# Managing invasive aspergillosis: impact on health and personalized prevention or treatment strategies

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# Chapter 2

## The burden of invasive aspergillosis in patients with haematological malignancy: a meta-analysis and systematic review.

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## ABSTRACT

**Objectives** Successful treatment of haematological malignancies is hampered by invasive aspergillosis (IA), a life-threatening fungal infection that occurs in at least 10% of haemato-oncological patients all over the world. Case fatality rates (CFR) may fluctuate over time, depending on host pathogen interactions as well as treatment and quality of patient care. We conducted a systematic review and meta-analysis of current - i.e. 2008-revised EORTC-MSG criteria era - incidence and CFR of IA in patients with a haematologic malignancy.

**Methods** A systematic search was performed to identify all literature reporting populations with a haematologic malignancy and the incidence of IA, defined according to the EORTC/MSG 2008 criteria. Pooled cumulative incidences and CFR within 100 days were estimated using a random effects model for predefined patient populations and stratified by antifungal prophylaxis use.

**Results** The systematic literature search yielded 1285 publications of which 49 met the inclusion criteria. Overall, 16.815 patients were involved of which 1056 (6.3%) developed IA. Incidence of IA ranged from 4% (during remission-induction, with prophylaxis) and 11% (during remission-induction, without prophylaxis). Use of antifungal prophylaxis was associated with a lower rate of IA, most prominent in the pre-HSCT population. The pooled CFR within 100 days was 29% (95%CI: 20% – 38%).

**Conclusions** This study confirms that IA poses a relevant threat in the treatment of haematologic cancer worldwide despite the universal use of antifungal prophylaxis. These outcomes inform scientists and other stakeholders about the current burden of IA and may be used globally to direct, implement and improve antifungal stewardship programs.

# INTRODUCTION

As an increasing number of patients survive with chronic or temporary conditions that compromise the immune system, the population at risk for invasive aspergillosis (IA) increases steadily. The advances in antileukaemic and antifungal therapy have contributed to an increased incidence and a decreased mortality risk of IA over time respectively (1-3). The increasing number of patients at risk has been mitigated by the implementation of different strategies to prevent IA (4). Guidelines concerning the use of antifungal prophylaxis, air filtration in haematology wards and pro-active diagnostic strategies have all been implemented in clinical practice. Emerging resistance of *Aspergillus* spp. against the triazoles, the class of antifungals most often used in prophylaxis and treatment of IA (5-8), forms a new challenge in managing IA.

New criteria for the diagnosis of IA have been published by the European Organization for the Treatment of Cancer in 2008 (9). The impact of these new criteria has been demonstrated in the analysis of historical cohorts and randomized controlled trials (RCTs) using the new criteria (10, 11). It is expected that this has influenced our view on the incidence and mortality of IA.

However, despite the developments in diagnostic strategies and prophylaxis regimens, estimations of the impact of IA in this population remain substantial (12). The incidence and mortality within patient populations treated for haematological malignancy is especially high due to their prolonged and severe immunocompromised status. Two treatment phases can be distinguished when assessing the impact of IA in patients treated with haematological malignancy: during remission-induction and consolidation chemotherapy and after allogeneic haematopoietic stem cell transplantation (HSCT). The reported incidence of IA ranges from 8% after allogeneic transplantation (13) to 12% before transplantation (1). Autologous transplantation yields a considerably lower risk (2%) (13).

Not only the incidence, but also the mortality rates differ according to the underlying condition. A systematic review about mortality rates according to the underlying condition has last been performed in 2001 by Lin et al (2), and it was found that case fatality rates (CFRs) are high (up to 88% in patients with haematological malignancy) and may differ according to the underlying condition. Current guidelines emphasise the importance of local incidence in the decision to use universal mould-active prophylaxis (14, 15). However, changes in CFR should also be taken into account when assessing the harm-benefit balance of prophylaxis.

To be able to make a rational choice for local measures to prevent and treat IA, it is critical to have knowledge of how institutional incidence and mortality rates relate to global rates. This necessitates an up-to-date analysis based on contemporary data. We therefore conducted a systematic review and meta-analysis to provide an up-to-date overview of the current incidence of IA in this patient population. Secondly, we performed a meta-analysis of the CFRs for all studies where this rate was available.

## METHODS

### Systematic literature review

We conducted a systematic literature review according to PRISMA guidelines (16) to identify RCTs and cohort studies reporting the incidence rates of IA in patients with haematological malignancies. A search of PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases was performed on April 15$^{th}$ 2016. The search strategy is available in the supplemental data. We limited our strategy to studies in English. In addition, the references of key articles were searched to identify other eligible studies.

### Eligibility criteria

The eligibility of a study was assessed according to the following items: (A) it was a cohort study or randomised controlled trial (RCT) (B) the population underwent remission-induction/ consolidation therapy or HSCT for haematological malignancy, (C) the number of included patients was >50, (D) incidence was reported or could be extracted or estimated from reported data, (E) IA diagnosis was classified as proven, probable or possible IA according to the revised 2008 EORTC criteria for the diagnosis of invasive fungal disease. Only proven and probable cases have been taken into account in the calculation of incidence and CFR. As the primary goal of the study was to evaluate the incidence rates, the report of CFR was not used as an inclusion criterion.

