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Defining Breakthrough Invasive Fungal Infection– Position Paper of the Mycoses Study Group Education and Research Consortium (MSG-ERC) and the European Confederation of Medical Mycology (ECMM)

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Abstract

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Author contributions: Review, study selection and data extraction were performed separately for hematology (OAC, MH), intensive care (GRT, COM, SCAC, OAC, CLF), and solid-organ transplantation (SCAC, COM, GRT, CLF, MH). A draft proposal for definitions was developed by OAC, CLF, SCAC, MH, DPK, COM, and GRT, and was circulated within the two organizations. The authors addressed any comments received, and circulated the updated document again for final approval.

Breakthrough invasive fungal infections (IFI) have emerged as a significant problem in patients receiving systemic antifungals; however, consensus criteria for defining breakthrough IFI are missing. This position paper establishes broadly applicable definitions of breakthrough IFI for clinical research. Representatives of the Mycoses Study Group Education and Research Consortium (MSG-ERC) and the European Confederation of Medical Mycology (ECMM) reviewed the relevant English literature for definitions applied and published through 2018. A draft proposal for definitions was developed, and circulated to all members of the two organizations for comment and suggestions. The authors addressed comments received, and circulated the updated document for approval.

Breakthrough IFI was defined as any IFI occurring during exposure to an antifungal drug, including fungi outside the spectrum of activity of an antifungal. The time of breakthrough IFI was defined as the first attributable clinical sign or symptom, mycological finding or radiological feature. The period defining breakthrough IFI depends on pharmacokinetic properties and extends at least until one dosing interval after drug discontinuation. Persistent IFI describes IFI that is unchanged/stable since treatment initiation with ongoing need for antifungal therapy. It is distinct from refractory IFI, defined as progression of disease and therefore similar to non-response to treatment. Relapsed IFI occurs after treatment, and is caused by the same pathogen at the same site, although dissemination can occur.

These proposed definitions are intended to support the design of future clinical trials and epidemiological research in clinical mycology, with the ultimate goal of increasing the comparability of clinical trial results.

Keywords

Breakthrough; invasive fungal disease; aspergillosis; mucormycosis; treatment failure; relapse; persistence; refractoriness

Introduction

Major improvements have been achieved in the prophylaxis, treatment and outcome of invasive fungal infections (IFIs), however persistence, refractory disease, relapse or the development of breakthrough IFI continue to complicate antifungal treatment (Figure 1). Breakthrough IFIs in particular have emerged as a significant problem in patients receiving systemic antifungals [1–3]. In the absence of consensus criteria, definitions and classifications of breakthrough IFI vary widely between clinical trials. These differences complicate accurate comparisons between clinical trials and hinder epidemiologic interpretation.

Furthermore, differentiating breakthrough IFI from clinically unapparent, but pre-existing IFI prior to the initiation of antifungal therapy, is often difficult and involves accurate interpretation of individual host characteristics, laboratory and radiographic studies, and fungal and iatrogenic factors. These interpretations are further complicated by differences between neutropenic and non-neutropenic patients [4], impacting clinical presentation,

radiological findings and the performance of diagnostic assays [5]. Similarly, the differentiation of relapsing infection and reinfection remains challenging.

The European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSG-ERC) have recently released updated consensus definitions of proven, probable, and possible IFI for clinical trials [6, 7]. In brief, proven infection is defined as detection of fungal elements in normally sterile body sites. Proven IFI applies to patients regardless of their immune status and underlying disease, whereas probable and possible IFI require a host risk factor for development of disease (e.g., prolonged neutropenia). Since clinical, radiological, and mycological findings vary between host groups, the International Society for Heart and Lung Transplantation issued IFI consensus criteria for cardiothoracic solid organ transplantation (SOT) recipients [8]. Currently, the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), the European Confederation of Medical Mycology (ECMM) and MSG-ERC are developing consensus criteria for ICU patients (FUNDICU) [9]. The EORTC/MSG also proposed consensus definitions for treatment outcomes in clinical trials for highly immunocompromised patients [10]. These definitions of complete response and partial response to antifungal treatment, as well as treatment failure enabled comparability of endpoints in clinical trials on prophylaxis [11–15] and treatment of IFI [16, 17].

