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Mixed treatment comparison of prophylaxis against invasive fungal infections in neutropenic patients receiving therapy for haematological malignancies: a systematic review

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Objectives: Patients receiving therapy for haematological malignancies have a higher risk of invasive fungal infections (IFIs). Antifungal prophylaxis is an effective strategy against IFIs, but relative effectiveness estimates across agents are inconclusive. A mixed treatment comparison (MTC) was conducted to estimate the relative effectiveness of all agents for a number of outcomes of interest.

Methods: A systematic review was performed to collect evidence from randomized controlled trials (RCTs) on the risk of IFIs and on mortality after antifungal prophylaxis. The agents analysed were no prophylaxis/placebo, fluconazole, itraconazole, micafungin, caspofungin, liposomal amphotericin B and posaconazole. Meta-analyses and MTCs were used to synthesize the evidence. The primary outcome was the risk of proven or probable IFI. Secondary outcomes were risk of candidiasis/aspergillosis, risk of IFI mortality and risk of all-cause mortality.

Results: Antifungal prophylaxis was more effective than no prophylaxis/placebo in reducing IFI risk. The IFI risk after voriconazole or posaconazole was lower than after fluconazole [relative risk (RR) 0.38, 95% CI 0.14–0.83 and RR 0.34, 95% CI 0.14–0.83] or itraconazole tablets (RR 0.22 95% CI 0.06–0.72 and RR 0.20 95% CI 0.05–0.72). Posaconazole was also found to be more effective than no prophylaxis/placebo in reducing all-cause mortality (RR 0.56, 95% CI 0.30–0.98). Posaconazole had the highest probability of being the most effective agent in reducing IFI risk and all-cause mortality.

Conclusions: IFI prophylaxis has a positive effect on IFI risk reduction. However, its effect on all-cause mortality is not as pronounced. The analysis has additionally pinpointed posaconazole as potentially the most effective IFI prophylaxis in neutropenic patients.

Keywords: antifungals, evidence synthesis, IFIs

Introduction

Patients with haematological malignancies undergoing chemotherapy or haematopoietic stem-cell transplantations (HSCTs) are at high risk of acquiring invasive fungal infections (IFIs). Because of the increasing population of this and other at-risk patient groups, the incidence of IFIs has increased over the last two decades.[1–4] In acute leukaemia and HSCT patients, overall incidence rates of 5%–40% have been reported across different countries and institutions.[5–7]

Like all serious complications, IFIs are associated with high morbidity and mortality. The predominant causative agents of IFI are the *Candida* and *Aspergillus* species. In most epidemiological studies, *Candida albicans* is the most common cause of candidiasis, but cases of non-*albicans Candida* species are increasing.[8,9] In a prospective, multicentre surveillance study, almost half of all nosocomial invasive candidaemia and 65% of breakthrough candidaemia cases were due to non-*albicans Candida* species.[10] Epidemiological studies have also reported an increase in mould infections over the last decade.[11] The incidence of invasive aspergillosis (IA) infections may be as high as 10%–20% in patients undergoing allogeneic HSCT.[12] Moreover, mortality rates from aspergillosis have been reported to be at least 50% in patients with neutropenia alone and 86% in patients who have undergone HSCT.[13]

Early treatment of IFIs is a key factor in improving health outcomes. However, antifungal treatment is often delayed because

of difficulties relating to non-specific symptoms of IFIs, diagnostic challenges and the high cost of IFI treatment. Despite advances in diagnostic tools, the accurate and timely diagnosis of IFIs remains difficult.[14,15] Although antifungal prophylaxis is proven to be an effective strategy in reducing the incidence of IFIs in high-risk settings in haemato-oncology, the choice of antifungal prophylaxis remains controversial.[16,17] Furthermore, there are several concerns with regards to prophylaxis, including higher costs, toxicity, emergence of drug resistance and shifting fungal epidemiology.[18]

Evidence-based, clinical or policy-related decisions require the comparison of all relevant treatment options. This requirement, however, is almost never met within the randomized controlled trial (RCT) setting, which is prohibited by cost and regulatory approval-driven strategies. As a consequence, new treatments are not compared with each other, but are compared with standard therapies or placebo.[19,20]

Mixed treatment comparison (MTC) models (also called network meta-analyses) allow the comparison of all relevant treatment options, including those for which head-to-head comparisons do not exist.[21,22] The synthesis of a network of evidence serves two functions. First, MTC models may strengthen the relative efficacy estimate between two treatments through the inclusion of both direct and indirect comparisons.[21] Second, MTCs facilitate the simultaneous comparison of all treatments and allow the designation of the best treatment. The methods used in MTC are consistent with and represent a generalization of standard pair-wise meta-analysis methods.[21]

This study aimed to identify the optimal antifungal prophylactic strategy in preventing IFIs among patients undergoing chemotherapy or HSCT procedures for haematological malignancies. MTC methodologies are used to capture the whole body of available RCT evidence within a single evidence-synthesis framework. Bayesian approaches to fixed- and random-effect MTC regression models are used to estimate the relative effectiveness of fluconazole, itraconazole, voriconazole, posaconazole, micafungin, caspofungin, liposomal amphotericin B and placebo against a number of outcomes, including overall IFIs, invasive candidiasis (IC), IA and IFI- and non-IFI-related mortality. In addition, the strategies are ranked in accordance with their probability of being the best treatment option.

