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Duration of antifungal treatment in mold infection: When is enough?

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Abstract

Purpose of review: Although invasive mold infections (IMI) are a major complication in high-risk populations, treatment duration has not yet been well defined.

Recent findings: Guidelines suggest documenting clinical/radiological resolution and immunological recovery before stopping antifungal treatment, after a minimum duration of treatment of 3 months for invasive pulmonary aspergillosis, while longer (up to 6 months) duration is proposed for the treatment of invasive mucormycosis. However, data on and definitions of clinical/radiological resolution and immune recovery remain scarce. Limited real-life data suggest that often much longer courses of treatment are given, generally in the context of continuous immunosuppression, occasionally defined as secondary prophylaxis. However, clearcut definition and distinction of secondary prophylaxis from antifungal treatment remain to be defined.

Summary: Decisions to stop antifungal treatment are based on poorly defined treatment responses and immune reconstitution and experts' opinions. More evidence is needed to determine the optimal duration of treatment of IMI. Well-designed, easy to use, and realistic algorithms to help clinicians decide when to stop antifungal treatment are urgently needed.

Keywords: Antifungal treatment, invasive mold infection, immunocompromised host, secondary antifungal prophylaxis.

Key-points:

- **Optimal duration of treatment for invasive mold infections is poorly defined.**
- **Decision of stopping treatment is based on resolution of clinical signs and symptoms and imaging findings, as well as immune recovery. There are no clear definitions of treatment response or immune reconstitution. Standardization of biological (e.g. galactomannan) or imaging monitoring tools is required to homogenize approaches and facilitate decision making.**
- **Based on experts' opinion, a minimum of 3 months is recommended f or invasive pulmonary aspergillosis, with longer courses of treatment (up to 6 months) often employed for invasive mucormycosis.**
- **Real life data suggest that longer courses of treatment are often administered, generally in the context of persistent immunosuppression, likely as secondary prophylaxis.**
- **The above may help to propose algorithms that -when validated, could help to decide when to stop antifungal treatment.**

Introduction

Invasive mold infections (IMI) remain a frequent complication in high-risk patient populations, associated with an important morbidity and mortality, despite recent advances in diagnostics and therapeutics (1). Highest-risk populations include patients with acute myeloid leukemia (AML) and allogeneic hematopoietic cell transplantation (HCT) recipients, with IMI incidence between 5 and 15% (2–5). The higher numbers of HCT and new treatments rapidly introduced in the field of hematologic malignancies, including venetoclax, alkylating agents, ibrutinib and an endless list of monoclonal antibodies, may further increase the number of patients at risk for IMI in the years to come (6–8). On the other hand, fungal epidemiology is rapidly changing, with more frequent identification of previously rarely seen molds, such as non-*fumigatus Aspergillus* spp. and non-*Aspergillus* molds (3,9). This may, in part, reflect the effect of universal antifungal prophylaxis with mold-acting azoles leading to the emergence of breakthrough IMI (10). Considering the relevant risk factors and clinical and radiological findings in high-risk patient populations, empirical, preemptive, or targeted antifungal treatment is promptly started upon clinical suspicion for IMI. However, as easy as it may be to initiate anti-mold active treatment in high-risk patients, treatment discontinuation may be a complex and difficult task. Furthermore, prolonged antifungal treatment is not innocuous. Adverse events and drug-drug interactions are frequent and they may often lead to treatment changes or discontinuation (11,12). In this article we review the existing evidence and gaps for when and how to stop antifungal treatment for IMI.

Definitions and key questions

Invasive mold infections are a heterogeneous group of diseases caused by microbiologically different fungi in different sites, in patients with variable host criteria. For this review, we will mostly focus on sinus and pulmonary invasive aspergillosis (IA) and mucormycosis, in the context of high-risk hematology patients with AML and allogeneic HCT recipients. We will not discuss treatment duration for patients with disseminated IMI or osteoarticular, hepatosplenic, endovascular, or central nervous

system infections. The main questions addressed in this review include the following: (i) what is the optimal total duration of antifungal treatment for IMI in high-risk hematology patients and what variables can be used to guide clinicians when to stop it, (ii) how is secondary prophylaxis defined and when and how long should it be administered for, and (iii) what are the future considerations for treatment duration and secondary prophylaxis administration.