While consensus criteria for defining the presence of IFI are readily available, consensus definitions of persistent, refractory, relapsed, and breakthrough IFI are urgently needed to: (i) enable epidemiologic studies estimating the true burden of disease, (ii) facilitate comparisons between clinical studies, and (iii) guarantee fair assessments of antifungal drug and management strategies. Based on existing IFI definitions of our and other groups [6, 7, 9, 10] the goal of this position paper is to establish broadly applicable definitions of breakthrough, persistent, refractory, and relapsed IFI for use in clinical research.

Methods

Executives of the MSG-ERC and the ECMM selected a group of authors from Australia, Europe, and the United States. MSG-ERC comprises infectious diseases physicians with expertise in medical mycology and laboratory medical mycologists (www.msgerc.org); ECMM is the umbrella organization of 27 national mycological societies, comprised of one delegate from each of the 27 nations forming the ECMM council (www.ecmm.info) [18, 19]. Both organizations are collaboratively engaged in the design and conduct of clinical studies on IFI.

The authors searched PubMed for relevant English language articles on clinical studies of antifungal prophylaxis and treatment through December 2018. Search terms included “antifungal prophylaxis”, “antifungal treatment”, “breakthrough fungal infection”. The references of articles retrieved were reviewed for additional relevant reports. Study selection and data extraction were performed separately for hematology, intensive care, and solid-organ transplantation. The definitions of IFI and breakthrough IFI were abstracted from each relevant manuscript. There was no intent to grade the quality of the studies. The executive

committee reviewed each study and drafted recommendations for defining breakthrough IFI, as well as persistent, refractory, and relapsing IFI.

A draft proposal for definitions was developed, and was sent out by the respective presidents of both organizations to all members (MSG-ERC) / council-members (ECMM) for comments and suggestions. The authors addressed all comments received, and circulated the updated document again for final approval.

Recommendations/Position Statements

Review of the literature

Definitions used in clinical trials in hematology.—Most patients with underlying hematologic malignancy and, in particular those with acute leukemia, share neutropenia as the major risk factor for IFI and are thus a relatively homogeneous population to study. Non-neutropenic patients may still carry high risk to acquire IFI, in particular when treated with targeted antineoplastic drugs and immunosuppressive agents [20].

Prophylaxis.: In prophylaxis studies, it is especially important to define breakthrough IFI, as it typically represents the primary study endpoint. Current EORTC/MSG definitions are used to classify IFI [11, 12], however there is substantial variation in the definition of what constitutes breakthrough IFI. Importantly, the diagnosis of IFI often requires an assessment and correlation of patient symptoms, laboratory and radiographic results over several days increasing the difficulty in defining a precise day of breakthrough infection. The majority of clinical trials studying antifungal prophylaxis do not report how they addressed this issue [11–15, 21, 22]. Others used a clinical approach assigning breakthrough infection as the first day of patient symptoms consistent with fungal disease [23]. Some refer to the day of the first positive mycological test or radiographic finding consistent with IFI as confirmatory for breakthrough infection [24–27], whilst others require the presence of all necessary diagnostic criteria (host, clinical, microbiological) for diagnosis [28, 29] (Figure 2). Another area of substantial difficulty is the elapsed antifungal exposure time that separates pre-existing ("baseline") IFI from breakthrough IFI. Some studies do not report on this aspect [13, 15], while others refer to the beginning of chemotherapy [22]. The majority of studies reviewed, used a very early time point, such as the day of randomization, which frequently take place prior to the first antifungal dose [12, 14], at the day of first dose [11, 23, 25], day 3 [24, 26] or at day 7 [27, 29] after initiation of prophylaxis. Some of this variability may reflect PK/PD considerations of the drugs studied, including the time necessary to reach pharmacologic steady state (Table 3). Lastly, definitions describing the end of the period in which IFI are defined as breakthrough infections is inconsistent. Definitions include the end of neutropenia [22], or a precise duration of days, i.e. ≤7 days [12, 25], ≤15 days [23] or ≤30 days [21] post cessation of antifungal prophylaxis. A recent Italian consensus statement focusing on patients with acute myeloid leukemia receiving induction chemotherapy, defined breakthrough IFI as occurring from 7 days after initiation of prophylaxis until 7 days after discontinuation of prophylaxis [30].

