3A4)	≥ 1/10 headache, gastrointestinal symptoms, raised liver enzymes	●	400–800 mg	●	●	●	●	●	●	●	●
	Itraconazole	R	R	R	R	R	R	R	R	R	R	R	+*2	+	---	Common, CYP450 inhibition (3A4), CYP450 substrate (3A4)	≥ 1/100–<1/10 gastrointestinal symptoms, skin rash	●		●	●	●	●	●	●	●	
	Isavuconazole	R	R	R	R	R	R	R	R	R	R	●	+	+	---	Common, CYP450 inhibition (3A4), CYP450 substrate (3A4)	≥ 1/100 to <1/10 hypokalemia, headache, somnolence, gastrointestinal symptoms, raised liver enzymes, skin rash	●	Day 1+2: 200 mg every 8 h i.v., then 200 mg every 24 h	●		●	●	●	●	●	
	Posaconazole	R	R	R	R	R	R	R	R	R	R	●	+	+	---	Common, CYP450 inhibition (3A4)	≥ 1/100 to <1/10 gastrointestinal symptoms, hypokalemia, paresthesias, dizziness, somnolence, headache, raised liver enzymes, skin rash	●	Day 1: 300 mg every 12 h, then 300 mg every 24 h, TDM	●	●	●	●	●	●	●	
	Voriconazole	R	R	R	R	R	R	R	R	R	R	●	+	+	Local, intraocular	Common, CYP450 inhibition (2B6, 2C9, 3A4), CYP450 substrate (2C19)	≥ 1/10 headache, impaired vision, gastrointestinal symptoms, raised liver enzymes, skin rash, ≥ 1/100 to <1/10 hallucinations	●	Day 1: 6 mg/kg/d every 12 h, then 4 mg/kg/d, TDM	●	S	S	S	S	●	●	●

Class	Substance	Candida				Aspergillus				Mucorales		Application			Interactions/ *†	Common adverse effects*†	Treatment of neurological infections	Dosage (i. v.)	Licensed/recommended indications									
		albicans	dubliniensis	glabrata	krusei	parapsilosis	fumigatus	flavus	terreus	Lichtheimia spp.	Mucor spp.	Rhizopus spp.	Fusarium spp.	i. v.					p. o.	Other	Propylaxis Aspergillus	Propylaxis Candida	Therapy Aspergillus	Therapy Candida	Therapy: other fungal species	Empirical treatment		
Polyenes	Liposomal Amphotericin B	●	●	●	●	●	●	●	●	●	●	●	●	+	-	Local, intraocular, intrathecal, nebulized	No	≥ 1/10 hypokalemia, gastrointestinal symptoms ≥ 1/100 to <1/10 electrolyte imbalances, headache, tachycardia, hypotension, dyspnea, raised liver enzymes, skin rash, backache, raised creatinine levels	●	3–10 mg/kg	●	●	●	●	●	●	●	●
Echinocandins	Anidulafungin	●	●	●	●	●	●	●	●	●	●	●	+	-	---	No	≥ 1/10 hypokalemia, gastrointestinal symptoms ≥ 1/100 to <1/10 headache, hypotension, hypertension, raised liver enzymes, skin rash	●	Day 1: 200 mg, then 100 mg every 24 h	●	●	●	●	●	●	●	●	●
	Caspofungin	●	●	●	●	●	●	●	●	●	●	●	+	-	---	No	≥ 1/100 to <1/10 hypokalemia, headache, gastrointestinal symptoms, raised liver enzymes, skin rash	●	Day 1: 70 mg, then 50 mg every 24 h for KG <80 kg; otherwise 70 mg every 24 h	●	●	●	S	●	●	●	●	
	Micafungin	●	●	●	●	●	●	●	●	●	●	●	+	-	---	No	≥ 1/100 to <1/10 hypokalemia, headache, gastrointestinal symptoms, raised liver enzymes, skin rash, changes to blood count	●	100 mg every 24 h	●	●	S	●	●	●	●	●	

Effectiveness spectrum: green – usually effective, yellow – limited effectiveness, red – usually not effective; R – (acquired) relevant resistances, K – use only on the context of combination therapies.