### Data extraction

Studies were categorized according to underlying haematological disease, haematological treatment phase, antifungal prophylaxis and study method (cohort or RCT). Cumulative incidences and CFRs were extracted or calculated using the total number of patients, the total number of proven and probable IA, and the total number of deaths within 100 days of diagnosis of proven or probable IA. In case of a missing CFR in an included article, the corresponding author was contacted and requested for the additional data.

### Risk of bias assessment

Several study characteristics that reflect risk of bias were assessed at the study level. Because it was expected that most eligible studies would be observational, the most important items that determine the risk of bias were assessed according to the Newcastle-Ottawa guidelines for observational studies (17). Most items that concern accuracy of the selection of the population at risk and outcome ascertainment have been included as selection criteria. Only the adequacy of follow-up remained to be appraised for each study. A proportion of lost to follow-up of >5%, or an unknown proportion, was considered a high risk of bias.

### Statistical analysis

A meta-analysis based on risks of individual studies was performed using the STATA metaprop command (18). To increase the homogeneity of the different populations, four different categories of patient populations were defined for subgroup analyses. These categories are: during remission induction with (I) or without (II) mould-active antifungal prophylaxis, and after allogeneic HSCT with (III) or without (IV) mould-active prophylaxis. Only studies that reported the incidence rates of IA divided in discernible treatment groups of at least 25 participants were included in this subgroup analysis. To obtain the pooled CFRs, only studies that reported at least 10 cases of IA were considered. The data for all subgroup analyses were pooled at the aggregate patient data level. A random effects model was the most appropriate method to pool the results due to the expected clinical heterogeneity. All analyses were performed and figures were constructed using Stata Statistical Software: Release 12.1. College Station, Texas: StataCorp LP.

## RESULTS

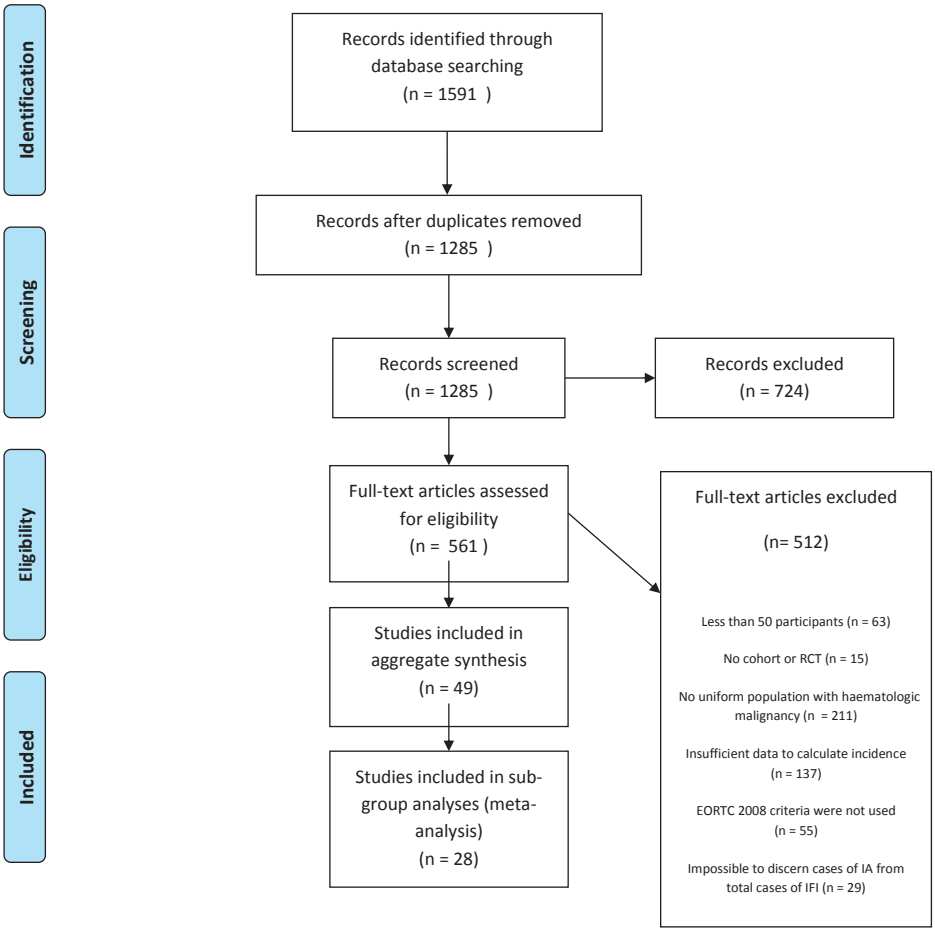
### Total population

The systematic literature search yielded 1285 publications of which 49 met the inclusion criteria. Figure 1 shows the flowchart of the selection process. From the 49 publications, 68 distinct study populations were identified (table 1). From these 68 populations, 31 could be grouped according to the four categories we defined in the methods section: (I) 8 populations (19-24) during remission-induction therapy, with prophylaxis, (II) 8 populations (21, 23, 25-30) during remission-induction therapy, without prophylaxis, (III) 7 populations (31-37) after allogeneic HSCT, with prophylaxis, (IV) 9 populations (27, 32, 35, 38-43) after allogeneic HSCT, without prophylaxis. For the analysis of CFRs, 18 populations (23, 26-30, 32-34, 37-40, 44-46) were eligible for inclusion in the meta-analysis, of which 14 were also included in the meta-analysis of incidence rates. I-squared statistics for most analyses yielded high values with significant p-values, suggesting large heterogeneity between populations.