Empiric treatment.: The same inconsistencies seen in antifungal prophylaxis trials are also applicable to empiric antifungal therapy trials. Empiric antifungal therapy is defined as

treatment in neutropenic patients who are persistently febrile despite broad-spectrum antibacterial therapy, in the absence of typical radiologic signs or mycological evidence for fungal infection. Most of these trials used the modified EORTC/MSG 2002 definitions [31–33] and the lack of uniform definitions for the day of breakthrough IFI onset and timeframes used to classify an IFI as breakthrough varied from day 1 [34] to day 3 [31] of initiation of empiric treatment until 7 days after cessation of treatment [31, 34].

Pre-emptive treatment.: Pre-emptive antifungal therapy is defined as treatment in patients with typical radiological signs and mycological evidence via direct or indirect markers of IFI (e.g., galactomannan). Diagnosis driven randomized controlled clinical trials [35–38], prospective [35, 39–41], and retrospective [42, 43] studies followed either the 2002 [7, 39–41, 43] or the 2008 EORTC/MSG criteria [6, 42]. Some studies introduced modifications of serum galactomannan optical density index use [36–38, 43]. Definitions of the day of diagnosis were not reported [35–43].

Targeted treatment.: Similarly, the large randomized controlled clinical trials published on targeted treatment of fungal infection in hematology patients did not define a day of diagnosis of breakthrough IFI [16, 44–46]. Some did not analyze separately those patients who had received prior prophylaxis or who were actually patients with breakthrough IFI from those with primary IFI [16, 17, 44].

Definitions used in clinical trials in intensive care units.—ICU patients frequently develop conditions consistent with severe immunosuppression placing them at increased risk for IFI [47]. After the initial pro-inflammatory phase, septic patients enter a period of relative immunosuppression. In addition, ICU patients frequently possess overlapping factors predisposing to IFI, e.g., recent antibiotic exposure, central venous catheters, parental nutrition, gastrointestinal procedures, and multiple comorbidities, for example malignancy, HIV, influenza, or emphysema requiring corticosteroid therapy [48, 49]. Despite the recognition of increased risk factors over the past few decades, it remains difficult to define which specific patient groups may benefit from targeted prophylaxis. Risk scoring systems have been developed and prospectively evaluated to determine their utility in predicting the development of invasive candidiasis [50–55]. Stratification of patients using these systems allows for early antifungal strategies, and/or through the utilization of newer diagnostic tests for pre-emptive antifungal therapy [5, 56–60].

Prophylaxis.: Randomized clinical trials evaluating fluconazole prophylaxis in ICU patients defined invasive candidiasis as histologically proven invasion or ≥1 positive culture from normally sterile body sites [61, 62]. In addition, these studies utilized a variety of other definitions ranging from intraabdominal peritonitis to urinary tract infection if $>10^5$ colony forming units of *Candida* were present in urinary specimens. Observation periods were from randomization until day 7 after end of study drug [62] or day 3 after discharge from ICU [61].

Empiric treatment.: Two randomized clinical trials evaluated empiric antifungal treatment [63, 64]. The definition of invasive candidiasis and candidemia was in line with current guidelines for proven infection [6, 65]. The period for the primary endpoint analysis

commenced on day 1 of empirical antifungal treatment and ended on either day 4 [63] or on day 28 [64] post treatment.

Pre-emptive treatment.: The single randomized study on pre-emptive treatment applied EORTC/MSG 2008 criteria for the definition of breakthrough infection. The period of assessment started with the first dose of study treatment and concluded on day 28 after end of treatment [66].