Methods

Search strategy and study selection

A systematic literature review was performed to collect evidence to creating a network of relative effectiveness of antifungal agents. In particular, searches were conducted in MEDLINE, Embase, the US NIH clinical trials registry (http://www.clinicaltrials.gov) and Google Scholar during April 2013 using the following search terms: ('invasive fungal infections' or 'ifi' or 'fungus' or 'fungal' or 'fungemia' or 'mycosis' or 'candidiasis' or 'Candida' or 'Aspergillus' or 'invasive mould infections' or 'imi' or 'aspergillosis') and ('prophylaxis' or 'prophylactic' or 'prevention') and ('antifungal' or 'amphotericin' or 'azoles' or 'triazoles' or 'fluconazole' or 'itraconazole' or 'isavuconazole' or 'voriconazole' or 'posaconazole' or 'ravuconazole' or 'echinocandin' or 'micafungin' or 'caspofungin' or 'anidulafungin'). The search was limited to randomized trials using the Cochrane Highly Sensitive Search Strategy for identifying randomized trials.[23] In addition, bibliographies of selected studies and systematic reviews on the topic were perused for relevant studies.

All RCT studies on antifungal agents that were newly introduced or are currently being used as IFI prophylaxis among adult patients with haematological malignancies undergoing chemotherapy or HSCT were eligible for inclusion.[24] However, studies were limited to those written in English and published in international peer-reviewed journals. Because the focus was on IFI, studies that reported only non-invasive, single-site fungal infections were excluded. Additionally, studies that investigated antifungal agents that are not suggested for prophylactic use by current guidelines or agents of outdated formulations such as (non-liposomal) amphotericin B, ketoconazole, miconazole and nystatin were excluded. However, placebo-designed studies were included to serve as a baseline measure for estimating the relative effectiveness of each antifungal agent. In the analysis, no relative effectiveness difference between placebo and no prophylaxis was assumed. Studies that analysed only graft-versus-host disease patients were excluded as this patient population is at a significantly higher risk of IFI and inclusion of such studies was expected to increase the heterogeneity within the evidence network.[25,26] Finally, because of well-documented pharmacokinetic differences between the available administration forms of itraconazole,[27,28] we distinguished between itraconazole tablets and itraconazole intravenous/oral solution.

Two investigators (P. P. and H. H. L.) independently scanned all titles and abstracts for RCT studies investigating the prophylactic use of antifungal agents among high-risk neutropenic patients. Following identification of relevant abstracts, the full text of each publication was obtained and thoroughly evaluated for inclusion. Risk of bias was assessed on the basis of sequence allocation, allocation concealment, blinding, incomplete outcomes and intention-to-treat analysis in accordance with the Cochrane tool for bias assessment.[23] Studies that reported no cases of an outcome in both treatment arms were excluded from the analysis on that outcome.

Data collection

The same investigators also independently conducted the data extraction. Using pre-formulated data extraction sheets, the primary and secondary outcome measures were recorded. The primary outcome was the total number of proven or probable IFIs, while secondary outcomes were the number of proven or probable IFIs caused by *Candida* or *Aspergillus* as well as IFI-related and all-cause mortality. Whenever possible the definitions from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group were used for a proven or probable IFI. Covariates such as age, gender, dosing regimens, maximum days of follow-up, average duration of prophylaxis and neutropenia, proportion of chemotherapy and HSCT patients, and proportion of patients with acute myeloid leukaemia (AML), myelodysplastic syndromes, acute lymphoblastic leukaemia, chronic myeloid leukaemia, chronic lymphocytic leukaemia, non-Hodgkin lymphoma and multiple myeloma as the underlying disease were recorded. Medians were used when means were not reported for age and duration of prophylaxis and neutropenia. Inconsistencies in data extraction were resolved through discussion and review of the material.

Statistical analysis

Meta-regression and network meta-regression approaches were used to synthesize the evidence network.[29] The regression approach was used in order to explain any observed between-study heterogeneity and to reduce evidence inconsistency.[29] Initially, pairwise mixed-effects Poisson meta-regressions were performed for each outcome separately, using direct comparative information from the studies in the network.[30] Subsequently, mixed-effects, Poisson network meta-regression models were developed within a Bayesian framework for each outcome separately. These models were used to estimate the relative effectiveness of each

strategy on the outcomes of interest. A more detailed description of the structure of the MTC regression models is given below.

For a set of i RCT studies and a network of k treatments, the number of patients experiencing an event of interest (e.g. IFI) Y_{ik} was assumed to follow a Poisson distribution:

$$Y_{ik} \sim \text{Poisson}\ (\lambda_{ik}E_{ik})$$

where E_{ik} is the offset parameter controlling for differences in sample sizes and follow-up time in person (N_{ik}) days (T_{ik}) (hence $E_{ik}=T_{ik}N_{ik}$) and λ_{ik} is the corresponding mean parameter, which is linked to the prophylactic effect and the covariates X_{ik} through the log link:

$$\log(\lambda_{ik}) = \mu_i + \delta_{ik}I_{k\neq b} + \beta_i X_{ik}.$$

Above, the parameter μ_i is the study-specific baseline estimate and δ_{ik} is the study- and treatment-specific, relative effectiveness, random effect estimates. The indicator function I indicates that δ_{ik} exists only when $k \neq b$, where b is the baseline, study-specific treatment. For δ_{ik} we made the assumption that it is normally distributed with mean $d_k - d_{ib}$ and variance $1/\tau^2$, where $d_k - d_{ib}$ is the average relative effectiveness of treatment k against the baseline treatment of study i and τ^2 is the between-study precision parameter. Finally, β_i represents the trial-specific, random coefficients of the covariates X_{ik}. All continuous covariates were standardized to the mean. Additionally, an alternative model was applied to the above model, where δ_{ik} was assumed to be fixed. The deviance information criterion (DIC) was used to facilitate the decision on the final form of the model (e.g. fixed or random effects and number of covariates included).[31]