Suitable for treating neurological infections: green – medication of choice for treating CNS infections, yellow – limited recommendation/lacking data for treating CNS infections, red – not suitable to treat CNS infections.

Dosage: We include a range of standard dosages. A therapeutic dose should be chosen individually and cannot be deduced from this table. TDMI: therapeutic drug monitoring is recommended.

Licensed indications: green – licensed for this indication, red – not licensed for this indication and/or not recommended, S – the license is restricted to certain patient populations.

*† For reasons of space, this table shows only selected drug interactions and adverse effects. A more detailed list can be found in the relevant specialist information.

*2 Intravenous application of itraconazole not universally available in Germany.

Since the 1990s, azole-resistant strains of *A. fumigatus* have been described in particular in the Netherlands and in Great Britain (26). The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommends testing for resistance to azole antimycotics (16). Overall, we hold that resistance in Germany is currently not a problem. However, raised resistance rates have been found in patients with cystic fibrosis who were chronically colonized with *A. fumigatus* (e12). Only where rates of azole resistant *A. fumigatus* have increased locally, consideration should be given to whether, until a susceptible pathogen has been confirmed, a treatment should be selected that includes strains with azole resistance. In Essen, Germany, for example, a resistance rate of 30% in cases of invasive aspergillosis was found in isolates of *A. fumigatus* that were detected on culture (9). A recent Dutch guideline recommends—in view of the high rates of azole resistant *A. fumigatus* in the Netherlands (12.9%)—for the first time treatment with a combination of voriconazole and either echinocandin or liposomal amphotericin B (L-AmB) until sensitivity/susceptibility has been confirmed (e13).

Systemic therapy

Principles

Depending on the indication, a choice needs to be made between prophylactic treatment, empirical treatment, or pre-emptive treatment. Antimycotic prophylaxis is recommended primarily for hematology/oncology patients (27). After allogeneic stem cell transplantation, prophylaxis against yeasts is usually sufficient. By contrast, a high-risk constellation—such as granulocytopenia after myelosuppressive induction therapy or graft-versus-host disease—requires prophylaxis that is effective against molds. Data for other patient populations are less clear-cut. For patients with complications after abdominal surgery, for patients requiring intensive care and who have relevant risk factors, and for patients who have undergone lung transplantation surgery, prophylaxis can make sense (12). However, these indications are not sufficiently supported by study results. Empirical therapy is used if an invasive fungal infection is suspected. The therapeutic approach described in the following section is based on confirmation of the pathogen and should follow available guidelines (eTable 2). Essentially, the main therapeutic options are substances from three classes of antimycotic drugs (Table 2).

Invasive *Candida* infection

Several guidelines are available to support the selection of treatment of invasive *Candida* infections (eTable 2). The therapeutic schemes depend on the underlying disease and organ involvement (12–14, 17, 28, 29). Determining the species is extremely important because of intrinsic resistance patterns (Table 2). In most clinical situations, echinocandins are the treatment of choice in adult patients. In a randomized study of the treatment of candidemia, anidulafungin was at least equivalent to fluconazole; a secondary analysis even found that it was

superior (response rate for fluconazole 60.2%, for anidulafungin 75.6%, difference 15.4% [95% confidence interval: 3.9; 27.0]). For this reason, fluconazole should be used only in patients without critical illness and at a high initial dosage (800 mg/d) (12). Fluconazole is, however, still relevant for oral treatment continuation after successful initial treatment with an echinocandin. L-AmB constitutes an alternative where resistance to other classes of substances is confirmed. Furthermore, L-AmB is important in treating chronically disseminated candidosis/candidiasis, endocarditis due to *Candida*, and in pediatric patients (12, 13). Voriconazole usually does not provide any additional benefits over fluconazole—with the exception of infection with *C. krusei* or where additionally a mold infection is suspected.

