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Breaking the mould: challenging the status quo of clinical trial response definitions for invasive fungal diseases—a debate

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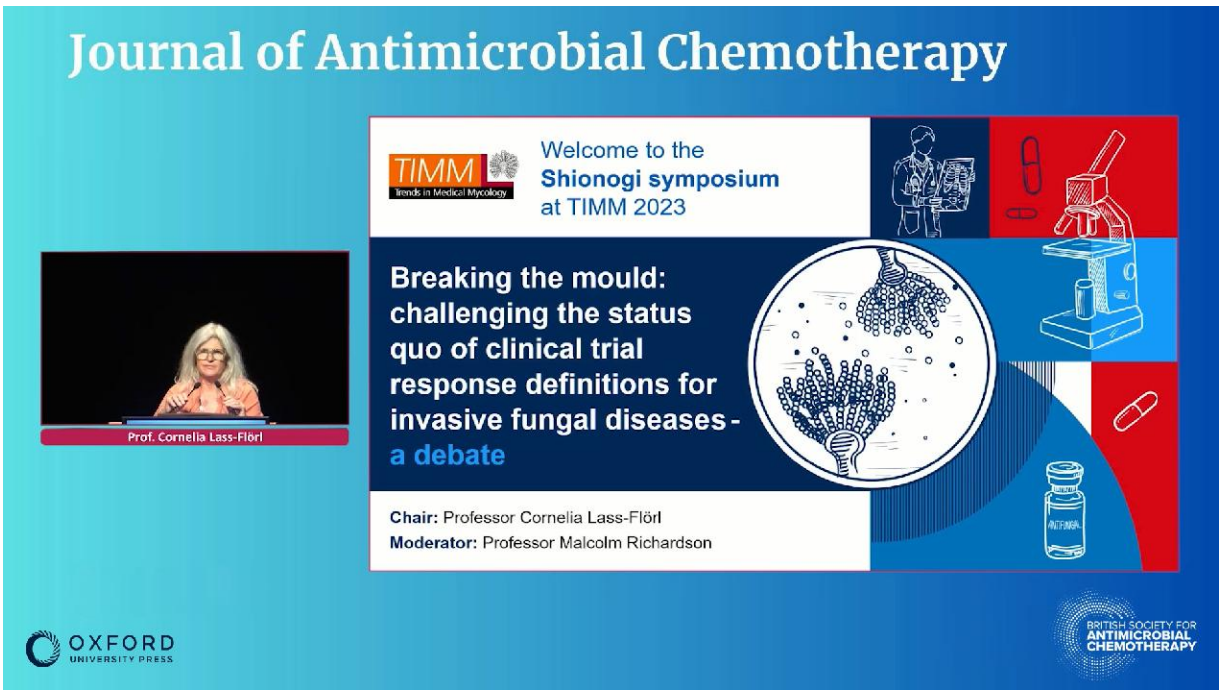

Video 1. Video of the virtual roundtable 'Breaking the mould: challenging the status quo of clinical trial response definitions for invasive fungal diseases - a debate'. The video is playable in the HTML version.

Preface

The field of invasive fungal disease (IFD) continues to evolve rapidly as new antifungals, including those with novel mechanisms of action, are being developed or have recently been approved for the treatment of IFD.[1–9] To ensure therapeutic responses to these treatments are evaluated in clinical trials in an appropriate and standardized manner, with sufficient applicability to clinical practice, robust consensus definitions for assessing treatment response are of foremost importance. This will allow for effective therapies (including those with potential use as first-line treatment) to reach patients who currently have limited treatment options.

The current definitions of response and outcomes in clinical trials assessing antifungal efficacy were drafted following the 2002 publication of consensus definitions for IFD diagnosis,[10] and published in 2008 by leading experts from Europe and the USA in the European Organisation for Research and Treatment of Cancer (EORTC) and Mycoses Study Group (MSG).[11] These included general criteria for global responses (Table 1) and responses to antifungal therapy in cases of well-defined IFD, including invasive mould disease (Table 2), candidaemia and invasive candidiasis, cryptococcal meningitis and histoplasmosis. Response definitions for invasive mould disease were largely based on responses to first-line treatment in patients with pulmonary aspergillosis and heavily immunosuppressed or haematology patients, reflecting the population in which pipeline antifungals were being evaluated at the time.[12–17] Response definitions for other fungi were organism-specific.