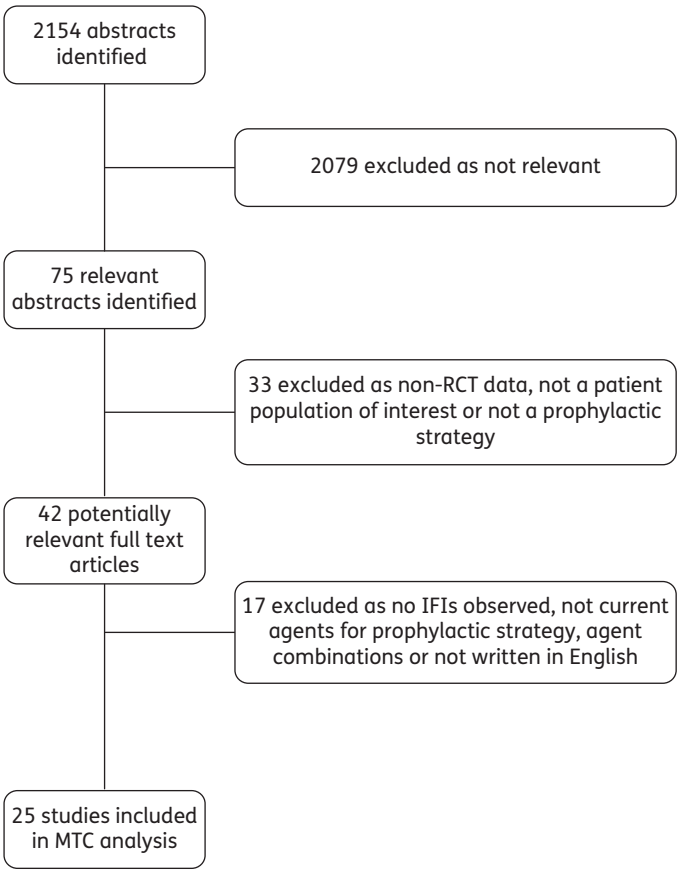

Figure 1. Flow chart of the study selection process.

Since a Bayesian approach to the estimation of the above model was used, prior probabilities were assumed for each parameter. However, because no prior information to direct the posterior effectiveness estimates was available, a vague normal prior probability [$N(0,1000)$] was used. Additionally, a gamma probability [$\Gamma(0.001,0.001)$] was used for the prior distribution describing the precisions of the random effect parameters. All models were simulated for 100 000 iterations. Treatment options were ranked at every iteration according to their effectiveness from best to worst. Subsequently, the proportion of iterations in which each treatment option was ranked best, second best and so on was calculated. This proportion served as a proxy for ranking the treatment options.

A major assumption of MTC models is that of consistency among direct and indirect comparisons in a network.[31] In other words, MTC models make the assumption that direct and indirect comparisons do not disagree beyond chance. In order to investigate the potential presence of inconsistency within loops, an illustrative informal inconsistency check method was used.[32] Convergence of the model was assessed through (i) visual inspection of the trace plots, (ii) calculation of potential scale reduction factors[33] and (iii) inspection of convergence in multiple chains with different initial values.

All estimations were performed using the statistical software R, ver. 2.14.1 (R Development Core Team, Vienna, Austria) and WinBUGS, ver. 1.4[34] (MRC Biostatistics Unit, Cambridge, UK). Missing data in any of the covariates were handled using a cross-sectional imputation method.[35]

Results

Through the systematic review, 25 RCTs were identified that satisfied the inclusion and exclusion criteria.[16,20,24,36–57] One RCT comparing fluconazole and itraconazole solution in patients with allogeneic HSCT was excluded because of the language restriction.[58] A flow diagram illustrating the systematic review process is presented in Figure 1. From the included studies, a network of

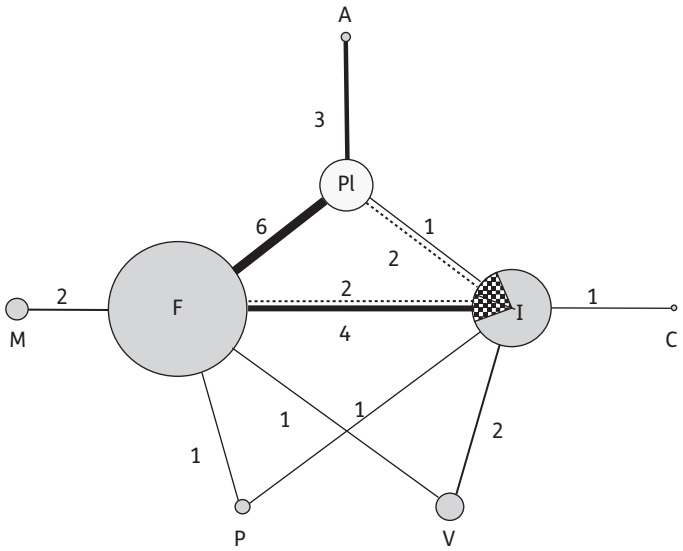

Figure 2. A schematic of the network of evidence used in MTC analysis. The links between the nodes indicate direct comparisons. The number of RCTs between direct comparisons is represented by the thickness of the links and by the numbers next to them. The size of the nodes represents the total number of patients for that treatment. Itraconazole is split into two categories: itraconazole solution (solid pattern) and itraconazole tablets (chequered pattern). P, posaconazole; V, voriconazole; F, fluconazole; I, itraconazole; M, micafungin; C, caspofungin; A, liposomal amphotericin B; Pl, placebo.