Targeted treatment.: Five large randomized clinical trials on treatment of candidemia and/or invasive candidiasis were evaluated [67–71]. None reported a definition of the day of diagnosis of a breakthrough infection [67–71]. In fact, one study did not explicitly define a breakthrough infection [71]. Some studies more recently have defined breakthrough infections as proven IFI by a species different from the baseline pathogen [67–69]. The observation time for such findings began at enrollment up to 72 hours thereafter, and ended at six [67, 68], or 12 [69] week follow-ups.

Definitions used in clinical trials in solid organ transplantation (SOT).—SOT recipients are a heterogeneous group, but many are at high risk of de novo IFI, and also of breakthrough infection. The individual risk is determined by epidemiological exposures and the qualitative net state of immunosuppression, often determined by the type of organ transplanted [72, 73].

Prophylaxis.: Antifungal prophylaxis is recommended for lung transplant recipients for the first 3–4 months after transplantation [74]. The course may be prolonged in those receiving more aggressive immunosuppressive regimens [75]. Few prospective trials have been performed to evaluate prophylaxis for other SOT recipients [75]. The majority of published studies do not explicitly state a definition of the day of diagnosis of breakthrough IFI [76–80]. Two studies defined the day of diagnosis as occurrence of the first sign of infection [81] and the day on which all necessary criteria were fulfilled [82], respectively. Study definitions of breakthrough IFI followed EORTC/MSG consensus criteria for proven and probable fungal infection in all but one study, which used assessment by an independent data review board [83]. One study in lung transplant recipients defined *Aspergillus* tracheobronchitis as a separate entity, defined by positive culture from a tracheobronchial ulcer or the bronchial anastomosis in addition to histologic proof of invasion [8, 79]. This study used airway colonization in the absence of signs of invasive disease as a further endpoint [79]. A retrospective study on liver transplant recipients, defined probable invasive candidiasis upon colonization of 2 or more non-cutaneous sites along with otherwise unexplained sepsis [81]. The period defining breakthrough IFI began on the first day of prophylaxis [78, 83] or the day of SOT [76, 79, 81, 82] and ended at 2 [82], 3 [76], 6 [78, 83], or 12 months [79], and for one retrospective study at 5 years post SOT [81]. Two studies did not provide temporal definitions [77, 80].

Empiric treatment.: A prospective cohort study on various organ transplant types defined the day of breakthrough IFI as the day of the first positive culture or pathology report. The study applied EORTC/MSG 2008 definitions, and focused on the period from SOT to 3 months post SOT to define breakthrough IFI [84].

Pre-emptive treatment.: The few studies on pre-emptive treatment in SOT patients are methodologically heterogeneous. Two studies defined breakthrough IFI on the day all IFI criteria were met [85, 86], and one did not give a definition [87]. Breakthrough IFI were defined as positive culture or histology from physiologically sterile sites [87], which is close to the 2002 EORTC/MSG criteria for proven IFI [7]. These were used in another study, with the exception of classifying candidemia as probable IFI [85]. Where reported the observation period for breakthrough IFI ranged from SOT to 12 months thereafter [85], and from first dose of preemptive antifungal treatment to 6 months post SOT [86].

Targeted treatment.: Studies on targeted antifungal treatment in SOT recipients defined the day of diagnosis of breakthrough IFI as the day when EORTC/MSG criteria were met [88, 89]. Observation periods, when reported, began on days 1 [89] or day 6 [88] of pre-emptive treatment and ended one week [88] and 3 months [89] after treatment.

Definitions proposed by MSG-ERC and ECMM

Resulting from the significant heterogeneity in prior clinical trials, we propose definitions for breakthrough IFI, and for clinical scenarios of treatment failure that need to be differentiated from breakthrough IFI (Table 1). Causes of breakthrough IFI are multifaceted, and can be grouped into host, pathogen, and iatrogenic causes (Table 2).