### Summary statistics

Table 1 shows the characteristics of included studies that report the incidence of IA in patients with a haematological malignancy. Overall, 16.815 patients were involved of which 1056 (6.3%) were diagnosed with probable or proven IA. In 31 studies, describing 645 cases of IA, the CFR within 100 days was available; the crude aggregate amounts to 33%. These summary estimates are derived from a diverse population, with different prophylactic regimes and underlying disease.

**Figure 1.** Flowchart of literature selection




## Risk of bias assessment

The adequacy of follow-up is shown in table 1. Most studies (n=32) did not report loss to follow-up rates but did exclude patients that failed to complete the entire treatment episode in the same hospital. Some studies report moderately high rates of loss to follow-up up to 9.8%. All studies with more than 5% of loss to follow-up were classified as "increased risk of bias". Egger's test for small-study effects yielded a p-value of <0.001 for the analysis of incidence rates and a p-value of 0.094 for the analysis of CFR. This indicates that a risk of publication bias may be present in the analysis of incidence rates.

## Incidence

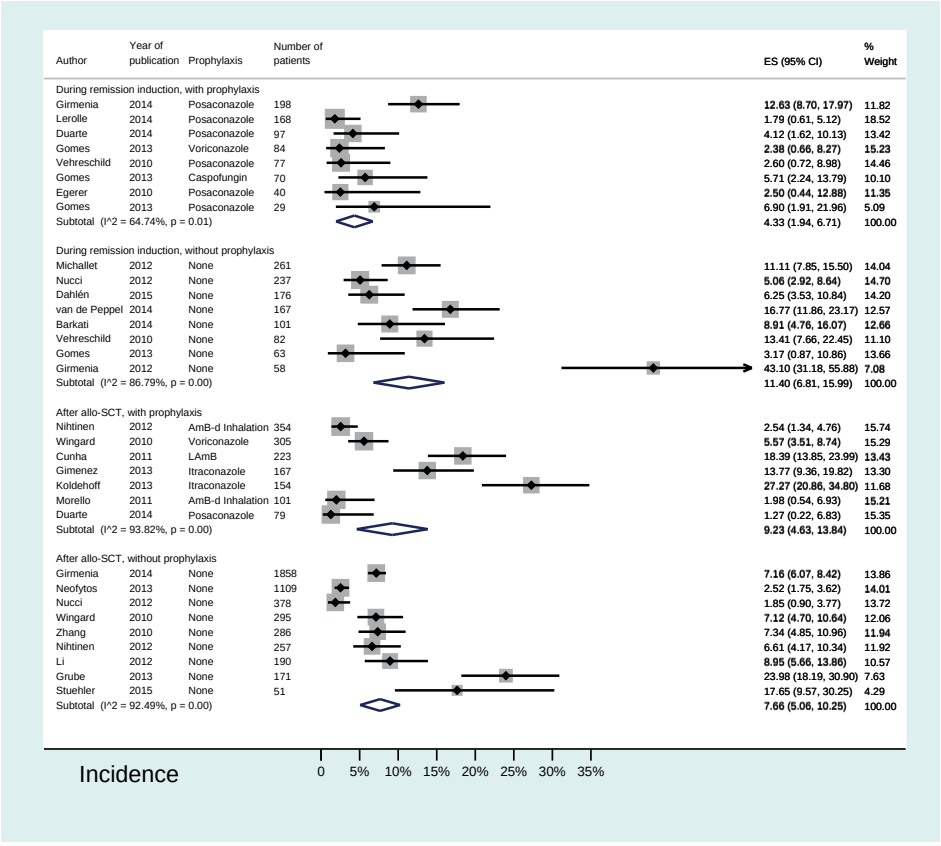
The meta-analysis of the IA incidence for the four subgroups is shown in figure 2. Statistical heterogeneity between studies was shown for all subpopulations. The pooled risks in our four subgroups are: (I) During remission-induction, with prophylaxis: 4% (95%CI: 2%-7%) (II)

During remission-induction, without prophylaxis: 11% (95%CI: 7%-16%) (III) After allogeneic HSCT, with prophylaxis: 9% (95%CI: 5%-14%) (IV) After allogeneic HSCT, without prophylaxis: 7% (5%-10%).

### Case fatality rates

Figure 3 shows a forest plot of the CFRs within 100 days of the date of diagnosis of IA. The CFR varies clearly between studies, and ranged from 5% to 65%. The pooled CFR within 100 days for all 18 populations (reporting 535 cases of IA) is 29% (95%CI 20% - 38%). No evident difference between population categories was found. Six of our included studies (22, 24, 25, 27, 29, 32) had available information on the CFR of proven cases of IA, yielding a CFR of 78% in 27 proven cases of IA.

**Figure 2.** Meta-analysis of incidence of invasive aspergillosis in different subpopulations




**Legend**: Allo-SCT denotes allogeneic stem cell transplantation; ES estimate; CI confidence interval. The black dot represents the individual studies effect. The size of the grey squares represents the study weight according to the random effects model. The black lines represent the 95% confidence intervals of different studies. The diamonds represent the overall (or subgroup) effects, the outer edges of the diamonds represent the 95% confidence intervals.