Table 1. Main clinical outcomes reported by each of the included studies

				IFI				Mortality				
Study name	Treatment	Follow-up (days)	Sample size	overall	IC	IA	other	overall	IFI	non-IFI	IC	IA
Goodman[54]	fluconazole	84	179	5	3	1	1	55	1	54	0	1
	placebo	84	177	28	25	2	1	46	10	36	8	2
Winston[36]	fluconazole	>90	123	5	1	3	1	26	NR	NR	NR	NR
	placebo	>90	132	10	6	2	2	24	NR	NR	NR	NR
Schaffner[40]	fluconazole	>40	75	8	0	7	1	4	2	2	0	1
	placebo	>40	76	8	4	4	0	5	2	3	1	1
Slavin[41]	fluconazole	110	152	10	4	3	3	31	11	20	NR	NR
	placebo	110	148	32	28	2	2	52	19	33	NR	NR
Rotstein[45]	fluconazole	60	141	9	4	1	4	15	2	13	0	0
	placebo	60	133	32	20	1	11	15	5	10	5	0
Yamac[57]	fluconazole	NR	41	4	4	0	0	NR	NR	NR	NR	NR
	placebo/control	NR	29	9	9	0	0	NR	NR	NR	NR	NR
Vreugdenhil[38]	itraconazole (tablets)	180	46	7	1	4	2	10	7	3	NR	NR
	placebo	180	46	10	4	3	3	14	7	7	NR	NR
Menichetti[43]	itraconazole (solution)	56	201	5	1	4	0	15	1	14	0	1
	placebo	56	204	9	7	1	1	18	5	13	3	1
Nucci[46]	itraconazole (tablets)	40	104	5	2	0	3	8	3	5	2	0
	placebo	40	106	9	6	1	2	7	1	6	1	0
Tollemar[37]	liposomal AMB	100	36	1	1	0	0	16	1	15	1	0
	placebo	100	40	3	3	0	0	17	3	14	3	0
Kelsey[42]	liposomal AMB	45	74	0	0	0	0	11	0	11	0	0
	placebo	45	87	2	2	0	0	12	1	11	1	0
Penack[51]	liposomal AMB	30	75	5	3	2	0	4	2	2	1	1
	placebo	30	57	20	10	10	0	8	7	1	4	3
Annaloro[55]	itraconazole (tablets)	70	31	4	4	0	0	2	0	0	0	0
	fluconazole	70	28	1	1	0	0	2	0	0	0	0
Ito[56]	itraconazole (tablets)	NR	103	0	0	0	0	NR	NR	NR	NR	NR
	fluconazole	NR	106	3	1	2	0	NR	NR	NR	NR	NR
Morgenstern[44]	itraconazole (solution)	120	288	1	1	0	0	3	0	3	0	0
	fluconazole	120	293	6	2	4	0	10	4	6	1	3
Winston[39]	itraconazole (solution)	180	71	6	2	3	1	32	6	26	2	3
	fluconazole	180	67	17	8	9	0	28	12	16	NR	NR
Oren[50]	itraconazole (solution)	90	96	8	2	6	0	16	0	16	0	0
	fluconazole	90	99	9	1	8	0	17	3	14	0	3
Glasmacher[47]	itraconazole (solution)	56	248	4	1	2	1	25	2	23	1	1
	fluconazole	56	246	5	1	3	1	28	3	25	1	1
Hiramatsu[52]	micafungin	100	50	1	0	0	1	2	1	1	0	1
	fluconazole	100	50	1	0	1	0	1	1	0	0	1
van Burik[16]	micafungin	70	397	7	4	1	2	18	1	17	0	0
	fluconazole	70	433	11	2	7	2	26	2	24	0	2
Wingard[20]	voriconazole	180	303	14	3	9	2	3	NR	NR	NR	NR
	fluconazole	180	289	24	5	17	2	5	NR	NR	NR	NR

Continued

Table 1. *Continued*

Study name	Treatment	Follow-up (days)	Sample size	IFI				Mortality				
				overall	IC	IA	other	overall	IFI	non-IFI	IC	IA
Cornely[19]	posaconazole	100	239	8	5	1	2	36	4	32	NR	NR
	fluconazole	100	240	26	4	18	4	55	13	42	NR	NR
	posaconazole	100	65	6	3	1	2	4	1	3	NR	NR
	itraconazole (solution)	100	58	7	0	6	1	9	3	6	NR	NR
Mattiuzzi[48]	caspofungin	38	106	7	2	2	3	7	4	3	0	2
	itraconazole (solution)	38	86	5	4	1	0	7	2	5	0	2
Mattiuzzi[49]	voriconazole	35	71	0	0	0	0	6	0	6	0	0
	itraconazole (solution)	36	52	2	1	0	1	6	1	5	0	0
Marks[53]	voriconazole	180	224	3	2	1	0	1	0	41	0	0
	itraconazole (solution)	180	241	5	0	5	0	1	1	45	0	1

NR, not reported; AMB, amphotericin B.

evidence for nine alternative antifungal prophylaxis agents was constructed (Figure 2). The nodes represent antifungal agents and the links between the nodes represent direct comparisons in RCTs. The diameter of the nodes and the width of the links vary according to sample size and number of direct comparisons, respectively. The itraconazole formulations are represented in one node to simplify the figure. With the exception of the study by Cornely *et al.*,[19] there was no multi-arm RCT identified. In that study, application of prophylactic agents was split within the study into different centres. Hence, treatment randomization was not performed across centres. To address this issue, the two comparisons (i.e. posaconazole versus itraconazole solution and posaconazole versus fluconazole) were treated as separate studies.

