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Cost Benefit and Cost Effectiveness of Antifungal Prophylaxis in Immunocompromised Patients Treated for Haematological Malignancies

Reviewing the Available Evidence

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Abstract

There has been a large increase in the incidence of invasive fungal infections (IFIs) over the past decades, largely because of the increasing size of the population at risk. One of the major risk groups for IFIs are patients with haematological malignancies treated with cytotoxic chemotherapy or undergoing haematopoietic stem cell transplantation. These IFIs are associated with high morbidity and mortality rates. Consequently, as the diagnosis of IFIs is difficult, antifungal prophylaxis is desirable in high-risk patients. Furthermore, as the economic impact of IFIs is also significant, it is important to assess the cost benefit and cost effectiveness of each prophylactic agent in order to aid decisions concerning which prophylactic agent provides the best value for limited healthcare resources. This article systematically reviews the available pharmacoeconomic evidence regarding antifungal prophylaxis in immunocompromised patients treated for haematological malignancies. Furthermore, specific points of interest concerning economic analyses of antifungal prophylaxis are briefly discussed.

Considering the available evidence, antifungal prophylaxis in immunocompromised patients treated for haematological malignancies seems to be an intervention with favourable cost-benefit, cost-effectiveness and cost-saving potential. Furthermore, recently introduced antifungal agents seem to be attractive alternatives to fluconazole from a pharmacoeconomic point of view. However, due to wide heterogeneity in patient characteristics, underlying diseases, hospital settings and study methods in the included economic studies, as well as the lack of 'head-to-head' trials, it is difficult to find clear evidence of the economic advantages of a single prophylactic agent. Furthermore, we show that the results of cost-effectiveness analyses are highly dependent on several crucial factors that influence the baseline IFI incidence rates and, therefore, differ per patient population or region.

There has been a large increase in the incidence of invasive fungal infections (IFIs) over the past decades, largely because of the increasing size of the population at risk.[1-4] One of the major risk groups for IFIs are patients with haematological malignancies treated with cytotoxic chemotherapy or undergoing haematopoietic stem cell transplantation (HSCT).[3,4] Improvements in supportive care, increasing numbers of HSCTs, increased use of antibacterials and more intensive regimens have resulted in more profound levels of immunosuppression in these patients, leading to a higher susceptibility for IFIs. Although incidence rates of IFIs vary considerably among countries and institutions, overall incidence rates of 5–40% have been reported in acute leukaemia and HSCT patients.[3,5-7]

In Europe and North America, the main causative agents are *Aspergillus* and *Candida* species. However, in recent years, the epidemiology of yeast infections has changed substantially. Although *Candida albicans* is still commonly encountered, a shift has been observed toward non-*albicans* species.[8-10] Unlike the total incidence of yeast infections, which appears to remain stable, the incidence of mould infections is still increasing.[11,12] These mould infections are mainly caused by *Aspergillus* species.

These IFIs are associated with significant morbidity and mortality. In particular, for *Aspergillus* infections, very high mortality rates of 60% have been reported.[13] Furthermore, the economic impact of IFIs is significant. Wilson et al.[14] assessed the direct and indirect costs of IFIs in patients with different underlying conditions. They estimated that the average per-patient cost attributable to an IFI during the first year, in 1998, was $US31 193. Among the different types of fungi, *Aspergillus* infections were estimated as the most costly to treat, with an incremental cost per patient of $US72 792. Furthermore, recently, Jansen et al.[15] estimated the cost per patient for treating invasive aspergillosis in the Netherlands in 2005. They reported a mean total treatment cost of approximately €30 000 per patient.

The general management of IFIs can be divided into four main strategies:[16] (i) prophylaxis; (ii) empirical therapy for at-risk patients with signs of infection of unclear aetiology (usually persistent fever) despite treatment with broad-spectrum antibacterials; (iii) pre-emptive therapy for high-risk patients whose signs, symptoms or diagnostic tests are suggestive of an (incipient) IFI; and (iv) directive treatment of a proven or probable infection. Antifungal drugs applicable in the clinical setting belong to three major categories: (i) the polyenes, of which amphotericin B desoxycholate is the prototype that has been replaced by the newer, less toxic, but more expensive, liposomal amphotericin B (L-AmB) [AmBisome® and Abelcet®]; (ii) the azoles, such as fluconazole, itraconazole, voriconazole and posaconazole; and (iii) the echinocandins, such caspofungin, anidulafungin and micafungin. Although diagnostic tests have improved, even, to date, early diagnosis of IFIs remains very difficult.[11,17] Together with a considerable failure rate of IFI treatment associated with significant morbidity and mortality, this has resulted in a considerable increase in the use of prophylactic and empirical antifungal strategies in high-risk patients in daily practice during recent years.[18,19]