**Table 1.** Characteristics of all included studies

| Author | Study design | Country | Pub year | Study period | Prophylaxis |
|---|---|---|---|---|---|
| **During Remission-induction therapy, with prophylaxis** | | | | | |
| Gomes et al(21) | Cohort | Texas, USA | 2014 | 2009-2011 | Anidulafungin |
| Gomes et al(21) | Cohort | Texas, USA | 2014 | 2009-2011 | Caspofungin |
| Gomes et al(21) | Cohort | Texas, USA | 2014 | 2009-2011 | Micafungin |
| Duarte et al(20) | Cohort | Spain | 2014 | 2007-2011 | Posaconazole |
| Lerolle et al(22) | Cohort | France | 2014 | 2007-2010 | Posaconazole |
| Girmenia et al(19) | Cohort | Italy | 2014 | 2007-2010 | Posaconazole |
| Gomes et al(21) | Cohort | Texas, USA | 2014 | 2009-2011 | Posaconazole |
| Vehreschild et al(23) | Cohort | Germany | 2010 | 2006-2008 | Posaconazole |
| Egerer et al(24) | Cohort | Germany | 2010 | 2006-2009 | Posaconazole |
| Gomes et al(21) | Cohort | Texas, USA | 2014 | 2009-2011 | Voriconazole |
| **Crude total** | | | | | |
| **During Remission-induction therapy, without prophylaxis** | | | | | |
| van de Peppel et al (29) | Cohort | The Netherlands | 2014 | 2005-2012 | None |
| Barkati et al(25) | Cohort | Canada | 2014 | 2008-2010 | None |
| Gomes et al(21) | Cohort | Texas, USA | 2013 | 2009-2011 | None |
| Girmenia et al(30) | Cohort | Italy | 2012 | 2006-2007 | None |
| Michallet et al(26) | Cohort | France | 2012 | 2004-2007 | None |
| Nucci et al(27) | Cohort | Brazil(MC) | 2013 | 2007-2009 | None |
| Vehreschild(23) | Cohort | Germany | 2010 | 2003-2005 | None |
| Dahlén et al(28) | Cohort | Sweden | 2016 | 2008-2013 | None |
| **Crude total** | | | | | |
| **After allogeneic SCT, with prophylaxis** | | | | | |
| Morello et al(31) | Cohort | Italy | 2011 | 1999-2009 | AmBd inhalation |
| Nihtinen et al(32) | Cohort | Finland | 2012 | 2001-2005 | AmBd inhalation |
| Koldehoff et al(33) | Cohort | Germany | 2013 | 2002-2012 | Itraconazole |
| Giménez et al(34) | Cohort | Spain | 2013 | 2005-2011 | Itraconazole |
| Wingard et al(35) | RCT | USA (MC) | 2010 | 2003-2006 | Voriconazole |
| Duarte et al(36) | Cohort | Spain | 2014 | 2007-2011 | Posaconazole |
| Cunha et al(37) | Cohort | Italy | 2011 | 2003-2010 | LAmB |
| **Crude total** | | | | | |

| Study population | Notes | # pts | # IA cases | IA incidence | CFR within 100 days | CFR provided by author | Lost to follow-up |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| During RI-therapy | Not included in forest plot due to number of patients <25 | 18 | 1 | 5.5% | NA | NA | <5% |
| During RI-therapy | | 70 | 4 | 5.7% | NA | NA | <5% |
| During RI-therapy | Not included in forest plot due to number of patients <25 | 11 | 1 | 9.0% | NA | NA | <5% |
| During RI-therapy | | 97 | 4 | 4.1% | NA | NA | NA |
| During RI-therapy | | 168 | 3 | 1.8% | 66% | NA | <5% |
| During RI-therapy | | 198 | 25 | 12.6% | 44% | NA | NA |
| During RI-therapy | | 29 | 2 | 6.8% | NA | NA | <5% |
| During RI-therapy | | 77 | 2 | 2.6% | 50% | Yes | None |
| During RI-therapy | | 40 | 1 | 2.5% | 0 | NA | NA |
| During RI-therapy | | 84 | 2 | 2.3% | NA | NA | <5% |
| | | **792** | **45** | **5,7%** | **47% (in 30 cases of IA)** | | |
| | | | | | | | |
| During RI-therapy | | 167 | 28 | 16.7% | 39% | NA | None |
| During RI-therapy | | 101 | 9 | 8.9% | 11% | Yes | NA |
| During RI-therapy | | 63 | 2 | 3.2% | NA | NA | <5% |
| During RI-therapy | Renovation work during study period | 58 | 25 | 43.1% | 36% | NA | NA |
| During RI-therapy | | 261 | 29 | 11% | 31% | NA | NA |
| During RI-therapy | | 237 | 12 | 5.1% | 33% | Yes | <5% |
| During RI-therapy | | 82 | 11 | 13.4% | 27% | Yes | None |
| During RI-therapy | | 176 | 11 | 6.25% | 9% | NA | 9% |
| | | **1145** | **127** | **11.1%** | **30% (in 125 cases of IA)** | | |
| | | | | | | | |
| After allo-HSCT | | 101 | 2 | 2.0% | NA | NA | NA |
| After allo-HSCT | | 354 | 9 | 2.5% | 55% | NA | NA |
| After allo-HSCT | Only AML patients | 154 | 42 | 27.2% | 21% | Yes | NA |
| After allo-HSCT | | 167 | 23 | 13.8% | 13% | Yes | NA |
| After allo-HSCT | | 305 | 17 | 5.6% | NA | NA | None |
| After allo-HSCT | | 79 | 1 | 1.3% | NA | NA | NA |
| After allo-HSCT | | 223 | 41 | 18.4% | 5% | Yes | NA |
| | | **1383** | **135** | **9,8%** | **17% (in 115 cases of IA)** | | |