1. Optimal duration and variables considered for antifungal treatment discontinuation of IMI

a. Guidelines

Historically, antifungal treatment for IA and mucormycosis has been continued for 12 weeks in the context of clinical trials (13–18). However, this duration was not decided based on clear-cut criteria, but rather on the general concept that this would be a reasonable treatment duration for those infections and the relative ease of a 3-month follow-up. In fact, more recent data suggest that the direct effect of IA on overall survival may be seen as early as 6 weeks after treatment initiation (19). Current guidelines suggest a treatment duration between 3 and 6 months for the treatment of IMI, shorter for IA, longer for mucormycosis, determined by the overall response to treatment and reversal of the underlying deficit in host defenses (1,20–22). Longer courses are generally given for non-IA IMIs, but the optimal duration of treatment remains unknown (21). For instance, in the case of mucormycosis data are variable, including single-arm clinical trials or studies of salvage therapy, with overall treatment duration having varied from 3 to 6 months (17,23–26).

Considering the most recent guidelines, continuing treatment is recommended until complete response and immune function resolution are documented (1,20–22). To assess treatment response, additional criteria have been proposed, based on which a patient may have complete, partial, or stable response, or treatment failure (27). To assess the above, a combination of clinical, radiological, and microbiological criteria has been suggested. However, assessment is usually based on either clinical and/or radiological variables assessment. The latter includes repeating a sinus and chest computed

tomography (CT) and/or a sinus magnetic resonance imaging (MRI) at predefined time-points (1, 27). Although not well established, historically repeat imaging is routinely obtained at 6- and 12-weeks post-treatment initiation. Microbiological response monitoring heavily depends on the diagnostic test based on which the diagnosis was established. In case diagnosis was based on an invasive procedure, such as a sinus surgical intervention or a bronchoscopy, repeating a similar diagnostic procedure would be required to accurately assess microbiological eradication (27). However, this is very rarely performed, even in the context of clinical trials. Hence, reliable, and easier to use microbiological tests are required to document microbiological response in patients treated for an IMI. Fungal biomarkers assessed in blood specimens (e.g. galactomannan enzyme immunoassay, GM EIA) were not included in the guidelines proposed by Segal et al, although they are commonly used today (28). For instance, for patients with IA, whose diagnosis was established based on a positive serum GM EIA, recent data suggest that serum GM EIA monitoring may be useful to assess treatment response in appropriate patient subpopulations (e.g. hematologic malignancy, HCT) (29–31). In terms of immune reconstitution as a contributing factor to discontinuing antifungal treatment, clearcut definitions are still lacking. Historically and in real life variables such as neutropenia or lymphopenia resolution and the administration of immunosuppressive agents, such as corticosteroids, are considered as surrogate markers of immune suppressions assessment. However, the level and duration of lymphopenia resolution or corticosteroid daily dose have not been well defined, as yet.

b. Real life

In a European survey, based on a questionnaire answered by 112 physicians (only 13 of whom were infectious disease specialists) from 14 European countries describing the current practices on the management of IA in European hematology centers, antifungal treatment duration ranged between 6 and 11 weeks (28). Treatment duration was at a median of 6 (IQR 3-12) weeks for patients with AML, 11 (IQR 4,12) weeks for HCT recipients with graft versus host disease (GvHD), and 6 (IQR 3,12) weeks for patients with lymphoproliferative disease. Treatment duration varied significantly across different