Risk of bias

All studies included were RCTs (Table S1, available as Supplementary data at *JAC* Online). High risk of bias regarding sequence generation and allocation concealment was not found in any of the studies, but 48% and 40% of the studies, respectively, were characterized as having an unclear risk of bias because detailed descriptions of the randomization process were not provided. High risk of bias relating to blinding of participants and personnel was found in 36% of the studies. However, no studies were un-blinded to the outcomes. The majority of the studies relied on per-protocol analysis while others provided unclear information regarding the type of analysis conducted. Finally, the older studies did not use the EORTC/MSG definition for proven or probable IFIs.

Subject characteristics

The selected RCTs comprised a total of 7062 patients receiving one of nine alternative prophylactic strategies. The main patient characteristics of the included studies are presented in Table S2 (available as Supplementary data at *JAC* Online). Patients were on average 41.9 years of age, 53.5% of them were male and 54.4% were undergoing HSCT or bone marrow transplantation (BMT) at baseline. The most common underlying malignant disease was AML. On average, patients were followed for a maximum of 951 days and the average prophylaxis period was 33.8 days. Dosage regimens varied within studies for itraconazole tablets and solution, fluconazole and liposomal amphotericin B. Additionally, differences across studies in the formulation administered were observed for fluconazole, itraconazole solution and voriconazole. Micafungin, caspofungin and liposomal amphotericin B were only administered parenterally.

The main clinical outcomes reported in each of the included studies are presented in Table 1. An overall proven or probable IFI was identified in 6% of the followed individuals. Of these IFIs, 46.3% were caused by *Candida*, 38.4% by *Aspergillus* and 15.3% by other species. Approximately 11% of the followed individuals died during follow-up and around 38% of the patients with an IFI died as a result of the infection.

Overall IFIs

Estimates from pairwise and network meta-regressions of the relative effectiveness of all agents against IFIs are presented in the upper and lower triangles of Table 2, respectively. Both fixed- and random-effects models were used and the goodness of fit after correction for various study-level covariates (percentages of AML and HSCT/BMT patients and average age) was assessed. Inference from goodness of fit measures revealed that the random-effects models with no explanatory covariates were the most appropriate model form (data not shown).

Through the meta-analyses in Table 2 (upper triangle), it was observed that fluconazole and liposomal amphotericin B were significantly better than placebo/no prophylaxis in reducing proven or probable IFIs. Additionally, posaconazole prophylaxis was found to be more effective in comparison with fluconazole prophylaxis. Through the MTC regression models, all antifungal agents, with the exception of caspofungin and itraconazole tablets, were observed to have a significant prophylactic effect against placebo/no prophylaxis. In addition, posaconazole was found to be significantly more effective than fluconazole and itraconazole tablets in antifungal prophylaxis.

Table 2. Meta-analysis (upper triangle) and MTC (lower triangle) RR estimates (and their credible intervals) of an IFI

PLA	**0.33 (0.15–0.79)**	0.79 (0.21–2.92)			**0.14 (0.03–0.78)**	0.56 (0.13–2.39)		
0.36 (0.22–0.61)[a]	**FLC**	0.44 (0.13–1.21)	0.56 (0.29–1.05)	0.54 (0.09–3.29)		3.31 (0.39–28.03)	**0.31 (0.14–0.67)**	
0.22 (0.11–0.46)[a]	0.61 (0.35–1.07)[a]	**ITC (solution/iv)**	0.21 (0.01–1.73)				0.76 (0.27–2.14)	1.14 (0.37–3.46)
0.14 (0.05–0.34)	**0.38 (0.14–0.83)**[a]	0.62 (0.22–1.44)[a]	**VRC**					
0.22 (0.06–0.73)	0.60 (0.19–1.75)[a]	0.98 (0.28–3.35)	1.59 (0.40–6.98)	**MCF**				
0.17 (0.05–0.49)[a]	0.48 (0.12–1.50)	0.78 (0.18–2.75)	1.27 (0.28–5.61)	0.80 (0.13–3.96)	**LIP AMB**			
0.62 (0.27–1.44)[a]	1.72 (0.671–4.26)[a]	2.81 (0.96–8.03)	**4.54 (1.39–17.37)**	2.89 (0.68–12.36)	3.59 (0.94–15.82)	**ITC (tablets)**		
0.12 (0.04–0.35)	**0.34 (0.14–0.83)**[a]	0.55 (0.21–1.43)[a]	0.89 (0.28–3.41)	0.56 (0.13–2.51)	0.71 (0.17–3.66)	**0.20 (0.05–0.72)**	**POS**	
0.23 (0.05–1.14)	0.64 (0.14–2.92)	1.05 (0.25–4.35)[a]	1.70 (0.34–9.94)	1.08 (0.16–7.16)	1.35 (0.2–10.01)	0.37 (0.06–2.18)	1.89 (0.34–10.44)	**CAS**

PLA, placebo; FLC, fluconazole; ITC, itraconazole; VRC, voriconazole; MCF, micafungin; LIP AMB, liposomal amphotericin B; POS, posaconazole; CAS, caspofungin; iv, intravenous.
Significant comparisons are presented in bold. For the upper (lower) triangle RRs lower than 1 favour the column (row)-defining treatment.
[a]Direct head-to-head RCTs exist for these comparisons.