**Table 1.** Characteristics of all included studies (continued)

| Author | Study design | Country | Pub year | Study period | Prophylaxis |
|---|---|---|---|---|---|
| **After allogeneic SCT, without prophylaxis** | | | | | |
| Girmenia et al(19) | Cohort | Italy (MC) | 2014 | 2008-2010 | None |
| Grube et al(39) | Cohort | Germany | 2013 | 1998-2006 | None |
| Neofytos et al(40) | Cohort | USA | 2013 | 2000-2009 | None |
| Li et al(41) | Cohort | China | 2012 | 2000-2007 | None |
| Nihtinen et al(32) | Cohort | Finland | 2012 | 1996-2001 | None |
| Nucci et al(27) | Cohort | Brazil (MC) | 2013 | 2007-2009 | None |
| Zhang et al(42) | Cohort | China | 2010 | 2000-2007 | None |
| Wingard et al(35) | RCT | USA (MC) | 2010 | 2003-2006 | None |
| Stuehler et al(43) | Cohort | Switzerland | 2015 | 2012-2013 | None |
| **Crude total** | | | | | |
| **Other populations, with prophylaxis** | | | | | |
| Lerolle et al(22) | Cohort | France | 2014 | 2007-2010 | Posaconazole |
| Barnes et al(56) | Cohort | UK | 2013 | 2005-2009 | Itraconazole |
| Cattaneo et al(57) | RCT | Italy (MC) | 2011 | 2007-2009 | Caspofungin |
| Chabrol et al(45) | Cohort | France | 2009 | 2003-2006 | Voriconazole |
| Chong et al(44) | Cohort | The Netherlands | 2015 | 2005-2008 | Itraconazole |
| Chong et al(44) | Cohort | The Netherlands | 2015 | 2008-2012 | Itraconazole + Aerosolized LAmB |
| Vehreschild et al(58) | Cohort | Germany | 2014 | 2009-2011 | Posaconazole and micafungin |
| Nachbaur et al(59) | Cohort | Austria | 2015 | 2011-2012 | Micafungin |
| Nicolle et al(60) | Cohort | France | 2011 | 2004-2007 | Posazonazole |
| Parody et al(61) | Cohort | Spain | 2015 | 2003-2009 | Mixed (66% voriconazole or posaconazole, 22% itraconazole, 11% Amb-d inhalation) |
| Springer et al (62) | Cohort | Austria | 2016 | NA | Mixed (micafungin and/or posaconazole and/or voriconazole, proportions unknown) |
| Takagi et al(63) | Cohort | Japan | 2014 | 2006-2008 | Voriconazole |
| **Total** | | | | | |

| Study population | Notes | # pts | # IA cases | IA incidence | CFR within 100 days | CFR provided by author | Lost to follow-up |
|---|---|---|---|---|---|---|---|
| After allo-HSCT | | 1858 | 133 | 7.1% | 49% | NA | NA |
| After allo-HSCT | | 171 | 41 | 2.4% | 29% | NA | NA |
| After allo-HSCT | | 1109 | 28 | 2.5% | 43% | NA | NA |
| After allo-HSCT | | 190 | 17 | 8.9% | 60% | NA | None |
| After allo-HSCT | | 257 | 17 | 6.6% | 65% | NA | NA |
| After allo-HSCT | | 378 | 7 | 19% | 0% | Yes | <5% |
| After allo-HSCT | | 286 | 21 | 7.3% | NA | NA | NA |
| After allo-HSCT | | 295 | 21 | 7.1% | NA | NA | None |
| After allo-HSCT | | 51 | 9 | 17.6% | 22% | Yes | 9.8% |
| | | **4595** | **294** | **6,4%** | **44% (in 252 cases of IA)** | | |
| With GvHD | | 96 | 0 | 0% | 0% | NA | <5% |
| Mixed (during RI and after allo-HSCT) | | 549 | 53 | 9.8% | NA | NA | NA |
| During RI-therapy for AML, MDS or ALL | | 93 | 5 | 5.4% | 0% | NA | None |
| During RI-therapy for AML or ALL | Renovation work during study period | 88 | 3 | 4.5% | 33% | NA | None |
| Mixed (during RI and after allo- or auto-HSCT) | | 108 | 12 | 9.4% | 25% | NA | NA |
| Mixed (during RI and after allo- or auto-HSCT) | | 127 | 25 | 23.1% | 8% | NA | NA |
| RI or SCT for different hem. mal. | | 106 | 1 | 0.9% | 100% | NA | None |
| Mixed (during RI and after allo- or auto-HSCT) | | 100 | 2 | 2.0% | 0% | NA | NA |
| During RI or after allo-HSCT for AML | | 1019 | 31 | 3.0% | NA | NA | NA |
| After allo-HSCT from unrelated donor | | 299 | 55 | 18.4% | NA | NA | NA |
| During RI for different HM and after allo- HSCT | | 84 | 4 | 4.8% | NA | NA | NA |
| After cord-blood HSCT | | 52 | 1 | 1.9% | 0 | NA | NA |
| | | **2721** | **192** | **7,1%** | **24% (in 49 cases of IA)** | | |