Candidemia should be treated for at least two weeks after the bloodstream infection has disappeared (28). The exact treatment duration can be defined only after follow-up blood cultures have been produced. In continuing symptoms or granulocytopenia, the treatment should be continued for longer. Chronically disseminated candidosis should be treated for a minimum of 8–12 weeks, and in some cases for several months, until the lesions have resolved (12, 14, 17, 28). Central venous catheters should be removed if at all possible. If this is not possible then the patient should be treated with an echinocandin or L-AmB, because of their effectiveness against biofilms *in vitro* (12, 14, 17, 28). Because of possible relocation of the pathogen into the eyes, funduscopy is recommended during intravenous therapy (12, 14, 17, 28).

Invasive aspergillosis

The prognosis for invasive aspergillosis has improved substantially over the past decade. The treatment of choice usually consists of the administration of voriconazole or isavuconazole. Both azoles are effective fungicides against *A. fumigatus* (16, 31, 32) (e14) (Table 2). In a randomized controlled study, voriconazole was superior to treatment with conventional amphotericin B (21.2% greater response [52.8% versus 31.6%], 95% confidence interval [10.4; 32.9]; longer survival rates for voriconazole (33). Voriconazole reaches effective concentrations even for neurological infections (Table 2) (e15). In a randomized controlled clinical trial of the treatment of invasive mold infections, isavuconazole was non-inferior to treatment with voriconazole (34). L-AmB is an alternative—after taking into consideration prior prophylactic administration of azoles (the class should be changed), comorbidities, resistance of the pathogen, medication interactions, and local epidemiology. L-AmB is also recommended for initial therapy if co-infection with *Mucorales* is suspected. The value of combination therapy (for example, using voriconazole plus echinocandin) is unclear (e16). In addition to systemic administration, local instillation of L-AmB may make sense, for example in aspergillosis of the central nervous system (e17). In all cases, surgical treatment should be considered in addition to medication treatment (16, 31). Supportive measures

include the administration of granulocyte colony stimulating factor (G-CSF) or, in long-term granulocytopenia, granulocyte transfusions (16, 31).

The duration of treatment depends on the patient's individual clinical development while taking into account the type and extent of immunosuppression (16); it usually takes about 6–12 weeks (31). Radiological checkups make sense, but the guidelines currently do not provide any indication of optimal time points (35). After the start of the treatment and especially after granulocyte levels have risen in patients with neutropenia, the radiological imaging will usually show an increase in lesion size. But a week after the start of therapy, lesions should not enlarge any more but can be expected to shrink until day 14 (35). In order to undertake these checkups, serial CT scans at the start of therapy and one and two weeks subsequently are our current recommendation. Changes to the galactomannan titer during treatment also provide information about the course (e18).

Rare invasive mycoses

No randomized controlled trials exist of the treatment of invasive mycoses caused by rare pathogens. Therapy is guided by the broad spectrum effectiveness of the antimycotics and by case series (Table 2). Mycormycoses are caused by a large group of different pathogens with different sensitivity/susceptibility profiles. To treat these, L-AmB (at a minimum dosage of 5 mg/kg; 10 mg/kg if the central nervous system is affected) and azoles with effectiveness against Mucorales (isavuconazole, posaconazole) are the medications of choice (11). The surgical resection of infected tissue is an essential component of the therapeutic concept (11).

Invasive infections with *Fusarium* spp. should be treated with voriconazole or L-AmB—in combination until the results of sensitivity/susceptibility testing become available—with posaconazole available as second-line treatment (15). Surgical removal of infected tissue should be considered, and possible immunosuppression should be lowered. Keratitis caused by *Fusarium* spp. requires local therapy using natamycin (eye-drops 5%) and systemic therapy with voriconazole (e19–e21). A Cochrane review found that local therapy with natamycin 5% was superior to other treatments (36). The benefits of systemic treatment with voriconazole was shown in a randomized controlled clinical trial (e20). In spite of antimycotic therapy, penetrating keratoplasty will be required in many cases (for example, in two thirds of cases in [7]). Individual guidelines also comment on the treatment of further, rare pathogens (10, 15). The search engine www.FungiQuest.net provides a web based tool that lists case histories for extremely rare invasive mycoses. However, this cannot be a substitute for expert consultation.