130 countries and appeared to be shorter in pediatric patients. Most (84%) physicians performed a CT after
131 treatment interruption at a median of 4 weeks and employed secondary prophylaxis after treatment
132 discontinuation in 79/84 (94%) centers. Response assessment was predominately based on chest CT
133 (110/112, 98%) and blood GM EIA (83/112, 74%). In clinically stable patients a repeat CT was requested
134 at a median of 2- and 6-weeks post-treatment initiation. For treatment discontinuation clinical
135 response was used in 89/103 (81%) centers in AML patients and in 78/109 (72%) in GvHD patients.
136 Reduction in GM EIA index was used to stop antifungal treatment in 60% (64/109) of AML patients and
137 50% (55/109) of GvHD patients. *Aspergillus* PCR in serum, B-D-glucan, or PET CT were barely used to
138 decide treatment discontinuation. Notably, 2/57 (3.5%) and 29/57 (51%) clinicians would recommend
139 shorter treatment durations, <1 and between 1 and 3 months, respectively. Most physicians suggested
140 that deciding on treatment discontinuation may be problem (53/84, 63%) and that an algorithm to
141 help decide when and how to stop treatment would be highly appreciated (75/84, 89%).
142
143 Similar findings were reported in a 10-year single-center Swiss cohort of consecutive adult allogeneic
144 HCT recipients with IMI (3). Amongst 61 patients with 66 proven or probable IMI, the median
145 treatment duration was 280 (IQR 110, 809) days. For patients who were still alive by 12 weeks post-
146 treatment initiation, treatment duration was at a median of 213 (IQR 90, 675) days: 200 (IQR 87, 577)
147 versus 293.5 (IQR 99, 809) for patients with IA and non-IA IMI (p=0.07). Most (87.5%) patients were
148 not neutropenic at the end of treatment (EOT), but they had low lymphocyte counts, with a median
149 absolute lymphocyte count of 0.31 (IQR 0, 2.4) G/L and CD4+ count of 99 (IQR 0, 759) cells/ul. Overall,
150 49.1% of patients were still receiving steroids at the EOT and 61.8% of patients were receiving another
151 type of immunosuppression. Treatment was continued beyond days 90 and 180 post-treatment
152 initiation in 32 (78%) and 22 (53.7%) patients, respectively. The main reason to continue treatment
153 beyond 90 days was persisting underlying immunosuppression (39/43, 90.7% patients), including
154 continued immunosuppressive treatment administration (27/43, 62.8%) and receipt of an allogeneic
155 HCT (11/43, 25.1%). Reasons for continuing treatment after 180 days were similar: persisting

underlying immunosuppression (23/30, 76.7% patients) in most cases, including continued immunosuppressive treatment administration (17/30, 56.7%) and receipt of an allogeneic HCT (5/30, 16.7%). A CT was performed in 56% of patients at the EOT and most imaging showed a complete or partial radiologic response. An important finding of that study was that treatment discontinuation was poorly documented in patient charts, with only 1 out of 5 patients having a dedicated Hematology or Infectious Disease consultation detailing treatment discontinuation.

In a more recent retrospective, multi-center Swiss study, IMI treatment duration and characteristics in AML patients was reviewed (manuscript submitted for publication). Overall, 71 patients with AML and one proven or probable IMI were included. In this cohort, total treatment duration was at a median of 227 days (IQR 115.5, 348.5): 238.5 (IQR 115, 374) days in IA and 197.5 (IQR 120, 318) days in non-IA IMI (p=0.85). Treatment duration heavily differed between those patients with AML who did and did not have a subsequent allogeneic HCT: 254 (IQR 197.5, 436) and 115.5 (64.5, 134.5) days, respectively (p=0.004). Treatment was continued beyond 90 days in 59/71 (83%) patients, mainly due to persistent immunosuppression, either due to continued immunosuppressive treatment (33/59, 55.9%) or in the context of an allogeneic HCT (28/59, 47.4%). Treatment was continued above 180 days in 39/71 (55%) patients, because of continued immunosuppression (24/39, 61.5%) or allogeneic HCT (11/39, 28.2%).

2. Secondary prophylaxis for IMI

Considering the above, it is obvious that treatment duration for IMI largely varies between guidelines and real life. This variability may, in part, be related to the definitions used for primary treatment and secondary prophylaxis of patients with IMI across different studies and centers. For instance, in the recent European survey presented above, clinicians clearly described duration of treatment versus secondary prophylaxis, with the majority (94%) of centers employing secondary prophylaxis mostly with voriconazole (82%) or posaconazole (53%) continued for >3 months in 46% centers and until the end of immunosuppressive regimen in 66% centers (28). In contrast, in the two retrospective Swiss

cohort studies, secondary prophylaxis was not defined, and the total duration of mold-acting agents administered was considered as antifungal treatment duration. The latter was due to the inability to accurately identify retrospectively at which point antifungal treatment was transitioned to secondary prophylaxis (11).

Secondary prophylaxis has been defined as "a treatment strategy to prevent recurrence of IA/IMI during a subsequent risk period of immunosuppression" (20). Historically, this is based on the presumption that additional not easily identifiable foci of IMI may still exist, despite adequate antifungal treatment, which may lead to disease relapse in case of persistent and profound immunosuppression, particularly feared in cases of invasive mucormycosis (22). What is the risk for a relapse and at what incidence this may happen remain poorly described (22,32). Nevertheless, based on this presumption and potential fatality of those infections, immune reconstitution has been included as an additional variable to consider in the current treatment recommendations for antifungal treatment duration (1,20–22). Currently, a clear-cut, valid definition of secondary prophylaxis is lacking, with the margin between end of antifungal treatment and initiation of secondary prophylaxis remaining in a gray zone.