**Table 1.** Characteristics of all included studies (continued)

| Author | Study design | Country | Pub year | Study period | Prophylaxis |
|---|---|---|---|---|---|
| **Other populations, without prophylaxis** | | | | | |
| Aguado et al(64) | RCT | Spain (MC) | 2015 | 2011-2012 | None |
| Chabrol et al(45) | Cohort | France | 2009 | 2003-2006 | None |
| Erdmann et al(65) | Cohort | Germany | 2016 | 2012-2013 | None |
| Falantes et al(66) | Cohort | Spain | 2014 | 2009-2012 | None |
| Gheith et al(67) | Cohort | Tunisia | 2015 | 2009-2011 | None |
| Kim et al(68) | Cohort | SE-Asia | 2012 | 2003-2009 | None |
| Mendes(69) | Cohort | Brazil | 2012 | 2001-2009 | None |
| Nicolle et al(60) | Cohort | France | 2011 | 2004-2007 | None |
| Parody et al(61) | Cohort | Spain | 2015 | 1997-2003 | None |
| Pomares et al(70) | Cohort | Spain | 2016 | 2007-2015 | None |
| Rocchi et al (71) | Cohort | France | 2014 | 2010-2012 | None |
| Springer et al(62) | Cohort | Austria | 2016 | NA | None |
| **Crude total** | | | | | |
| **Populations with unknown or mixed prophylaxis** | | | | | |
| Reischies et al(72) | Cohort | Austria | 2016 | 2014-2015 | Unknown |
| Morrissey et al(73) | RCT | Australia, MC | 2013 | 2005-2009 | Mixed (37% itraconazole, 62% non-mould-active) |
| Kurosawa et al(46) | Cohort | Japan, MC | 2012 | 2006-2008 | Unknown |
| Kurosawa et al(46) | Cohort | Japan, MC | 2012 | 2006-2008 | Unknown |
| Kimura et al(74) | Cohort | Japan | 2015 | 2007-2012 | Mixed (38% itraconazole, voriconazole or micafungin, 62% non-mould- active) |
| Cattaneo et al(57) | RCT | Italy (MC) | 2011 | 2007-2009 | Mixed (83% mould-active azole, 17% no mould-active prophylaxis) |
| Loschi et al(75) | Cohort | France | 2015 | 2003-2008 | Unknown |
| Loschi et al(75) | Cohort | France | 2015 | 2003-2008 | Unknown |

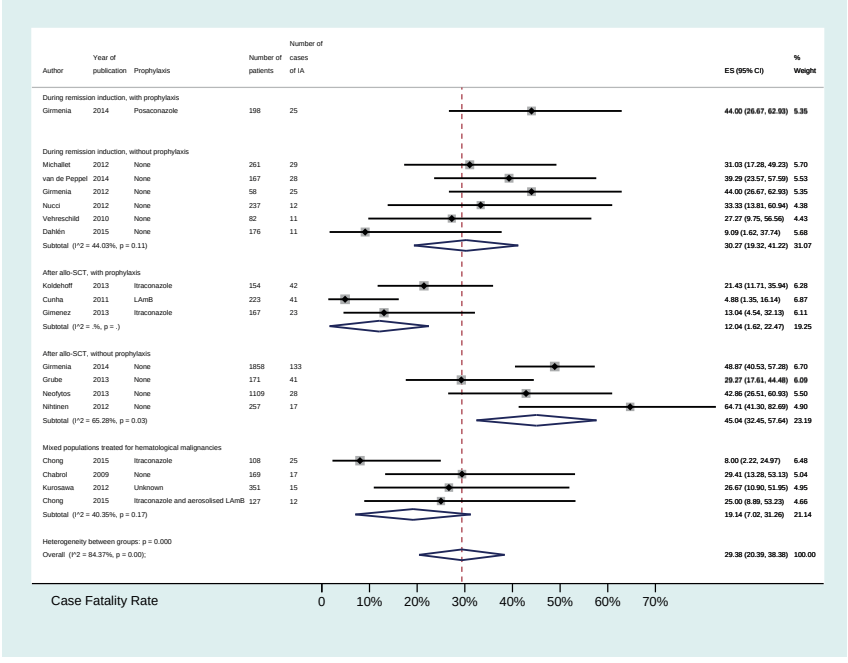
| Study population | Notes | # pts | # IA cases | IA incidence | CFR within 100 days | CFR provided by author | Lost to follow-up |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| During RI for different HM and after allo-HSCT | | 203 | 18 | 8.9% | NA | NA | <5% |
| During RI-therapy for AML or ALL | Renovation work during study period | 169 | 17 | 12.4% | 29% | NA | None |
| After allo- or auto-HSCT | | 104 | 6 | 5.8% | NA | NA | None |
| During RI-therapy with azacitidine as salvage therapy | | 64 | 6 | 9.3% | 33% | NA | NA |
| During RI-therapy for AML and ALL | Renovation work during study period | 91 | 9 | 9.9% | NA | NA | NA |
| Different HM treated with Alemtuzumab as frontline, salvage or conditioning regimen. | | 182 | 15 | 8.2% | NA | NA | NA |
| After allo or auto-HSCT | | 429 | 17 | 4.0% | NA | NA | NA |
| During RI or after allo-HSCT for AML | | 1059 | 60 | 5.7% | NA | NA | NA |
| After allo-HSCT from unrelated donor | | 135 | 32 | 23.7% | NA | NA | NA |
| AML or high-risk MDS treated with Azacitidine | | 121 | 1 | 0.8% | 100% | NA | NA |
| During RI for different HM and after allo- HSCT | | 53 | 9 | 16.9% | 11% | NA | NA |
| During RI for different HM and after allo- HSCT | | 129 | 14 | 10.9% | NA | NA | NA |
| | | **2739** | **204** | **7,4%** | **27% (in 33 cases of IA)** | | |
| | | | | | | | |
| After allo- or auto-HSCT | | 45 | 2 | 4.4% | 50% | Yes | NA |
| During RI for different HM and after allo- or auto-HSCT | | 140 | 18 | 12.9% | NA | NA | 3.8% |
| After allo-HSCT | Questionnaire-based | 351 | 15 | 4.2% | 27% | Yes | NA |
| During RI-therapy for different HM | Questionnaire-based | 2224 | 8 | 0.4% | 0% | Yes | NA |
| After allo-HSCT | | 96 | 0 | 0% | NA | NA | NA |
| During RI-therapy | | 82 | 3 | 3.7% | 0% | NA | None |
| During RI-therapy for AML | Renovation work during study period | 146 | 8 | 5.5% | 50% | Yes | 6.2% |
| During RI-therapy for ALL | Renovation work during study period | 49 | 0 | 0 | NA | NA | 6.2% |