Using the 2008 definitions, patients receiving antifungal therapy are assessed for treatment success (complete or partial

Table 1. EORTC/MSG clinical trial definitions of global responses to antifungal therapy[11]

		Clinical		Radiological	Mycological
		Survival[a]	Signs and symptoms	Abnormalities	Evidence of disease eradication
Success	Complete response	✓	Resolution	Resolution	✓
	Partial response	✓	Improvement	Improvement	Clearance of culture or reduced fungal burden[b]
Failure	Stable	✓	Minor/no improvement Composite of all criteria does not show evidence of progression		
	Progression		Composite of all criteria shows evidence of progression		
	Death	✗[c]			

✓ Criteria were met; ✗ Criteria were not met.
[a]In predefined assessment period.
[b]Determined with a quantitative, validated laboratory marker.
[c]Regardless of attribution.

Table 2. EORTC/MSG clinical trial definitions of response to antifungal therapy in patients with invasive mould disease[11]

		Clinical		Radiological	Mycological
		Survival	Signs and symptoms	Lesions	Infected site clearance
Success	Complete response	✓	Resolution	Resolution[a]	✓
	Partial response	✓	Improvement	≥25% decrease in diameter[b]	✓[c]
		✓	Resolution	0%–25% decrease in diameter (stable)	
		✓	Improvement	0%–25% decrease in diameter (stable)	No biopsy evidence of hyphae and a negative culture
Failure	Stable	✓	Minor/no improvement	0%–25% decrease in diameter (stable)	
		✓	Minor/no improvement		✗[d,e]
	Progression	✓	Worsening	Worsening/new	
		✓	Worsening		✗[c]
	Death	✗[f]			

✓ Criteria were met; ✗ Criteria were not met.
[a]Also applies if there is persistence of only a scar or postoperative changes.
[b]For fungal pneumonia, radiological improvement with persistence of fever/cough equates to a partial response.
[c]Evidence from infected sites that are accessible to repeat sampling (e.g. the palate, sinuses or cutaneous lesions).
[d]Persistent mould isolation from infected site.
[e]Or positive histology for invasive hyphae.
[f]In predefined assessment period (primary therapy ≥6 weeks; salvage therapy ≥12 weeks), regardless of attribution.

treatment response) or failure (stable or progressive disease, or those who died) based on a composite of clinical, radiological and mycological criteria (Tables 1 and 2).[11] These have guided efficacy assessments in clinical trials for many years.[18–20] However, there remains a significant unmet medical need and, based on extensive clinical experience and advances in the field of IFD, it is evident that the evaluation of antifungal efficacy in patients with mould disease is complicated by multiple factors that require consideration (Table 3). In particular, divergence among criteria can be common during assessment periods; for example, failure by radiological and mycological criteria may be at odds with success by clinical outcomes. This can compromise the interpretation of patient outcome data and definition of a therapeutic response. There is a risk that limitations of current definitions could impact the evaluation and approval of new agents that may provide notable mortality or morbidity benefit to patients in clinical practice.

The 11th Trends in Medical Mycology Congress (TIMM; 20–23 October, 2023, Athens) presented a unique opportunity to critically evaluate current response definitions, with leading experts in IFD in attendance at one forum. The aim was to determine whether these definitions remain appropriate and applicable 15 years following publication, with a focus on their use in clinical trials of mould disease.

Should we keep the current response definitions for IFD, modify them or redevelop them de novo*?*

A symposium debate was held to discuss the proposition, 'This house believes that the 2008 EORTC/MSG definitions of responses to antifungal therapy are no longer fit for purpose', the highlights of which have been summarized in this paper (Table 3). An accompanying video recording of the debate includes additional discussion points and data.

Key highlights

Proposition: this house believes that the 2008 EORTC/MSG definitions of responses to antifungal therapy are no longer fit for purpose

Identification of true treatment failures

According to current response definitions, patients with stable disease are considered to have failed antifungal treatment (Table 2).[11] However, stable disease may precede partial or complete resolution, and achieving stable disease in clinical practice is often a positive outcome for many clinicians and patients, particularly patients receiving long-term (salvage) therapy.[21] This is reflected in cases in which a study drug is continued following the clinical trial.[22] Therefore, a high treatment failure rate due to a high stable disease rate may hinder approval of an agent valuable to a specific patient subgroup. It may be more appropriate to consider stable disease with continuation of the study drug as a treatment success.