Breakthrough IFI.—Breakthrough IFI occurs during exposure to an antifungal drug irrespective of whether treatment intention is prophylactic, empiric, pre-emptive or targeted; breakthrough may occur early or late during the course of antifungal exposure [1]. As per definition, pre-emptive or targeted treatment is initiated only in patients with probable or proven IFI. Therefore, initial improvement of clinical, radiological or mycological signs of IFI under such treatment is an added requirement to differentiate breakthrough IFI from refractory IFI. In contrast, prophylaxis or empiric treatment is initiated in patients not fulfilling diagnostic criteria for IFI, therefore development of IFI is classified as breakthrough IFI (Figure 1). IFI should be defined according to published consensus criteria (e.g., for patients with underlying hematologic malignancies direct or indirect detection of a fungal pathogen is required for “probable” or “proven” cases of breakthrough IFI [6]). A common scenario in hematology patients is intercurrent bacterial pneumonia which needs to be differentiated from “possible” breakthrough IFI. Detection of any fungal pathogen causing disease outside the known spectrum of activity of an antifungal (or placebo) is also defined as breakthrough IFI/treatment emergent IFI [1].

Period for breakthrough IFI.: It is important to point out that pre-existing and unrecognized IFI is not a breakthrough IFI. Thus, breakthrough infections can be diagnosed only if first signs/symptoms or findings occur after a minimum antifungal exposure assuming optimal compliance. Minimum antifungal exposure is defined by the pharmacokinetic and pharmacodynamic properties of the antifungal (e.g., time to steady state) (Table 3). When these parameters are unknown, which may be the case in new antifungals, the period for breakthrough IFI should commence with the first dose of study drug [12, 14].

The period of breakthrough IFI also extends beyond the last dose of the antifungal evaluated. Given the differences in half-life and antifungal dosing intervals, with the latter currently ranging from 8 hours to 7 days, this period depends on the drug evaluated (Table 3). We suggest that an IFI occurring after antifungal drug discontinuation should definitely be classified as breakthrough IFI if the first sign, symptom, or finding of IFI occurs within less than one dosing interval after drug discontinuation. Necessarily, drugs with different dosing intervals will have different periods defining breakthrough IFI. IFIs occurring after the period of breakthrough IFI are either relapses or new IFIs.

Day of diagnosis of breakthrough IFI.: Breakthrough IFI begins on the day of the first radiological/clinical sign, or mycological finding attributable to breakthrough IFI, which should therefore be defined as the day of breakthrough IFI. The time it takes to diagnose an IFI by fulfilling all necessary criteria of the consensus definitions is determined by the biology of the disease process and other factors for example access to imaging and other facilities. The day of completion of diagnostics is thus highly variable, and should not be used to define the day of breakthrough IFI.

Persistent IFI.—This category describes IFI that is unchanged since treatment initiation and needs further treatment but is distinct from refractory disease (Figure 1). IFI mostly progress if left untreated in an immunosuppressed host, so that persistent - also known as stable – disease constitutes an early sign of control of the disease process, and thus the beginning of treatment success [10]. Definition of persistent IFI may vary by patient group, e.g. persistent disease may represent therapeutic response in persistently neutropenic and/or immunocompromised hosts, while it could represent lack of response in patients who are or have become more immunocompetent during the course of IFI.

Refractory IFI.—In the context of IFI, refractory disease is defined as progression of disease, worsening or new clinical signs or symptoms or radiological features attributed to IFI as a result of non-response to antifungal treatment [90]. Immune reconstitution can complicate assessment, as it may also lead to radiological and clinical progression that is temporary and coinciding with immune system recovery [91]. Immune reconstitution has therefore to be ruled out when defining an IFI as refractory (Figure 1). In clinical trials, Data Review Committees usually perform the final determination to assign clinical progression to refractoriness of IFI or immune reconstitution.

Relapsed IFI.—The term relapse describes IFI that occurs after antifungal treatment [10] and is caused by the same pathogen at the same site, although dissemination can occur [92]. The identity of a pathogen may be difficult to determine, and the full armamentarium of diagnostic methods should be utilized. For proven infection, the same species is sufficient to fulfill the definition. For probable or possible infection without isolation of the causative fungal pathogen, the same clinical picture including imaging results, as defined previously for e.g. chronic hepatosplenic candidiasis and – if applicable – an increase of non-culture based fungal biomarkers like galactomannan in cases of invasive aspergillosis is sufficient [6]. Relapse requires a response to antifungal treatment first, and is thus different from

persistent or treatment refractory IFI (Figure 1). Differentiation of relapse versus flare of the same infection during immune reconstitution syndrome is essential [93].

