

Current burden of Invasive Aspergillosis in patients with hematological malignancies: a meta-analysis and systematic review of the literature.

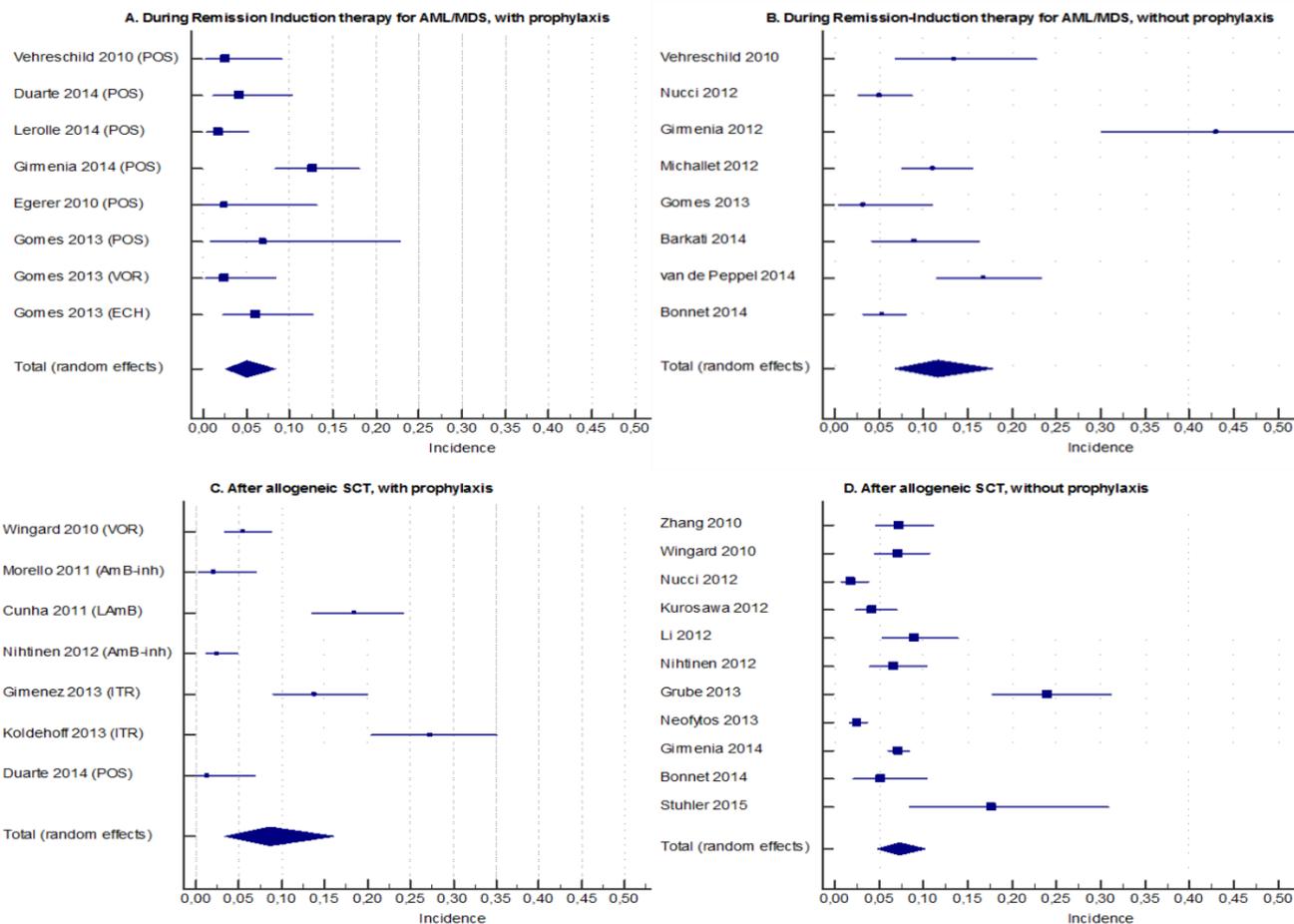
Background

Invasive aspergillosis (IA) is a major concern in hematology departments because of its associated morbidity and mortality. Reported incidence and mortality rates vary greatly in ever-changing circumstances including:

- changing antileukemic therapy
- advanced diagnostic methods
- emerging azole resistance
- intensive use of antifungal prophylaxis

We conducted a systematic review of the literature to present a comprehensive overview and meta-analysis of current - i.e. 2008-revised EORTC-MSG criteria era - incidence and case fatality rate (CFR) of IA.