In many institutions, the main antifungal agent used for prophylaxis has been fluconazole. However, a major shortcoming is that it lacks activity against *Aspergillus* and several non-*albicans* *Candida* species.[20] The recent introduction of various new broad-spectrum antifungal agents registered for prophylactic use, such as micafungin and posaconazole, has increased the number of possible strategies in high-risk patients.[21-23] In order to aid decisions concerning which prophylactic agent provides the best value for limited healthcare resources, it is important to assess the cost effectiveness of each option. This article will review the available pharmacoeconomic evidence regarding antifungal prophylaxis in immunocompromised patients treated for haematological malignancies. Furthermore, we will briefly discuss specific points of interest concerning cost-effectiveness analyses of antifungal prophylaxis.

1. Literature Search Strategy

Relevant cost-benefit or cost-effectiveness analyses were collected by conducting a computerized

search on the PubMed, EMBASE and Web of Science databases. We searched using the key words ('cost' or 'economic') and ('antifungal' or 'invasive fungal infections' or 'systemic fungal infections') and ('prophylaxis' or 'prevention' or 'treatment' or 'management'). Searches were carried out up until the end of September 2010. Furthermore, we manually searched in the references of identified articles for relevant economic evaluations not included in the above-mentioned databases.

We included studies if they met the following criteria: (i) they included a full cost-benefit or cost-effectiveness analysis (posters and abstracts were excluded due to a lack of detailed information); (ii) they were published in peer-reviewed journals restricted to the English language; and (iii) they were economic evaluations on antifungal prophylaxis in immunocompromised patients treated for haematological malignancies. Accordingly, we excluded both studies that focused on antifungal (empirical, pre-emptive or directive) treatment and studies on antifungal prophylaxis in patients with underlying diseases other than haematological malignancies (i.e. HIV/AIDS, organ transplantation). Studies were not excluded on the basis of their date of publication.

After excluding reviews, editorials and other non-original studies, the search strategy highlighted 15 potentially relevant cost-benefit or cost-effectiveness analyses. One study assessed the cost per successfully treated person comparing alternative modes of prophylaxis (i.e. oral fluconazole, amphotericin B and oral polyenes) against oropharyngeal infections.[24] Since oropharyngeal infections are not defined as systemic or invasive fungal infections, we excluded this study from further analyses. Additionally, three other studies were excluded as they did not include a full cost-benefit or cost-effectiveness analysis.[25-27] Poirier et al.[25] estimated the costs of different prophylactic itraconazole dosing regimens only including drug acquisition costs, while Sajben et al.[26] compared only costs of antibacterial treatment in patients who received prophylaxis (i.e. fluconazole plus ofloxacin) with those who did not. Al-Badriyeh et al.[27] compared the costs of prophylactic voriconazole versus posaconazole, but also specifically focused on the cost of drug therapy and hospitalization, without translating, in money terms, the health consequences of prophylaxis. This finally left a sample of 11 full economic evaluations included in this review.

Table I shows the main characteristics (i.e. year of publication, underlying disease, interventions and type of economic analysis) of the included economic studies. Of the 11 studies, three refer to the US,[34,36,37] two to Switzerland[28,38] and one each to the UK,[29] Germany,[31] the Netherlands,[35] Japan[30] and Korea,[33] and one to both the Netherlands and Germany.[32] The publication years ranged from 1995 to 2010, with the majority (9 of 11) being published after 2005.

2. Description of Selected Studies

The cost effectiveness of a wide variety of prophylactic agents were covered by the economic evaluations included in this review (table II). Schaffner and Schaffner[28] conducted a double-blind, controlled, single-trial to assess the effect of fluconazole prophylaxis versus no prophylaxis in patients undergoing chemotherapy for haematological neoplasis. Besides clinical outcomes, they focused on healthcare costs related to the management of fever and infection with data on resource use being collected alongside the clinical trial. Their cost-benefit analysis concluded that fluconazole did not reduce healthcare costs, which even tended to be higher in the fluconazole group (not statistically significant).