Conclusion

With these definitions, we intend to support the design of future clinical trials and epidemiological research in the field of clinical mycology. These definitions are not meant to guide clinical practice. Likely, the most important implication of consensus definitions of breakthrough IFI is to increase the comparability of clinical trial results. While these definitions represent the status of published literature, future studies are needed to fill important gaps.

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Potential Conflicts of Interest

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COM received research grants from Gilead, Merck Sharp and Dohme, is an advisor to Merck Sharp and Dohme.

GRT received research grants from Amplyx, Astellas, Cidara, F2G, Vical, is a consultant to Amplyx, Astellas, Cidara, F2G, Vical.

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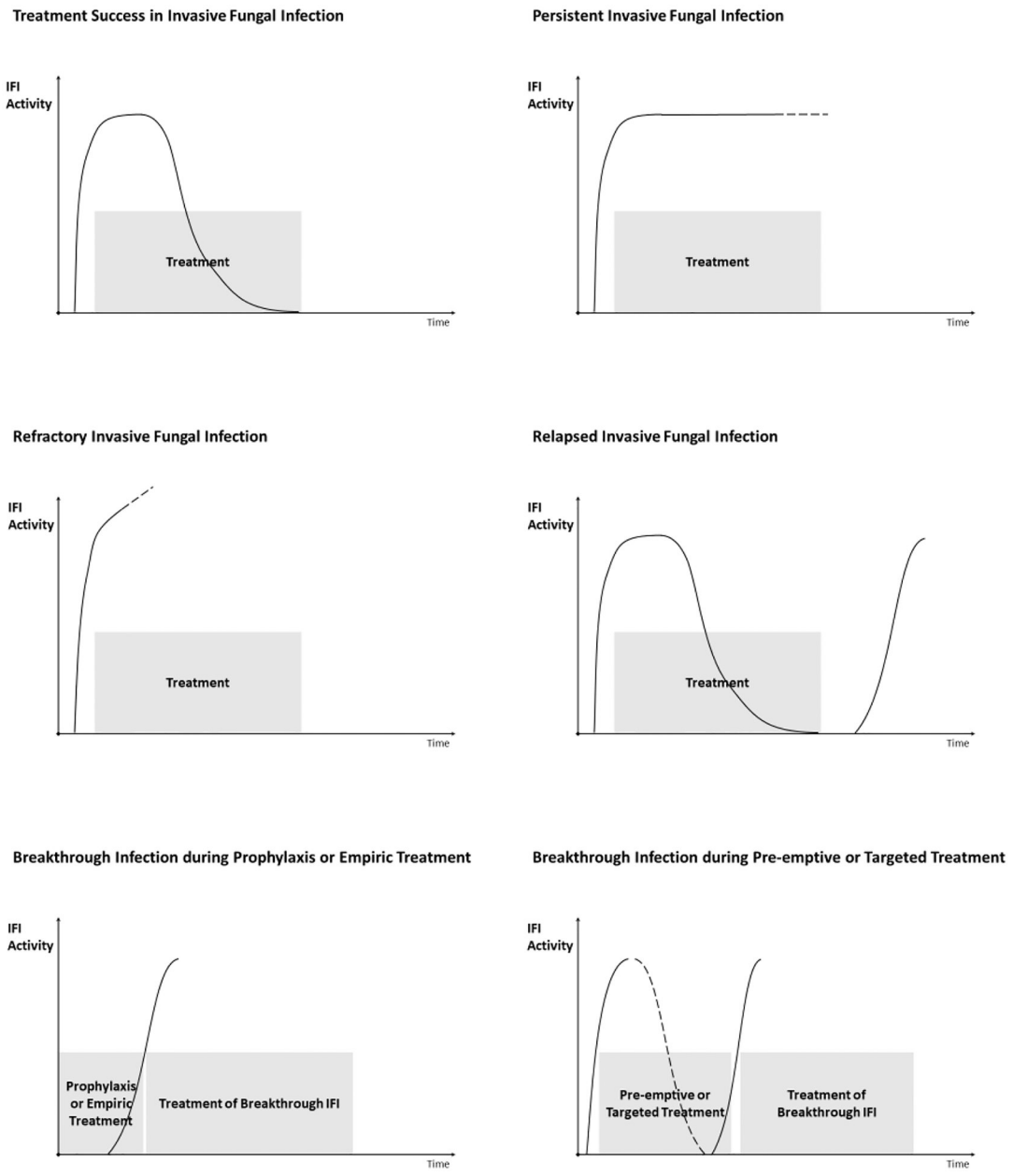