Invasive candidiasis/aspergillosis

When examining the risk of proven or probable IC, all agents, with the exception of micafungin, were observed to be more effective than placebo/no prophylaxis (lower triangle, Table 3). Additionally, itraconazole solution and caspofungin appeared to have a significant advantage against IC compared with fluconazole. With respect to IA infections, posaconazole was found to provide better prophylaxis when compared with placebo/no prophylaxis, fluconazole and itraconazole solution (upper triangle, Table 3). Liposomal amphotericin B and micafungin were significantly more effective against IA infections compared with placebo/no prophylaxis and fluconazole. Finally, voriconazole was found to be significantly more effective than fluconazole. No covariate was found to have a significant impact on the improvement of the model. Thus, an empty random-effects MTC model was applied in both cases.

All-cause/IFI-related mortality

MTC estimates of the relative effectiveness of all antifungal agents on all-cause and IFI-related mortality are summarized in Table 4. Posaconazole was the only agent achieving a significant reduction in the risk of all-cause mortality in comparison with placebo/no prophylaxis. With respect to reducing IFI-related mortality, all agents except micafungin and caspofungin were found to be significantly superior to placebo in reducing IFI-related mortality. Additionally, posaconazole was found to be superior to fluconazole and itraconazole tablets. The relative effectiveness of voriconazole could not be determined due to the absence of IFI-related deaths in all voriconazole studies.

Ranking and inconsistency

The ranking distributions in Figure 3 represent the proportions of simulations in which each agent was ranked in each position (from 'best option' to 'worst option') based on its effectiveness against proven or probable IFIs and all-cause mortality. With respect to prophylaxis against IFIs, posaconazole was pinpointed as the most preferable agent in more than one-third of the simulations (35%), followed by voriconazole (25%), liposomal amphotericin B (20%), caspofungin (11%), micafungin (9%), itraconazole solution, itraconazole tablets, fluconazole and placebo (0%). With respect to reduction in all-cause mortality risk, posaconazole was again the most preferable prophylaxis agent (34%), followed by caspofungin, (33%), micafungin (18%), itraconazole tablets (8%), liposomal amphotericin B (4%), voriconazole (2%), itraconazole solution (1%), fluconazole (0%) and placebo (0%).

We identified no evidence of inconsistency in all MTC analyses and in any of the closed loops in the data, as inspected through the coherence plots. Finally, sensitivity analysis on the prior assumptions showed no significant deviations on the relative risk estimates from all MTC analyses.

Discussion

This study compared using an MTC method the effectiveness of nine IFI prophylaxis strategies for patients with neutropenia who were undergoing chemotherapy or HSCT. The results of the analysis indicate that IFI prophylaxis has a clear positive effect on IFI risk

Table 3. RR estimates (and their credible intervals) from the MTC on IA (upper triangle) and IC (lower triangle) for all antifungal agents

PLA	1.13 (0.43–2.69)[a]	0.62 (0.19–1.82)[a]	0.34 (0.05–1.45)	**0.08 (<0.01–0.8)**	**0.13 (0.01–0.91)**[a]	0.59 (0.08–2.85)[a]	**0.06 (0.01–0.34)**	0.52 (0.03–8.64)
0.14 (0.07–0.25)[a]	**FLC**	0.55 (0.22–1.24)[a]	**0.30 (0.06–0.96)**[a]	**0.07 (<0.01–0.58)**[a]	0.11 (0.01–1.03)	0.52 (0.06–3.28)[a]	**0.05 (0.01–0.25)**[a]	0.47 (0.03–7.25)
0.06 (0.02–0.16)[a]	**0.44 (0.18–0.99)**[a]	**ITC (solution/iv)**	0.55 (0.11–1.99)[a]	0.13 (0.01–1.33)	0.20 (0.02–2.18)	0.95 (0.11–6.74)	**0.09 (0.01–0.51)**[a]	0.87 (0.06–11.93)[a]
0.05 (0.01–0.18)	0.34 (0.08–1.14)[a]	0.77 (0.19–2.614)[a]	**VRC**	0.24 (0.01–3.39)	0.37 (0.02–5.93)	1.76 (0.16–19.26)	0.16 (0.01–1.52)	1.58 (0.08–34.00)
0.18 (0.03–1.07)	1.36 (0.28–7.09)[a]	3.17 (0.51–19.06)	4.07 (0.55–33.65)	**MCF**	1.66 (0.06–110.69)	7.60 (0.36–418.57)	0.71 (0.03–35.73)	7.34 (0.19–586.24)
0.19 (0.05–0.56)[a]	1.40 (0.32–5.09)	3.14 (0.62–15.2)	4.06 (0.66–27.32)	1.00 (0.11–8.06)	**LIP AMB**	4.75 (0.27–82.16)	0.43 (0.02–8.68)	4.31 (0.12–175.57)
0.26 (0.08–0.77)[a]	1.92 (0.58–6.23)[a]	**4.35 (1.04–18.51)**	**5.57 (1.08–34.48)**	1.40 (0.19–10.03)	1.37 (0.27–7.49)	**ITC (tablets)**	0.09 (0.01–1.49)	0.94 (0.03–27.16)
0.14 (0.04–0.58)	1.03 (0.3–3.573)[a]	2.40 (0.63–9.33)[a]	3.10 (0.57–18.57)	0.76 (0.1–6.01)	0.76 (0.12–5.07)	0.55 (0.10–3.32)	**POS**	9.81 (0.41–297.5)
0.02 (0.01–0.14)	0.14 (0.01–1.02)	0.32 (0.04–1.95)[a]	0.42 (0.03–3.81)	0.10 (0.01–1.30)	0.10 (0.01–1.08)	**0.07 (0.01–0.65)**	0.13 (0.01–1.19)	**CAS**

PLA, placebo; FLC, fluconazole; ITC, itraconazole; VRC, voriconazole; MCF, micafungin; LIP AMB, liposomal amphotericin B; POS, posaconazole; CAS, caspofungin; iv, intravenous.
Significant comparisons are presented in bold. For the upper (lower) triangle RRs lower than 1 favour the column (row)-defining treatment.
[a]Direct head-to-head RCTs exist for these comparisons.