Similarly, all patients who die while receiving antifungal therapy are considered to have failed treatment (Table 2),[11] but the use of survival in defining IFD outcomes is complicated. In patients receiving antifungal therapy, and particularly in those receiving salvage therapy, a notable proportion of deaths are attributable to underlying comorbidities rather than IFD.[23] As such, clinicians may be less willing to enrol patients with severe comorbidities in clinical trials, thereby introducing selection bias. It may be pertinent to only consider deaths determined to be likely or possibly related to IFD as treatment failures.

Despite the value of clinical response in the clinical setting, radiological response can be the main driver of overall antifungal response with current definitions, particularly in the assessment of moulds and endemic dimorphic fungi.[11] As such, if radiological or mycological data are missing (due to challenges and risks associated with these assessments), a Data Review Committee may be unable to confirm treatment success, even if patients demonstrate a clinical response. Increasing the weighting of clinical criteria in the composite outcome should be considered to avoid categorizing such patients as treatment failures. Additionally, clinical criteria could incorporate assessments such as patient-reported outcomes to better reflect the value of patient experience in determining treatment success versus failure.

Time period of assessment

The defined assessment period is associated with challenges in evaluation of response to salvage therapy and patients with infection in extrapulmonary sites. At present, endpoints are typically assessed at 6 weeks for primary therapy and 12 weeks for salvage therapy (Table 2).[11] By nature of the patient and disease characteristics, a complete response is rarely seen at 6 weeks,[22] suggesting this relatively short time period fails to adequately assess the population. A longer assessment period of 3–6 months may be warranted in patients receiving salvage therapy or those with stable disease at early time points. Patients with other clinical presentations, such as central nervous system or bone disease, could also benefit from this assessment period, although those with coccidioidomycosis may require even longer.

New methods of patient assessment

Recent progression in the use of imaging tools and circulating biomarkers provide new opportunities to overcome some of the challenges associated with current response assessments (Table 2).[11]

The combination of computerized tomography (CT) with positron emission tomography (PET) allows for a comprehensive radiological and functional assessment of lesions.[24–26] Imaging solely with CT can be complicated by patient, treatment and disease characteristics, such as surgical treatment and the immune responses typical for patients with IFD.[10,27] Failure of current definitions to reflect the complexity of disease and patient diversity increases the potential for inaccurate outcomes in clinical trials.

Galactomannan is a promising biomarker for mycological assessments in patients with invasive aspergillosis: correlations have been reported between patient outcomes and serum galactomannan kinetics.[28–31] Testing (including serial testing) for serum galactomannan is also less invasive than the biopsies required by current criteria (Table 2),[11,32] which may not be in the best interest of unwell patients and are particularly challenging in those with difficult-to-reach foci. PCR analysis has this

Table 3. Summary of an evaluation of the EORTC/MSG clinical trial definitions of response to antifungal therapy in patients with invasive mould disease