Figure 1.
Treatment Courses of Invasive Fungal Infections

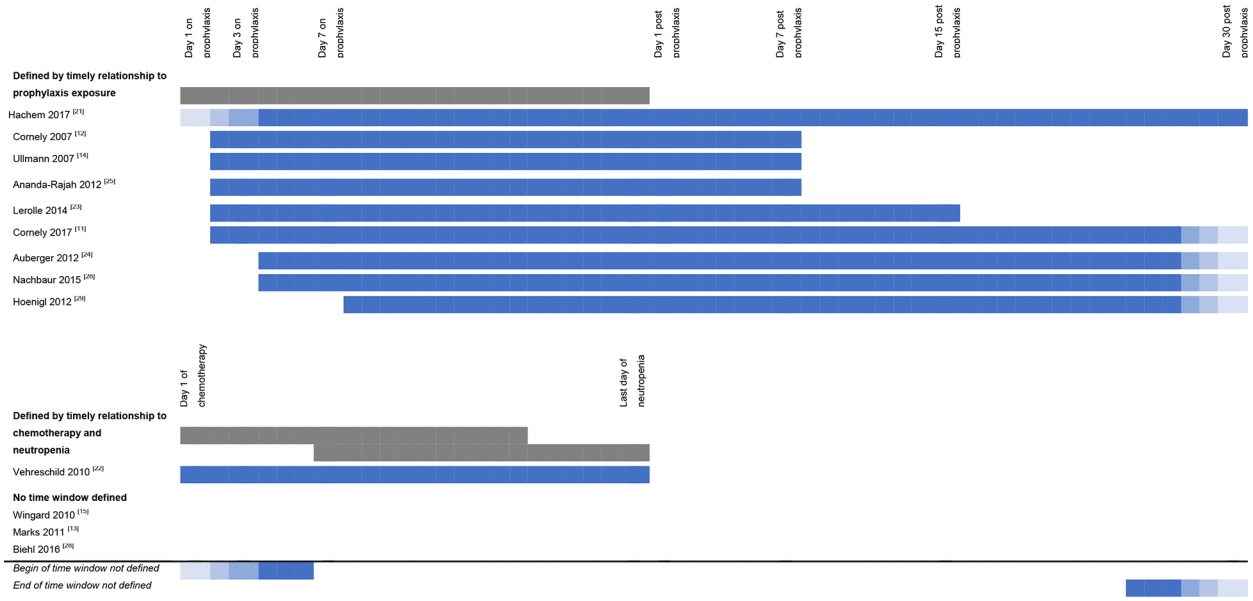

Figure 2.

Breakthrough Fungal Infections Definitions Used in Clinical Trials on Antifungal Prophylaxis in Hematology

Table 1.

Summary of Definitions for Invasive Fungal Infection

Term	Definition
Persistent IFI	IFI unchanged from baseline, may precede treatment success.
Refractory IFI	IFI with worsening or new attributable clinical signs or symptoms or radiological findings attributable to IFI while on treatment.
Relapsed IFI	IFI occurring after antifungal treatment discontinuation. IFI is caused by the same pathogen at the same site with or without dissemination.
Breakthrough IFI	IFI occurring during exposure to an antifungal drug, including fungi outside the spectrum of activity of an antifungal (treatment emergent IFI is a synonym); The time point of breakthrough IFI is the first attributable clinical sign or symptom, mycological findings or radiological feature; The period of breakthrough IFI depends on the pharmacokinetic properties of the antifungal evaluated.

Table 2.