3. Length of IMI treatment & secondary prophylaxis: future considerations

As previously mentioned, current treatment duration considerations include both treatment response and immune status evaluation in the decision making process (1,20–22). Treatment of 12 weeks has been the only duration used in the context of pivotal clinical trials over the last two decades (13–18). Large amounts of data have been produced using this length of treatment, despite the fact that this has never been compared head-to-head to another duration, neither shorter nor longer. Similarly, treatment responses have never been considered together with immune reconstitution in the context of clinical trials. Hence, perhaps antifungal treatment duration should be solely based on what has been validated in the existing body of literature, namely the 12 weeks of treatment, and be rather

dissociated from the patient's immune status. The latter could and should be considered when deciding whether to continue the administration of a mold-active antifungal agent, but rather defined as secondary prophylaxis in the setting of continued and significant immune suppression.

Considering the above, and based on current recommendations and experts' opinions, we propose a simple and pragmatic algorithm to be considered for validation in the future. We are proposing to use treatment response to decide on treatment duration and immune status for secondary prophylaxis administration (**Figures 1**). For this algorithm to work, treatment response and immune reconstitution definitions would be necessary, as presented in **Figure 2**, adjusted from existing guidelines (27). We propose close patient monitoring with weekly clinical assessment, serum GM EIA at 2-, 4-, 6-, 8-, 10-, and 12-weeks, and repeat imaging at 2-, 6-, and 12-weeks post-treatment initiation in stable patients for an overall treatment duration of 12 weeks in the setting of complete response (**Figure 1**). Complete response would include clinical, radiological, and microbiological resolution of the infection, as detailed in **Figure 2,** based on adapted definitions by Segal et al. and including serum GM EIA to define microbiological response (27). In case of partial response at 12 weeks, we propose treatment continuation and further assessment with serial evaluation of clinical response every 2-4 weeks until end of treatment. Of note, we are focusing on patients, who improve and for whom we are considering stopping treatment. Stable or worsening patients were not considered in this review. For patients who completed 12 weeks of treatment and have complete immune reconstitution, as defined in **Figure 2**, we propose to stop treatment and no subsequent secondary prophylaxis. In contrast, in case of persistent immune suppression, treatment discontinuation should be followed by the introduction of a mold-active antifungal agent as secondary prophylaxis. Immunological recovery is not clearly defined, but we propose a practical approach to roughly assess the net state of immunosuppression of patients, based on surrogate laboratory tests (absolute neutrophil count, ANC, and absolute leucocyte count, ALC), as well as administration of immunosuppressive treatment, and underlying diagnosis status (**Figure 2**). The inclusion of those variables was based on clinical experience and

common sense, although further validation is required in the future. For instance, at which level of ALC or dose of prednisone can someone consider a patient immune competent or not remains largely unknown. Other laboratory values, such as T-cell CD4+ counts or immunoglobulins, may be used to further assess a patient's immune status. Finally, we suggest a close collaboration between the hematology department and infectious diseases service to jointly make decisions concerning the end of antifungal treatment or secondary prophylaxis in complex cases. Furthermore, we recommend relevant documentation in patient charts, concerning date and reasons for stopping treatment or starting secondary prophylaxis.

Conclusions

The duration of treatment of IMI is not clearly defined and recommendations are based on weak evidence. For extrapulmonary IMI guidance is even more limited. Current recommendations suggest continuing treatment until complete clinical resolution and reversal of underlying immunosuppression, a minimum of 3 months for IA and up to 6 months for invasive mucormycosis. However, there seems to be a discrepancy between the proposed duration of IMI treatment in guidelines and real-life practice. This divergence is explained by the poor existing evidence, absence of universally accepted criteria of immunological recovery and clinical resolution, and the medical complexity of this population. Administration of secondary prophylaxis after treatment discontinuation has been also utilized, although there is an important gray zone between the two. In an era of polypharmacy, drug interactions, and antifungal resistance emergence it is important to better define antifungal treatment duration. Hence, multiple, and urgent questions arise, regarding treatment response and immunological recovery definitions, response monitoring timing and intensity, and treatment and/or secondary prophylaxis duration. Simple, easy to use, and pragmatic algorithms are required and need to be studied in the future to help in the treatment duration decision making process. This is a field for which more evidence is urgently needed in order to correctly handle this complex decision.