	Arguments in support of updating the current definitions	Arguments in support of the current definitions
Treatment success versus failure	• Stable disease is considered to be a treatment failure, but this can be a desirable outcome for clinicians and patients (particularly those receiving salvage therapy). • Not all deaths may be a result of antifungal treatment failure (particularly in patients with comorbidities receiving salvage therapy; clinicians may be less willing to enrol these patients in clinical trials, which can introduce selection bias).	• The current criteria are appropriately designed to differentiate treatment success versus failure based on objective evidence.
Clinical criteria and assessments	• Clinical signs and symptoms of IFD are often subjective and non-specific, and rely on clinicians to arbitrate outcomes in current assessments; clear, non-subjective criteria are important to ensure standardized antifungal assessment in clinical trials. • Treatment success in patients with clinical responses may not be determined if radiological or mycological data are missing; increasing the weighting of clinical criteria would avoid categorizing these patients as treatment failures. • The patient experience is not considered, e.g. through assessment of PROs.	• Although resolution of signs and symptoms can be seen as a success in the clinic, this alone (irrespective of radiological/mycological outcomes) may not be enough to ensure unequivocal efficacy of a new agent in clinical trials. • Different timepoints should be considered for the main endpoints of efficacy for clinical, mycological and radiological criteria, as not all of them appear or improve simultaneously.
Radiological criteria and assessments	• CT scans of lesions alone do not fully account for the effects of patient, treatment or disease characteristics. • PET/CT is not included as a method of assessment, despite evidence that it could provide a comprehensive assessment of lesions.	• PET/CT is not widely accessible, in both low- and high-income regions. • PET/CT has not been sufficiently validated and can be limited by lack of reimbursement for use in IFD.
Mycological criteria and assessments	• Documented fungal clearance (required for confirmation of a complete response) is difficult to obtain for many patients, including those with difficult-to-reach foci; the invasive biopsies required are not ideal for unwell patients. • New methods of assessment are undervalued; for example, serum galactomannan and PCR could provide clarity of treatment responses when other criteria are conflicting.	• Microscopy and culture are near universally available, while access to PCR and galactomannan tests is limited. • Current evidence on the use of PCR and galactomannan tests for IFD is limited in select populations, so may not be applicable for large clinical trials. • Serial PCR and galactomannan testing may only be useful if patients have a positive test at baseline, which is not universally achieved. • High false-positive rates have been reported from galactomannan tests in non-haematology patients, raising concerns regarding its validity as a method of assessment.
Time period of assessment	• Divergence among clinical, radiological and mycological criteria can be common during the defined assessment period; e.g. patients with cavitation or persistent mould isolation (radiological or mycological outcomes that indicate treatment failure) may still demonstrate an improvement in signs and symptoms (a clinical outcome that indicates treatment success). • The assessment period fails to consider patient and disease characteristics: stable disease may precede a complete or partial response, as response is rarely seen at 6 weeks in some patients (particularly those receiving salvage therapy).	• The time period of assessment is clinically relevant: natural immune reconstitution within 6 weeks of antifungal therapy may confound results, whereas underlying comorbidities may lead to worsening conditions over time, as is common in salvage settings.
Regulatory considerations		• Regulatory agencies require the type of clear and evidence-based definitions of treatment success versus failure provided in the current response definitions.
Diversity, inclusion and practicality	• Definitions were based on the clinical expertise and experience of a group of leading experts in 2008, which have since progressed.	• The current definitions have been designed to ensure that clinical trials are accessible to a geographical range of centres and countries, and translate to a global patient

Continued

Table 3. *Continued*

	Arguments in support of updating the current definitions	Arguments in support of the current definitions
	• Encouraging geographical diversity should not come at the cost of excluding patients with rarer and endemic IFDs (who are unlikely to be largely and evenly represented), as this could lead to issues with recruitment.	population, while ensuring recruitment targets are achievable.

PRO, patient-reported outcome.

Table 4. Summary of the key clinical trials for invasive aspergillosis

	Voriconazole versus conventional amphotericin B[12]	Voriconazole versus combination (anidulafungin)[18]	Voriconazole versus isavuconazole[19]	Voriconazole versus posaconazole[20]	Mean
Duration	July 1997–October 2000	July 2008–May 2011	March 2007–March 2013[a]	October 2013–September 2019	—
Duration, months	40	35	73[a]	72	55
Patients assessed, *n*	391	459	532	653	509
Patients in ITT, *n*	391 (197 versus 194)	422 (207 versus 215)	516 (258 versus 258)	575 (288 versus 287)	—
Sites, *n*	95	93	102	91	95
Countries, *n*	19	24	26	26	23
Mean patients in ITT per site, *n*	4.1	4.5	5.1	6.3	5
FDA approval	24 May 2002	Not applicable	6 March 2015	June 2021	1.5–2 years later

[a]Trial was suspended from January 2009–March 2011.
ITT, intention-to-treat.

benefit, and can be conducted on blood samples (including plasma and serum);[32,33] persisting PCR positivity can also be used to indicate poor outcomes.[34] A major limitation is that serum galactomannan and PCR are positive only in a subpopulation of patients with invasive aspergillosis, and utility of serial testing may be reduced in the absence of a positive test at baseline.[35] However, these alternative methods could provide clarity of treatment responses, particularly when criteria conflict in early assessments.

