



# Short Course of Voriconazole Therapy as a Risk Factor for Relapse of Invasive Pulmonary Aspergillosis

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## Abstract

### Background

Invasive pulmonary aspergillosis (IPA) is a life-threatening opportunistic infection which usually occurs in immunocompromised patients. Recommended duration of voriconazole therapy is a minimum of 6-12 weeks for IPA, despite the lack of any firm evidence. In addition, risk factors for relapse of IPA are still unclear. Here, we explored risk factors for IPA relapse after initial treatment.

### Methods

All patients with proven or probable IPA who had finished voriconazole treatment between 2005 and 2019 in a tertiary-care hospital were reviewed. IPA relapse was defined as re-diagnosis of proven or probable IPA at the same site within 1 year after treatment termination. Short course of voriconazole treatment was defined as a treatment less than 9 weeks, which is a median of the recommended minimum duration of therapy from the Infectious Disease Society of America. The radiological response was defined as a reduction in IPA burden by more than 50% on chest computed tomography (CT).

### Results

Of 87 patients who had completed voriconazole treatment, 14 (16.1%) experienced IPA relapse. Multivariable Cox regression identified that short voriconazole treatment duration (adjusted hazard ratio [aHR], 3.7; 95% confidence interval [CI], 1.1–12.3;  $P=0.033$ ) and radiological non-response (aHR, 4.6; 95% CI, 1.2–17.5;  $P=0.026$ ) were independently associated with relapse of IPA after adjusting for several clinical risk factors.

### Conclusions

Less improvement in CT, and short duration of voriconazole therapy were the independent risk factors for relapse after treatment of IPA. Longer duration of therapy should be considered for those at higher risk of relapse.

## Introduction

- Recommended duration of voriconazole therapy is a minimum of 6-12 weeks for IPA.
- Risk factors for relapse of IPA are still unclear.
- We hypothesized that short course of voriconazole treatment, defined as less than 9 weeks is associated with relapse of IPA.

## Methods

- A retrospective study conducted at Seoul National University Hospital
- Adults (age  $\geq 18$  years) with proven or probable IPA who had finished voriconazole treatment between January 2005 and July 2019 were reviewed.
- Relapse was defined as re-diagnosis of proven or probable IPA at the same site within 1 year after voriconazole treatment termination.
- Short course of voriconazole treatment was defined as a treatment less than 9 weeks (i.e., median of recommended duration by the Infectious Disease Society of America).
- Radiological response was defined as more than 50% reduction in the IPA burden on chest computed tomography (CT).

## Results

Variables	Relapse (N=14)	Non-relapse (N=73)	P
Age, median (interquartile range, IQR)	55 (48–62)	53 (45–66)	0.721
Male	11 (78.6)	44 (60.3)	0.218
Proven diagnosis (vs. Probable diagnosis)	3 (21.4)	22 (30.1)	0.749
Diabetes mellitus	9 (64.3)	25 (34.2)	0.035
Chronic lung disease	3 (21.4)	13 (17.8)	0.716

Variables	Relapse (N=14)	Non-relapse (N=73)	P
Charlson's comorbidity-weighted index score, mean ( $\pm$ standard deviation, SD)	6.4 ( $\pm$ 1.4)	4.8 ( $\pm$ 2.3)	0.017
Main underlying diseases			
Haematologic disease	11 (78.6)	49 (67.1)	0.535
Underwent stem cell transplantation	4 (28.6)	8 (11.0)	0.097
Underwent solid organ transplantation	4 (28.6)	21 (28.8)	1.000
Neutropenia > 7 days during initial treatment	9 (64.3)	38 (52.1)	0.400
Aspergillus antigen-positive week, median (IQR)	2.4 (0.0–3.9)	1.5 (0.0–2.0)	0.462
Duration of antifungal treatment			
Voriconazole (weeks), median (IQR)	15.8 (8.2–21.5)	19.5 (12.0–22.9)	0.251
Short voriconazole treatment duration	4 (28.6)	7 (9.6)	0.063
Voriconazole/all anti-mould agents (%), median (IQR)	89.5 (86.1–100)	89.9 (84.2–100)	0.516
Radiological treatment response			
Decreased number of involved lobes, median (IQR)	0 (0–1)	1 (0–2)	0.102
Decreased nodular size (cm), median (IQR)	1.8 (-1.4–3.4)	2.8 (0.9–4.1)	0.246
Radiological response	4 (28.6)	42 (61.8)	0.023
Complete response	3 (21.4)	10 (14.7)	0.687