**Table 1.** Characteristics of all included studies (continued)

| Author | Study design | Country | Pub year | Study period | Prophylaxis |
|---|---|---|---|---|---|
| Loschi et al(75) | Cohort | France | 2015 | 2003-2008 | Unknown |
| Loschi et al(75) | Cohort | France | 2015 | 2003-2008 | Unknown |
| **Crude total** | | | | | |
| **Crude total among all populations with prophylaxis** | | | | | |
| **Crude total among all populations without prophylaxis** | | | | | |
| **Crude total among all patient categories (including mixed or unknown prophylaxis)** | | | | | |

**Legend**: Pub year denotes year of publication, CFR: case fatality rate, IA: invasive aspergillosis, AML: acute myeloid leukaemia, MDS: myelodysplastic syndrome, ALL: acute lymphoid leukaemia, RI: remission-induction, Allo-: allogeneic, Auto-: autologous, HSCT: haematopoietic stem cell transplantation, LAmB: liposomal amphotericin B, AmbD: amphotericin B deoxycholate, HM: haematological malignancies, pts: patients, NA: not available

**Figure 3.** Meta-analysis of case fatality rates within 100 days of diagnosis of invasive aspergillosis in different subpopulations




**Legend:** Allo-SCT denotes allogeneic stem cell transplantation; ES estimate; CI confidence interval. The black dot represents the individual studies effect. The size of the grey squares represents the study weight according to the random effects model. The black lines represent the 95% confidence intervals of different studies. The diamonds represent the overall (or subgroup) effects, the outer edges of the diamonds represent the 95% confidence intervals.

| Study population | Notes | # pts | # IA cases | IA incidence | CFR within 100 days | CFR provided by author | Lost to follow-up |
|---|---|---|---|---|---|---|---|
| After allo-HSCT | Renovation work during study period | 58 | 1 | 1.7% | 0% | Yes | 6.2% |
| After auto-HSCT | Renovation work during study period | 249 | 4 | 1.6% | 0% | Yes | 6.2% |
| | | **3440** | **59** | **1,7%** | **22% (in 41 cases of IA)** | | |
| | | **# pts** | **# IA cases** | **IA incidence** | **CFR within 100 days** | | |
| | | **4896** | **372** | **7,6%** | **23% (in 94 cases of IA)** | | |
| | | **8479** | **625** | **7,4%** | **39% (in 410 cases of IA)** | | |
| | | **16815** | **1056** | **6.3%** | **33% (in 645 cases of IA)** | | |

# DISCUSSION

## Summary

This meta-analysis summarises all relevant published findings related to incidence and CFR of IA in cohorts of patients treated for haematological cancer in the age after the 2008 revised EORTC criteria for the diagnosis of IA (9). Incidence rates varied between 4% and 12% depending on the treatment phase and use of prophylaxis. The incidence of IA is lower in populations with mould-active prophylaxis, which is most evident in the pre-HSCT population. However, the incidence remained substantial despite prophylaxis with 4% in the pre-HSCT, and 9% in the post-HSCT population.

## Efficacy of antifungal prophylaxis

No conclusions can be drawn concerning the efficacy of the type of antifungal prophylaxis due to the study heterogeneity and non-comparative nature of the included studies. Most populations in the pre-HSCT period used posaconazole as antifungal chemoprophylaxis. In the post-HSCT period more different types of prophylaxis were used, possibly contributing to the observed increased heterogeneity in this group.

## Case fatality rates

The pooled CFR within 100 days was 29% with a large variety between studies. The relatively large variety is possibly due to the low number of participants and population heterogeneity. The CFR did not evidently differ between treatment phases or between populations with and without use of antifungal prophylaxis. As a higher fungal load is associated with more apparent radiological signs, increased chance of successful culture and higher levels of galactomannan in serum or BAL-fluid, increased diagnostic certainty impacts CFR as well. Only 6 of our

included studies had available information on the CFR of proven cases of IA aggregating to a CFR of 72%, which is remarkably higher than the total CFR.