Conclusions and outlook

The number and heterogeneity of patients at risk for invasive fungal infections have increased. For example, the number of stem cell transplantations in Europe

Key messages

- Invasive fungal infections present an often underrated risk for hospital inpatients or patients under immunosuppression.
- The diagnosis of an invasive fungal infection presents a clinical challenge and requires interdisciplinary collaboration; clinical, radiological, and microbiological findings have to be considered.
- Because of the development of resistance to important classes of antimycotics, cultures of the pathogen and species differentiation should always be performed and susceptibility testing should be aimed for.
- New substances from the azole and echinocandin groups provide additional therapeutic options.
- Because of the complicated diagnostics and the complex treatment, antimycotic therapy should be selected in cooperation with experienced specialists, and the therapy of fungal infections should be firmly anchored in antimicrobial stewardship programs.

almost doubled between 2000 and 2016 (e22, e23). At the same time, new at-risk populations were identified—examples include hospital inpatients with severe influenza or chronic obstructive pulmonary disease (19, 20). The emergence of new and/or resistant pathogens is matched by a growing repertoire of antimycotics. Antimycotic treatment needs to be initiated more frequently, and the selection of the optimal therapeutic strategy has become more complex. Additional classes of antimycotics are therefore well overdue (37) (e24). These trends have added to the challenges for mycological diagnostics, for example with regard to resistance testing. The treatment of fungal infections should be anchored in antimicrobial stewardship programs. Resistance development in fungal pathogens will need to be integrated into national action plans, such as the German Antimicrobial Resistance Strategy (*Deutsche Antibiotika Resistenzstrategie*, DART). Restricting such programs to bacterial infections means enabling the further spread of resistance to antimycotics.

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Figure 1: Tomography in the diagnostic evaluation of invasive fungal infections

Tomography can provide important pointers of an invasive fungal infection: a) nodular infiltrate with surrounding halo in invasive pulmonary aspergillosis in a patient with granulocytopenia (arrow); b) invasive pulmonary aspergillosis in granulocytopenia (the same patient as in a), luftschicht sign as an indicator of responsiveness to treatment (arrow); c) inverse halo sign in mucormycosis (arrow); d) Aspergilloma in a preformed cavity of unclear origin (arrow); e) multiple abscesses in liver and spleen in chronic disseminated candidiasis; f) bilateral sinusitis owing to Mucorales (*Lichtheimia corymbifera*).

Years in which available antimycotics were licensed for treating invasive fungal infections

eFIGURE 3

Antimycotics for the treatment of invasive fungal infections

Three main classes of antimycotics are mainly used for treating invasive fungal infections: polyenes, azoles, and echinocandins.

Polyenes

Amphotericin B, nowadays primarily given as a liposomal formulation (L-AmB), is the only polyene that can be applied systemically. L-AmB interacts with ergosterol and has a fungicidal effect thanks to extramembranous agglomeration and/or pore formation (e37). L-AmB has broad-spectrum effectiveness; acquired resistance is rare. A disadvantage is its toxicity—especially nephrotoxicity—which results in large numbers of adverse effects and discontinuation of treatment (for example, severe adverse effects in 24.3% of treated patients in (33)).

Azoles

Azole antimycotics inhibit the cytochrome P-450-mediated biosynthesis of ergosterol. All azoles are characterized by good to very good oral bioavailability. Their fungicidal effect is due to secondary effects that result in destruction of the fungal cell membrane (40). Their effectiveness vis-à-vis different fungal species differs for the different substances (Table 2). Azole antimycotics have hepatotoxic effects and also inhibit human CYP450 enzymes (especially CYP3A4), which triggers a large number of medication interactions.