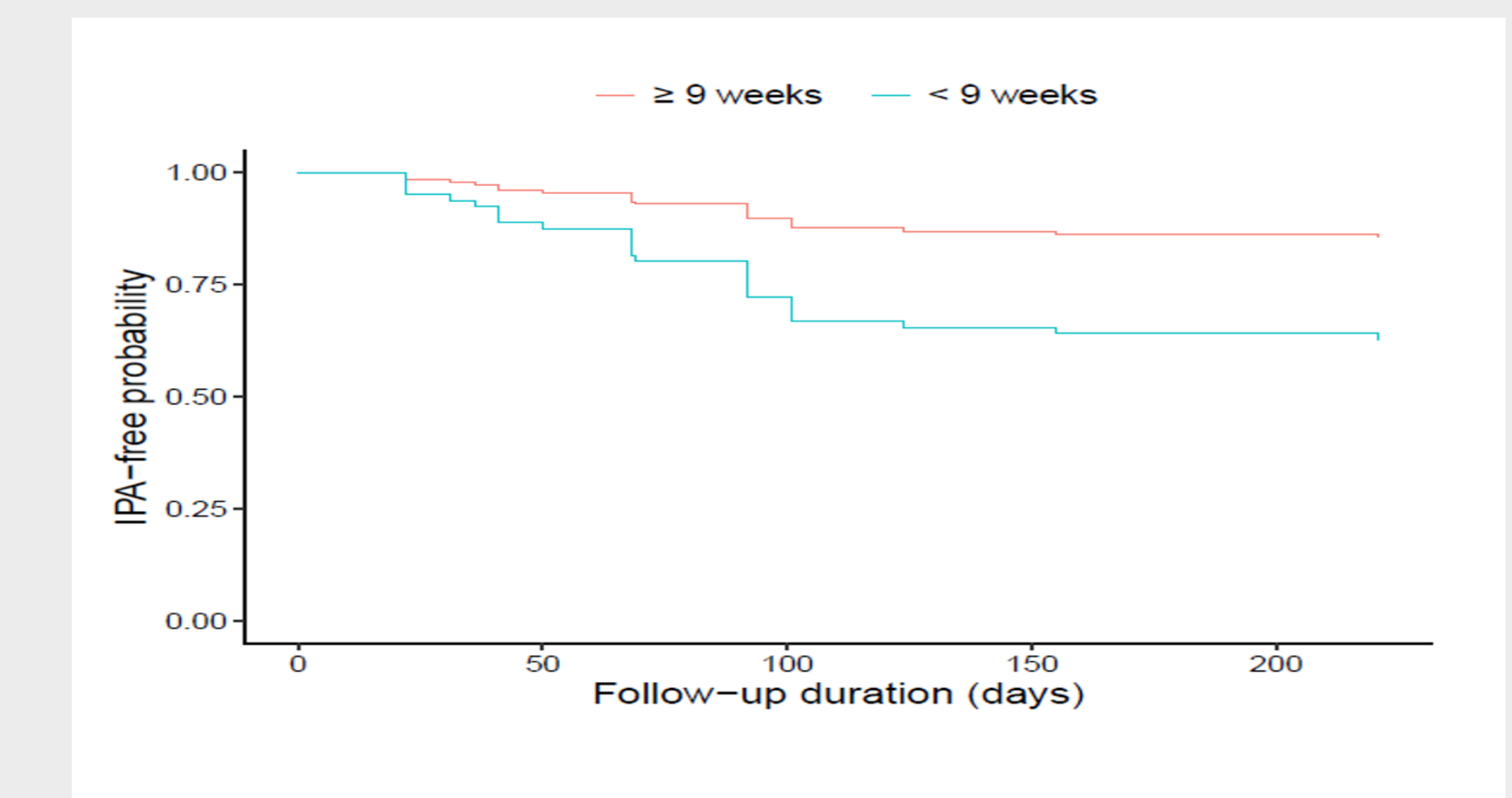
**Table 1. Clinical characteristics of all invasive pulmonary aspergillosis cases**

- Among 121 patients who had completed voriconazole treatment, 34 died or were lost to follow-up within 1 year after voriconazole treatment. Among all eligible patients (n=87), 14 (16.1%) experienced IPA relapse.
- Duration of voriconazole treatment tended to be shorter in the relapse group (median week [IQR], 15.8 [8.2-21.5] vs. 19.5 [12.0-22.9];  $P=0.251$ ).
- Radiological response (28.6% vs. 61.8%;  $P=0.023$ ) was significantly higher in the non-relapse group, but there was no significant difference in complete response (21.4% vs. 14.7%;  $P=0.687$ ).

Variables	aOR (95% CI)	P
Charlson comorbidity-weighted index score	1.8 (1.2–2.6)	0.003
Short voriconazole treatment duration	3.7 (1.1–12.3)	0.033
Radiological non-response	4.6 (1.2–17.5)	0.026

**Table 2. Risk factors for relapse of invasive pulmonary aspergillosis**

- Age, sex, number of initial involved lobes, any immunosuppressive events during treatment (neutropenia, graft-versus-host disease, rejection) were also included in the multivariable analysis, but they were not significantly related to relapse.



**Figure 1. Kaplan-Meier survival curves showing probability of being IPA-free based on duration of voriconazole therapy**

## Conclusion

- Short duration of voriconazole therapy and post-treatment radiological non-response were independent risk factors for relapse of IPA.
- Therefore, voriconazole treatment should be continued for at least 9 weeks in immunocompromised patients and the radiological response should be verified closely at the time of treatment termination.