Table 4. RR estimates (and their credible intervals) from the MTC on all-cause mortality (upper triangle) and IFI mortality (lower triangle) for all antifungal agents

PLA	0.90 (0.68–1.20)[a]	0.83 (0.56–1.23)[a]	0.78 (0.46–1.25)	0.67 (0.32–1.40)	0.85 (0.49–1.43)[a]	0.79 (0.41–1.51)[a]	**0.56 (0.3–0.98)**	0.63 (0.19–2.03)
0.38 (0.16–0.83)[a]	**FLC**	0.93 (0.68–1.25)[a]	0.87 (0.56–1.3)[a]	0.75 (0.38–1.46)[a]	0.95 (0.5–1.69)	0.87 (0.43–1.74)[a]	0.62 (0.36–1.01)[a]	0.70 (0.22–2.20)
0.13 (0.03–0.37)[a]	**0.33 (0.12–0.77)**[a]	**ITC (solution/iv)**	0.94 (0.62–1.41)[a]	0.81 (0.38–1.71)	1.01 (0.52–1.97)	0.94 (0.45–1.98)	0.67 (0.37–1.16)[a]	0.75 (0.24–2.30)[a]
- (-)	- (-)	- (-)	**VRC**	0.86 (0.4–1.91)	1.07 (0.52–2.28)	1.01 (0.45–2.24)	0.71 (0.36–1.33)	0.80 (0.24–2.69)
0.13 (0.01–0.97)	0.34 (0.04–2.10)[a]	1.04 (0.11–8.55)	- (-)	**MCF**	1.26 (0.5–3.19)	1.17 (0.45–3.08)	0.83 (0.34–1.92)	0.95 (0.22–3.49)
0.18 (0.03–0.70)[a]	0.47 (0.07–2.39)	1.39 (0.19–9.72)	- (-)	1.37 (0.09–21.35)	**LIP AMB**	0.94 (0.4–2.17)	0.66 (0.29–1.45)	0.74 (0.2–2.78)
1.08 (0.32–3.93)[a]	2.84 (0.71–14.37)[a]	**8.47 (1.74–63.09)**	- (-)	8.52 (0.80–127.7)	6.19 (0.98–54.67)	**ITC (tablets)**	0.71 (0.29–1.68)	0.80 (0.19–3.02)
0.09 (0.01–0.34)	**0.22 (0.05–0.74)**[a]	0.67 (0.15–2.58)[a]	- (-)	0.63 (0.06–7.9)	0.47 (0.05–4.37)	**0.08 (0.01–0.47)**	**POS**	1.12 (0.31–3.94)
0.16 (0.01–1.51)	0.43 (0.05–3.66)	1.27 (0.18–10.00)[a]	- (-)	1.26 (0.07–27.31)	0.94 (0.05–15.28)	0.15 (0.01–1.84)	1.90 (0.19–22.25)	**CAS**

PLA, placebo; FLC, fluconazole; ITC, itraconazole; VRC, voriconazole; MCF, micafungin; LIP AMB, liposomal amphotericin B; POS, posaconazole; CAS, caspofungin; iv, intravenous.
Significant comparisons are presented in bold. For the upper (lower) triangle RRs lower than 1 favour the column (row)-defining treatment.
[a]Direct head-to-head RCTs exist for these comparisons.