Predisposing Factors for Breakthrough Invasive Fungal Infections

Host Factors	Host immunosuppression [94–98], including presence and duration of neutropenia, receipt of corticosteroid therapy, and other immunosuppressive medications
	Intensive care unit stay [95, 97, 98]
	Exposure ≥2 antibiotics for at least 14 days [96]
	Failure of source control (e.g., undrained abscesses), and “sanctuary” sites allowing for suboptimal antifungal pharmacokinetics [99–101]
	Single nucleotide polymorphisms within genes encoding for proteins involved in innate and adaptive immune responses (e.g., dectin-1 and DC-SIGN, TLR4 and others) [102–106]
Fungal factors	Fungal virulence traits facilitating target adherence, host defense evasion, tissue-damage, thermotolerance and adaptation to unfavorable microenvironments including hypoxia and iron-poor conditions [107, 108]. Traits may be induced by antifungal drugs [109–112]
	Antifungal drug resistance or tolerance [110, 113–115]
	Outside the spectrum of activity
	Biofilm formation (often incorporating bacterial communities) [116–118]
	Antifungal exposure can select resistant pathogens causing breakthrough IFI (e.g., Mucormycosis in patients receiving voriconazole or echinocandins) [119–123]
	Mixed infection by bacterial or fungal co-pathogen
Iatrogenic factors	Inappropriate selection of antifungals and dosing [124, 125]
	Insufficient plasma and tissue drug levels despite correct dosing because of unpredictable pharmacokinetics with high inter- and intrapatient variability [126, 127]
	Absence of therapeutic drug monitoring (TDM) where recommended (e.g., intravenous and oral voriconazole, and posaconazole oral suspension [128][129] [130]
	Incorrect intake procedures [131, 132]
	Incorrect handling or antifungal therapy of fungal biofilms on vascular devices or foreign bodies [133, 134] [135] [133, 136–139], including incomplete source control, for example catheter management
	Incorrect interpretation of imaging studies: Assessment without comparison to previous baseline and follow-up studies

Table 3.

Antifungal Drug Key Pharmacokinetic Parameters Classifying Breakthrough IFI

Antifungal	Time to steady state*	Plasma elimination half-life	Dosing interval after steady State#	Reference
Echinocandins				
Anidulafungin	1 day	24 h	24 h	[140, 141]
Caspofungin	4–7 days	8–11 h	24 h	[142–144]
Micafungin	4–5 days	13–20 h	24 h	[145, 146]
Azoles				
Fluconazole	5–10 days (without loading dose)	30 h	24 h	[147]
Isavuconazole	4–7 days (with loading dose); 10–14 days (without loading dose)	80–120 h	24 h	[46, 148–153]
Itraconazole	7–14 days	30 h	12 h	[154–156]
Posaconazole	3–7 days	27 h 35 h	6–8 h (oral suspension) 24 h (tablet, iv formulation)	[157–161]
Voriconazole	1 day i.v. with loading dose; 5 days p.o. or i.v. without loading dose	6 h	12 h	[127, 162, 163]
Polyenes				
Amphotericin B, deoxycholate	4 days	24 h	24 h	[164, 165]
Amphotericin B, liposomal	4–7 days	6–24 h	≥24 h	[166–168]
Amphotericin B, lipid complex	1–2 days	5–10 h	24 h	[156, 169, 170]
Nucleoside analogs				
5-Flucytosine	1 day	3–6 h	6 h	[171, 172]
Allylamines				
Terbinafine	6 days	36 h	24 h	[173, 174]
In development				
Fosmanogepix	<1 day	48–72 h	24 h	[175, 176]
Ibrexafungerp	4 days	41 h	24 h	[177]
Olorofim	1–2 days	20–30 h	12 h	[178, 179]
Rezafungin	<1 day	133 h	168 h	[180–182]

*Steady state describes the dynamic equilibrium of overall intake and elimination of a drug, and thus depends on loading and maintenance doses and elimination half-life and in particular for antifungals under development may change from the above; steady state is a PK parameter different from drug concentration needed to treat IFI, which frequently are reached on day 1.

#Due to lack of published data time-to steady state calculated from elimination half-live × 4 [183].