The alleged association between breakthrough infection (i.e. occurrence of IA despite adequate mould-active prophylaxis) and increased mortality that was earlier reported (22, 47, 48) was not found in our meta-analysis. Our data contradict the hypothesis that occurrence of infection despite adequate triazole-based prophylaxis is more often caused by triazole-resistant *Aspergilllus* (22, 47). As resistant infection is associated with increased mortality, it would be expected to impact the case fatality rates (7, 49).

Recently, an increasing number of studies describing mortality after IA report the cause of death or the probability of IA-related death (50). From a clinical point of view, and supported by literature (50-52), death attributable to IA is hard to establish in the haematological patient that usually faces multiple competing risks with high mortality during their treatment. Factors associated with IA can contribute to an increased mortality risk, independently of the presence of IA (29, 41, 53). As an alternative to presenting IA-related death, a relatively short CFR of 100 days after diagnosis has been used. It is however plausible that a considerate proportion of patients die from a cause that has no relation to IA. Therefore, the crude mortality rates overestimate the IA-attributable mortality, although this is difficult to quantify (54, 55).

**Results in context of existing evidence**

To this date, no systematic studies on the incidence of IA in the era after the 2008 revised EORTC criteria have been published in English literature. CFRs in this population have last been presented in a meta-analysis published in 2001 which reports a CFR of 49.3% for patients with leukaemia or lymphoma and 86.7% for patients that underwent a HSCT (2). These numbers contrast with the aggregate rate of 29% in our meta-analysis. Since the publication of the aforementioned paper, the introduction of novel antifungals and improvements in diagnostic techniques have been important factors in diminishing the CFR. Our results are consistent with more recent studies of large cohorts of patients with haematological malignancies. Published in the pre-2008 revised EORTC-definitions era, the SEIFEM-cohort published by Pagano et al (1) in 2006, yields an overall incidence of invasive mould infection of 7% in the pre-HSCT period in AML patients and an overall CFR within 30 days of 38%.

Because this meta-analysis only included studies from the period after implementation of the EORTC-definitions, it is important to take the effect of the guidelines themselves on the reporting of incidence and mortality in consideration. Studies that have retrospectively reclassified patients at risk for IA found that implementation of the new criteria decreases the incidence of probable or proven IA (10, 11). As an increased diagnostic certainty is associated with an increased CFR (10), it is to be expected that the CFR would be higher after implementation of the new criteria. This phenomenon is not observed when comparing our estimate to the aforementioned literature.

## Strengths and weaknesses

An important strength of this study is the large quantity of data that could be analysed. A total of 49 studies describing 16815 patients were included in the analysis, of which 7915 remained in the subgroup analyses. Additionally, study authors have been contacted concerning incomplete fatality data to provide a more complete overview. Another strength is that all presented CFRs originate from studies where incidence rates were also available. This allows for interpretation of the data in specific populations at risk of IA. Weaknesses of the study mainly comprise different sources of bias. Selection bias is of general concern in all observational studies and comparisons that we can make between groups are in a non-randomized setting. Also, study heterogeneity contributes to increased difficulty of the interpretation of differences between groups. Although both the treatment of haematological malignancy and diagnosis of IA are globally regulated in guidelines, small individual differences between study centres are expected to impact the comparability of the different studies. To account for this observed heterogeneity, a random effect model has been used; however, this does not remove it. Publication bias is a known problem of systematic reviews and could have influenced our conclusions. However, since both an unexpectedly high or low incidence of IA could improve the chances of publication, this possible source of bias is expected to have a minor effect as compared to meta-analyses measuring treatment effects. This was confirmed by the lack of evident asymmetry in the forest plots sorted by number of study participants.

## Conclusion

Our first conclusion is that incidence rates are substantial despite the implementation of universal antifungal prophylaxis. Secondly, the pooled CFR of IA amounts to 29%, a relatively low rate when compared to historical cohorts and the last published meta-analysis (2). This study summarizes data of global occurrence and mortality of IA in a comprehensive manner and provides the background necessary for the rationale of preventive measures. It is shown that IA has an important clinical impact in patients treated for haematological malignancy. The disease poses a relevant threat in the treatment of haematological cancer worldwide. To attempt to reduce the burden, new solutions in the field are necessary as antifungal drugs are shown to be imperfect in both treatment and prevention of IA.

Therapeutic or prophylactic failure of antifungal agents, both associated with inherently limited drug efficacy and rising resistance all over the world, are currently the greatest challenges that we face in the field. Tackling the problem of resistance and managing breakthrough infection becomes an increasingly important part in the management of IA and we currently have only limited possibilities to do so. Future research should aim to provide clinicians with better options in facing these challenges.

These outcomes inform scientists and other stakeholders with evidence about the current burden of IA. This information may be globally used to direct, implement and improve antifungal stewardship programs.

**Contributions:** RP performed the data collection and wrote the first draft of the manuscript. RP and MB extracted the data in mutual agreement. RP, MB and LV were involved in the design of the study. Analyses were performed by RP in collaboration with OD. All authors critically revised all drafts of the manuscripts and approved the final version.

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