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Conflicts of interest

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Figure legends

Figure 1. Proposed algorithm to stop antifungal treatment of invasive mold infections in high-risk hematology patients.

Figure 2. Checklist and definitions of treatment response and immunological recovery in high-risk hematology patients with invasive mold infections.

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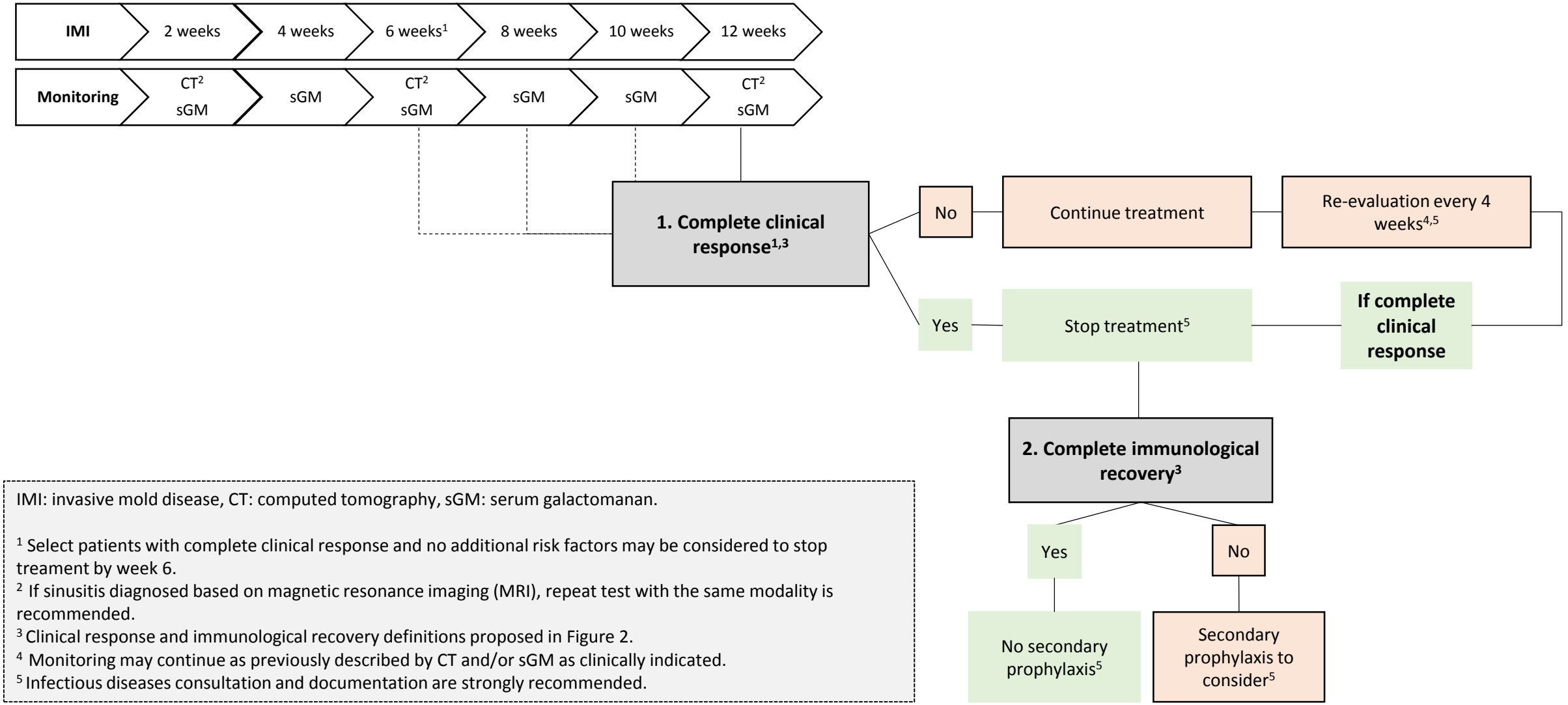
Figure

Figure 1. Proposed algorithm to stop antifungal treatment of invasive mold infections in high-risk hematology patients.