Opposition: this house believes that the 2008 EORTC/MSG definitions of responses to antifungal therapy remain fit for purpose

Regulatory compliance in clinical trials

Any revisions to the response definitions should remain appropriate for use in clinical trials of IFD and allow regulatory agencies, such as the EMA and FDA, to determine the efficacy of new antifungals in a specific patient population. This requires clear and standardized differentiation of treatment success versus failure, with sufficient supporting evidence, which current definitions (although conservative) provide. These are relied on heavily, as no independent EMA or FDA guidance on evaluating new antifungals is available.

Outcomes that could be considered a treatment success, such as resolution of signs and symptoms alone (irrespective of radiological or mycological outcomes), may be insufficient to ensure unequivocal efficacy of agents in clinical trials. In cases of stable disease, resolution of signs and symptoms may not be attributable to the antifungal, but rather the natural recovery of immunological control over time, after which the disease could progress. Alternatively, new immunomodulatory drugs may modify the natural course of disease and reduce signs and symptoms,[36] but these effects on IFD are not fully established. Should response definitions be revised to recognize stable disease with study drug continuation as treatment success, it may be challenging to determine antifungal efficacy in these patients, impairing regulatory evaluation.

Diversity, inclusion and practicality in clinical trials

The complexity of conducting sufficiently large clinical trials for IFD (Table 4) and the means of assessing treatment outcomes are important considerations. A balance of patient diversity, inclusivity, practicality and evidence-based use of assessment methods is required. This ensures data on new antifungals are generated in underserved patient populations and across high numbers of participating centres and countries, thereby translating to the global population.[37,38]

Equally, encouraging geographical diversity should not come at the cost of excluding patients with rarer and endemic IFDs (who are unlikely to be represented in large numbers across diverse regions), as this raises recruitment issues for sponsors. Low-income countries often bear the highest burden of fungal disease,[39] yet are frequently under-resourced, with limited access to clinical trials.

Alternative methods for assessing response to antifungals, such as PET/CT, serum galactomannan testing and PCR, are increasingly employed.[24,25,28–30,32,40] However, these must be accessible to a large number and variety of patients and centres before they can be used in clinical trials. Access to PET is limited even in high-income countries, and use of PET/CT for assessment of IFD is typically excluded from reimbursement in the clinical setting. Similarly, access to PCR and galactomannan assays is limited, particularly in Asia/Pacific and Africa.[41,42] It is important to note, however, that clinical trial sponsors are bound to ensure availability of necessary laboratory tests in participating centres.

Validation of new methods of assessment

Evidence on the use of PCR and galactomannan tests for IFD are limited (aside from in haematology patients),[28,29,32] particularly in paediatrics/neonates or patients with chronic granulomatous disease, HIV, COVID-19 and solid organ transplant.[43,44] Furthermore, the presence of false-positive results has been noted, particularly in non-haematology patients.[45–48] Consequently, the validity of these tests in all populations has not been determined; these challenges may render galactomannan an unsuitable biomarker in IFD for regulatory agencies. The unmet need for reliable biomarkers for mycological assessments suggests that research on this should be upscaled.

Conclusion

Following the evaluation of the EORTC/MSG response definitions at TIMM 2023, the symposium faculty concluded that these definitions are no longer appropriate or optimal for assessing new antifungal therapies in clinical trials. While nearly half (45%, 56/125 responders) of symposium attendees who voted were initially unsure whether the definitions remained appropriate, following the debate, most (84%, 86/102 responders) agreed that the definitions should be updated. Evidently, revised definitions from the relevant societies and leading experts in IFD are needed.

It is important that response definitions reflect the evolving clinical landscape and ensure effective antifungals reach the clinic. While current mould definitions are broadly applicable to pulmonary aspergillosis, evaluation of antifungals for rarer moulds and infection sites (such as extrapulmonary) remains an unmet need. Additionally, it is inappropriate to consider all patients with stable disease (especially in the salvage setting) and all patient deaths as treatment failures, and the rigidity of current assessment periods fails to account for the different characteristics of IFDs and treatment regimens. A revised composite outcome to assess treatment success versus failure at specific time points may reduce ambiguity in responses, and the use of new tools and biomarkers provide opportunities to improve assessment. However, we must ensure that redefined definitions have global utility, are feasible for clinical trial sponsors to implement and are compliant with regulatory requirements, so that new agents are evaluated in line with the necessary standards for patients.

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