Figure 1. Incidence of proven or probable invasive aspergillosis in different subgroups



1A. Incidence of IA in patients undergoing remission induction therapy for AML or MDS and using antifungal prophylaxis (Total number of patients: 1347. Pooled incidence 5.1%, 95%CI 2.6 – 8.3%). **1B.** Incidence of IA in patients undergoing remission induction therapy for AML or MDS not using antifungal prophylaxis (Total number of patients: 792. Pooled incidence 11.7%, 95%CI 6.7 – 17.9%). **1C.** Incidence of IA in patients after Allogeneic Stem Cell Transplantation and using antifungal prophylaxis (Total number of patients: 1383. Pooled incidence 8.6%, 95%CI 3.3-16.1%). **1D.** Incidence of IA in patients after Allogeneic Stem Cell Transplantation not using antifungal prophylaxis (Total number of patients: 5081. Pooled incidence 7.1%, 95%CI 6.0 – 8.4%)

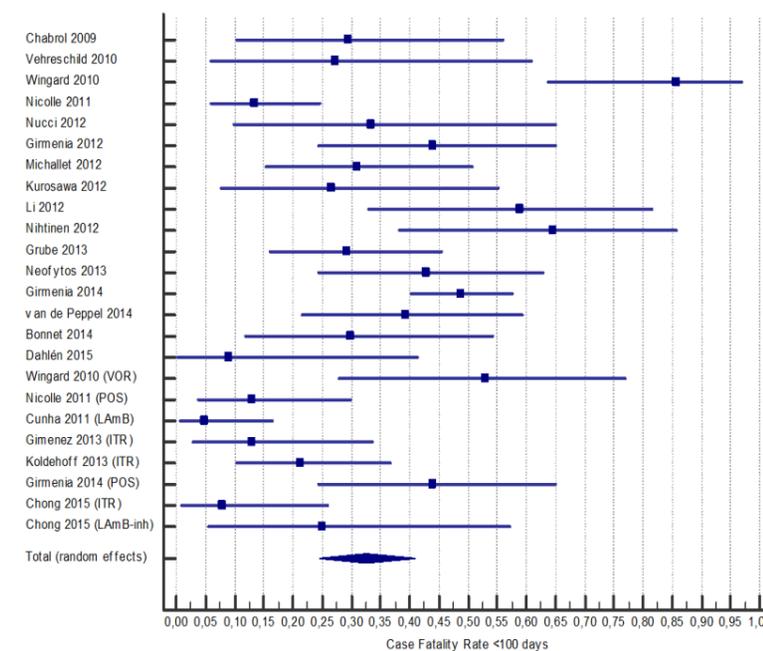
Legend: Size of squares represent relative study weight. Abbreviations between brackets denote method of prophylaxis used; POS denotes posaconazole; VOR voriconazole; ECH echinocandins; LAmB liposomal amphotericin B; AmB-inh amphotericin B deoxycholate inhalation; ITR itraconazole; AML acute myeloid leukemia; MDS myelodysplastic syndrome; SCT stem cell transplantation

Methods

A systematic search in PubMed, Embase and Web of Science was performed to identify all literature published between June 2008 and May 2016, reporting the incidence of IA in patient populations with an underlying hematological malignancy. Only studies with a cohort size of at least fifty adult patients and describing IA according to the updated EORTC/MSG 2008 criteria were eligible for inclusion. If incidence rates were reported but mortality rates were not, the authors were contacted to ask for the information.

Pooled incidence rates using a random effects model were calculated for specific patient populations and for using prophylaxis.

Figure 2. Reported Case Fatality Rate <100 days among all patients with Invasive Aspergillosis (IA) in studies with at least 10 cases. (Total number of cases of IA: 701. Total CFR100: 32.5%, 95%CI 24.6 – 40.8%)



Legend: Size of squares represent relative study weight. Abbreviations between brackets denote method of prophylaxis used; POS denotes posaconazole; VOR voriconazole; ECH echinocandins; LAmB Liposomal Amphotericin B; AmB-inh inhaled amphotericin B deoxycholate; ITR itraconazole.

Table 1. Incidence of invasive aspergillosis in patients with hematologic malignancy

Treatment phase	Number of patients	Number of cases of IA	Incidence/hematological disease episode, percentages (95%CI) [#]
RI-Therapy			
- All malignancies	6347	324	7.2 (4.8-11.6)
- AML and MDS only	3360	267	8.3 (6.1-10.8)
After Allogeneic HSCT	6991	528	8.6 (6.2-11.4)
Mixed populations*	6714	535	9.0 (6.7-11.6)
Total	20052	1387	8.2 (6.8-9.8)

Legend: #: Incidence rates are pooled using a Random Effects Model; RI denotes remission induction chemotherapy; HSCT Hematopoietic Stem Cell Transplantation; IA Invasive Aspergillosis; AML Acute Myeloid Leukemia; MDS Myelodysplastic Syndrome. *Mixed population includes all other study populations that could not be categorized elsewhere e.g. patients undergoing cord blood SCT. Data includes patients with and without mold-active antifungal prophylaxis.

Results

The systematic literature search yielded 1285 published articles and conference abstracts of which 69 publications met the preset inclusion criteria.

Overall, 20,052 patients were involved of which 1387 (6.9%) presented with probable or proven invasive aspergillosis within the study period.

Four forest plots that describe the incidence for different patient subgroups were constructed and shown in figure 1A-D. Another forest plot reflecting CFR's was constructed that includes all studies with at least 10 cases of IA and a reported CFR within 100 days (Figure 2, pooled CFR100: 0.325, 95%CI 0.246 – 0.408).

Conclusions

Pooled incidence rates of IA during Remission-Induction for AML or MDS differ considerably between populations with and without use of antifungal prophylaxis. Nonetheless, incidence in populations receiving prophylaxis remains substantial.

Reported CFR's showed great variability among the study populations. Most study data is observational and decisions on prophylaxis, treatment and diagnostic methods are not randomized. However, the data provides an extensive overview of real life clinical experience.