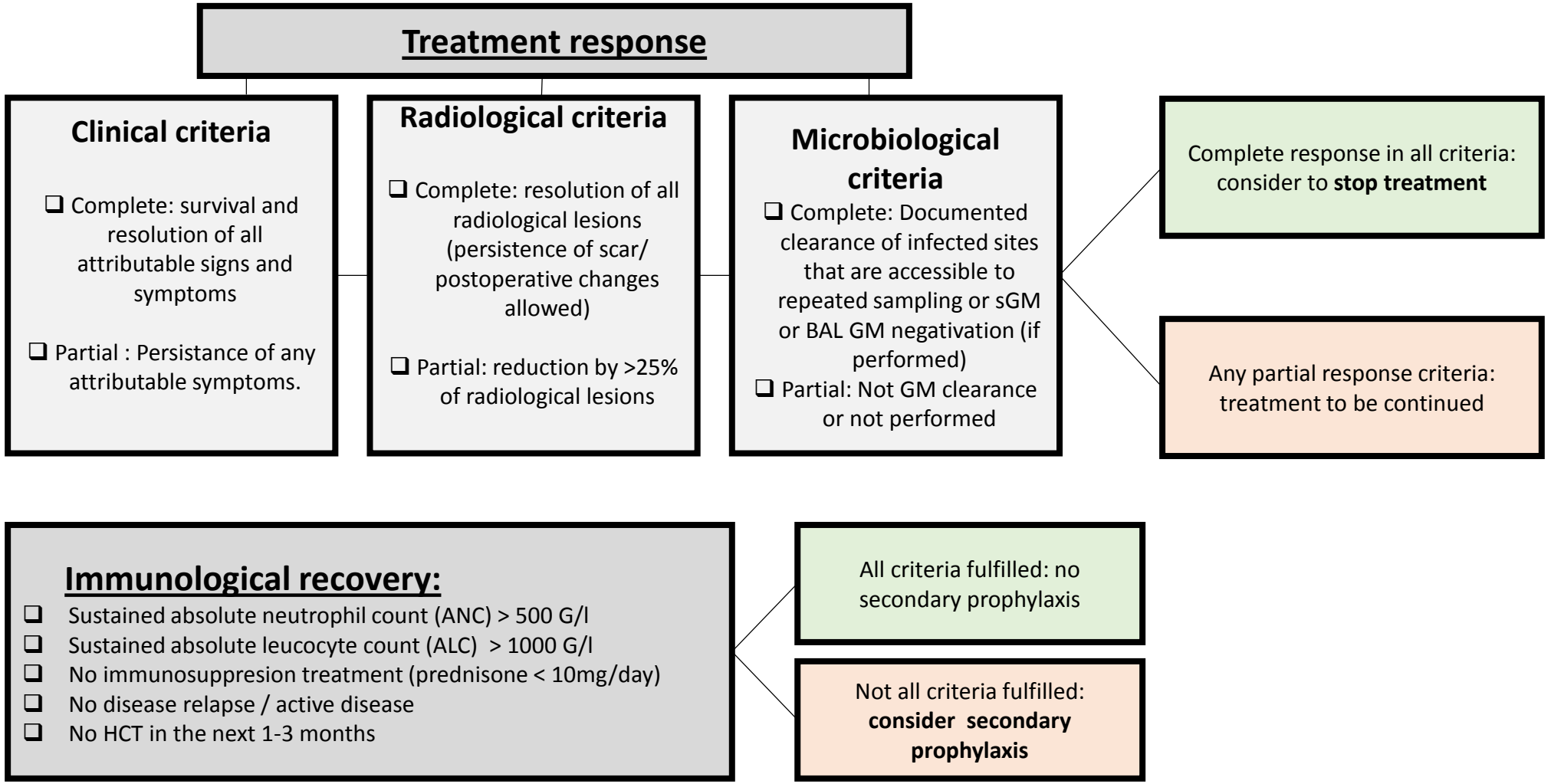


IMI: invasive mold disease, CT: computed tomography, sGM: serum galactomanan.

[1] Select patients with complete clinical response and no additional risk factors may be considered to stop treament by week 6.
[2] If sinusitis diagnosed based on magnetic resonance imaging (MRI), repeat test with the same modality is recommended.
[3] Clinical response and immunological recovery definitions proposed in Figure 2.
[4] Monitoring may continue as previously described by CT and/or sGM as clinically indicated.
[5] Infectious diseases consultation and documentation are strongly recommended.

Figure

Figure 2. Check-list and definitions of treatment response and immunological recovery in high-risk hematology patients with invasive mold infections.



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