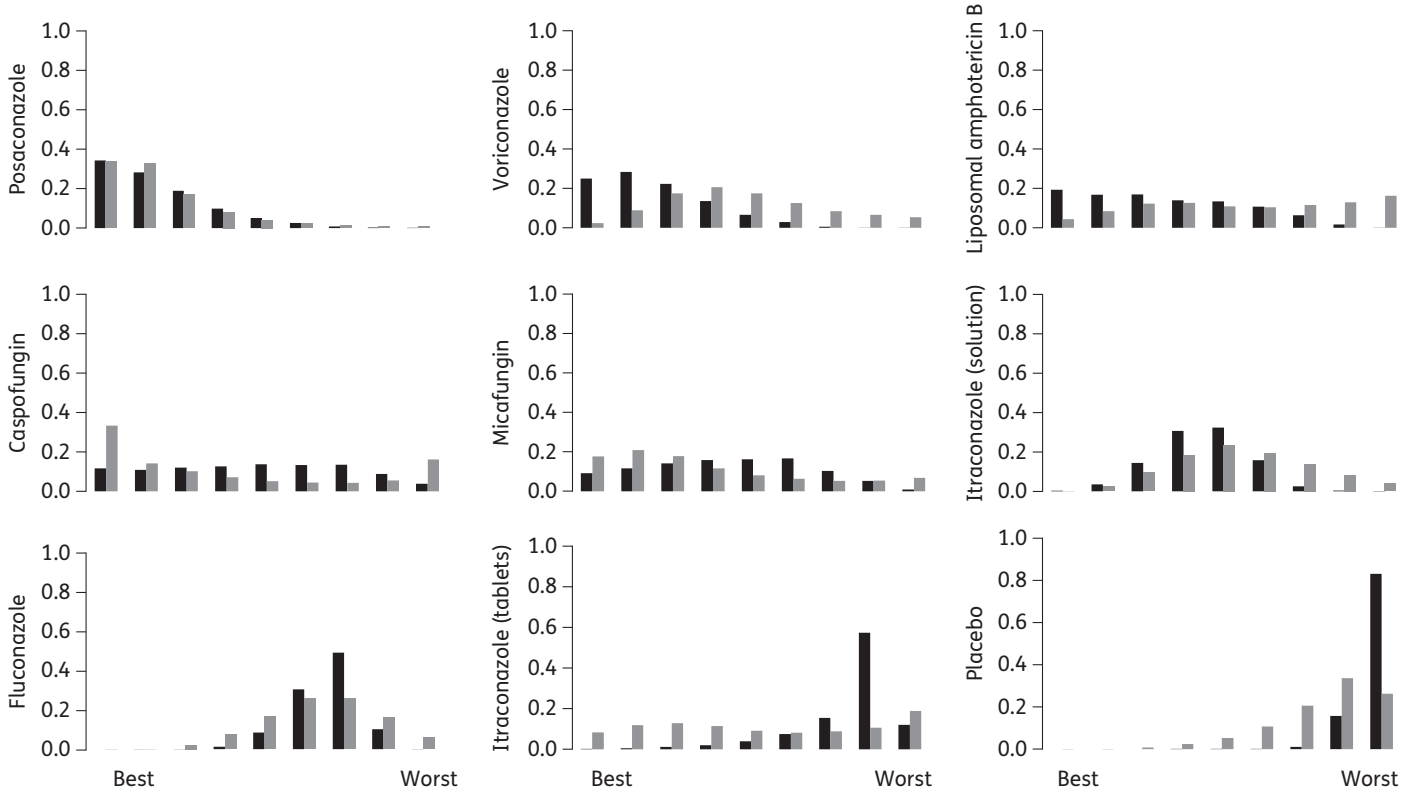

Figure 3. Ranking distributions of the alternative prophylaxis strategies with respect to IFI (black bars) and all-cause mortality (grey bars) risk reduction from 100 000 simulations. The horizontal axes depict the order from best (first) to worst (ninth) prophylactic option.

reduction, but its effect on all-cause mortality might not be as pronounced. The analysis has additionally supported posaconazole as potentially the most effective antifungal agent for prophylaxis against IFIs in neutropenic patients, especially those undergoing chemotherapy. Additionally, its relative effectiveness against *Aspergillus* was more pronounced compared with that against *Candida* infections. Pathogen-specific analysis also identified the inability of fluconazole to protect against *Aspergillus* species, as previously documented.[24,59] Differences in effectiveness across itraconazole formulations were also observed in our study, with the solution formulation performing better than the tablets.

The results of this study are consistent with the recommendations made in previous studies.[24,60,61] In particular, the order of antifungal preference identified through our model matches that recommended in a recent study of the German Society for Haematology and Oncology.[24] Additionally, the importance of prophylaxis in patients with neutropenia became even more evident through our analysis, where prophylaxis with any of the antifungal agents that are recommended for use in the UK (based on the British National Formulary) was found to be significantly more effective than placebo/no prophylaxis.

Reduction in all-cause mortality is generally difficult to achieve in RCTs with patients with severe neutropenia, and the results of this study support this finding. Regarding IFI-related mortality, however, the benefit from prophylaxis has been more obvious in our analysis, with posaconazole achieving the highest effectiveness among antifungals. The results from the MTC were fairly robust and no severe problems of inconsistency were observed in the data. We have found no evidence supporting our literature-based hypothesis that studies with a higher proportion of AML patients would show a higher risk of acquiring an IFI, compared with other types of leukaemia.[4]

Limitations and future work

Some RCT studies included in this analysis suffer from inconsistent reporting; mean estimates for the covariates studied were not always present, forcing the use of medians, where available, as the best estimate of the mean. Lack of reporting was also observed at the outcome level, since four studies failed to report IFI-related mortality rates.[20,36,56,57] In some studies the underlying disease status was also inconsistently reported. Despite the fact that the methods used have allowed us to utilize the information collected in the most efficient way, the collection of unreported data from the corresponding authors of the selected studies would be a more accurate solution.

Another major limitation in this analysis is that the underlying severity of the studied population makes isolation of the treatment effect difficult. As Rogers *et al.*[62] pinpointed, a prophylactic effect on IFI incidence or IFI-related mortality might be related to difficulties with diagnosis of IFI because of the underlying severity rather than the effect of the prophylaxis itself. In addition to the last limitation, the variation observed in the dosing regimens between RCTs complicates the estimation of an aggregate prophylactic effect for each strategy. Also, no distinction was made between patients with neutropenia or immunosuppression due to chemotherapy

or due to HSCT/BMT. Hence our results refer to a composite population which is potentially much more heterogeneous than we had assumed. A scenario analysis where results would be stratified depending on the underlying condition might be a more realistic alternative and a task for further research. From the current analysis, a summary and comparison of adverse effectiveness among different agents is missing as we were unable to synthesize this information quantitatively. Finally, the evidence synthesis process followed might have missed potential studies that would fit the inclusion criteria but were not written in English.

In conclusion, in the absence of head-to-head comparisons of the novel agents in an RCT setting, the estimates from this MTC analysis are supportive of prophylaxis with new agents in neutropenic haemato-oncology and HSCT patients, instead of a standard prophylactic option or placebo. However, this MTC is by no means a substitute for such RCTs. Head-to-head comparisons should be more intensively performed using both HSCT and chemotherapy populations in order to further facilitate decision making regarding the best prophylactic alternative. Finally, in addition to the establishment of the most effective prophylactic option(s), decision making should in parallel focus on the cost effectiveness of such antifungal agents.

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Supplementary data

Tables S1 and S2 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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