Echinocandins

All echinocandins are identical in their effectiveness spectrum and inhibit cell wall biosynthesis by blocking the (1→3)-β-D-glucan-synthase (GS). Echinocandins are usually well-tolerated and have a lower potential for interactions with other medications. Sufficiently high therapeutic concentrations are reached except in urine and central nervous system.

In rare cases, **flucytosine** is used in combination therapies with other antimycotics. This substance is deaminated in fungal cells and inhibits the biosynthesis of nucleic acid..

eTABLE 1

Diagnosing invasive fungal infections

	Microscopy		Culture		Serological methods			Molecular approaches	Imaging
	Method	Comment	Method	Comment	BDG ^{*,1}	GM ^{*,2}	Comment		
Candida	Direct, histology	C albicans develops filamentous forms, in contrast to other species	Standard mycological culture, blood culture	Sensitivity of blood culture <50%	+	-	BDG test not specific	Insufficient study data; new method (T2 Candida) positively evaluated in the USA (e38)	Abdominal infections (hepatolienal candidiasis): sonography or MRI ^{*,4}
Aspergillus	Direct, histology	No safe differentiation from other hyphomycetes	Standard mycological culture,	Confirmation on culture mostly not successful	+	+	BDG test not specific, GM screening not in effective antimycotic prophylaxis	EAPCRI ^{*,3} reference protocols available (23)	Respiratory tract: CT ^{*,5} diagnostics, neurological infections: MRI (cf eFigure 1)
Mucorales	Direct, histology		Standard mycological culture,	-	-	-	No serological diagnosis possible	No standardized molecular diagnostics	Respiratory tract: CT ^{*,5} diagnostics (cf eFigure 1)
Fusarium	Direct, histology		Standard mycological culture, blood culture	-	+	(+)	No specific serological diagnosis possible, BDG may yield positive result, GM may yield positive result	No standardized molecular diagnostics	Respiratory tract: CT ^{*,5} diagnostics, neurological infections: MRI
	In-vivo confocal microscopy (eye/cornea) (e39, e40)	Differentiation between bacterial-, mycotic and amoebic keratitis							

*BDG = beta-D-glucan, ²GM = galactomannan, ³EAPCRI = European Aspergillus PCR initiative, ⁴MRI = magnetic resonance imaging, ⁵CT = computed tomography

eTABLE 2

Selected guidelines for invasive fungal infections

Organization	Patients	Diagnostics	Therapy	Reference
Candida infections				
ESCMID	Pediatric patients	+	+	(13)
ESCMID	Hematological patients and und HSCT	+	+	(17)
ESCMID	Patients with HIV infection	+	+	(14)
ESCMID	Adults without neutropenia	+	+	(12)
IDSA	All	+	+	(28)
DMyKG/PEG	All	+	+	(29)
Aspergillus infections				
ESCMID/ECMM/ERS	All	+	+	(16)
IDSA	All	+	+	(31)
ECIL-6	HSCT	–	+	(e14)
AGIHO/DGHO	Oncological patients	–	+	(32)
Rare mycoses				
ESCMID/ECMM	All (mucormycoses)	+	+	(11)
ESCMID/ECMM	All (Fusarium- and hyalohypho-mycoses)	+	+	(15)

ESCMID, European Society for Clinical Microbiology and Infectious Diseases; IDSA, Infectious Diseases Society of America;

DMyKG, *Deutschsprachige Mykologische Gesellschaft* [German-speaking mycology society];

PEG, *Paul Ehrlich Gesellschaft für Chemotherapie* [society for chemotherapy]; ECMM, European Confederation of Medical Mycology; ERS, European Respiratory Society;

ECIL, European Conference on Infections in Leukaemia; AGIHO, *Arbeitsgemeinschaft für Infektionen in der Hämatologie und Onkologie* [working group for infections in hematology and oncology];

DGHO, German Society for Hematology and Medical Oncology; HSCT, hematopoietic stem cell transplantation