A cost-benefit analysis was performed by Wakerly et al.[29] to compare the cost implications of prophylactic treatment by means of fluconazole with oral polyenes, a combination of fluconazole and polyenes, and no prophylaxis. To assess the clinical outcomes and accompanying costs associated with the different prophylactic strategies, a decision tree was constructed. Data on treatment effectiveness, clinical outcomes and resource use were gathered through a literature survey and clinical interviews conducted in UK hospitals. Wakerly et al.[29] concluded that all strategies involving prophylaxis are cheaper options than the 'no prophylaxis' strategy. The most favourable prophylactic strategy, however, depends on the patient group as well as the source (i.e. the literature

Table I. Published economic evaluations on antifungal prophylaxis in immunocompromised patients (pts) treated for haematological malignancies

Study, country	Pt population	Intervention group (regimen)	Control group (regimen)	Evaluation type (outcome measure)
Schaffner and Schaffner,[28] Switzerland	Pts with AML, lymphoblastic leukaemia, or recurrent high-grade malignant lymphoma who received intensive chemotherapy	Fluconazole (400 mg/d PO or IV)	No prophylaxis	CBA
Wakerly et al.,[29] UK	Two categories of immunocompromised pts were distinguished: (i) chemotherapy only; and (ii) BMT pts	Fluconazole (100 mg/d PO)	1. Oral polyenes (nystatin 400 000 units/d + AmB [40 mg/d]) 2. Fluconazole + oral polyenes 3. No prophylaxis	CBA
Nomura et al.,[30] Japan	Pts with AML who were neutropenic as a result of chemotherapy	Fluconazole (400 mg/d PO)	1. Empirical AmB (IV) 2. No prophylaxis and no empirical tx	CEA (IC per LYG)
Penack et al.,[31] Germany	High-risk pts with haematological malignancies (acute leukaemia or HSCT) and prolonged neutropenia receiving chemotherapy	Low-dose IV liposomal AmB prophylaxis (50 mg as a 1-h infusion every other d)	No prophylaxis	CBA
de Vries et al.,[32] Netherlands, Germany	Immunocompromised pts with acute leukaemia receiving chemotherapy or pts receiving a BMT	Itraconazole (bioavailable dose ≥200 mg/d PO or IV)	1. Fluconazole (400 mg/d PO or 200 mg/d IV) 2. No prophylaxis	CEA (IC per IFI averted)
Sohn et al.,[33] Korea	Pts receiving an allogeneic HSCT for any indication, or autologous HSCT for haematological malignancy	Micafungin (50 mg/d or 1 mg/kg IV in pts weighing <50 kg)	Fluconazole (400 mg/d or 8 mg/kg IV in pts weighing <50 kg)	CEA (IC per LYG)
Schonfeld et al.,[34] US	Pts receiving an allogeneic HSCT for any indication, or autologous HSCT for haematological malignancy	Micafungin (50 mg/d or 1 mg/kg IV in pts weighing <50 kg)	Fluconazole (400 mg/d or 8 mg/kg IV in pts weighing <50 kg)	CEA (IC per tx success)
Stam et al.,[35] Netherlands	Neutropenic pts undergoing chemotherapy for AML or MDS	Posaconazole (600 mg/d PO)	Standard azole tx[a]	CUA (IC per QALY gained)
Collins et al.,[36] US	Neutropenic pts undergoing chemotherapy for AML or MDS	Posaconazole (600 mg/d PO)	Standard azole tx[a]	CEA (IC per IFI avoided)
O'Sullivan et al.,[37] US	Neutropenic pts undergoing chemotherapy for AML or MDS	Posaconazole (600 mg/d PO)	Standard azole tx[a]	CEA (IC per LYG)
Greiner et al.,[38] Switzerland	Neutropenic pts undergoing chemotherapy for AML or MDS[b]	Posaconazole (600 mg/d PO)	Standard azole tx[a]	CEA (IC per LYG)

a 81% received fluconazole 400 mg/d PO and 19% received itraconazole 400 mg/d PO.

b The study further included a decision-tree model with data from HSCT recipients who had developed graft-versus-host disease, but this analysis is outside of the scope of this article.

AmB = amphotericin B; **AML** = acute myeloid leukaemia; **BMT** = bone marrow transplantation; **CBA** = cost-benefit analysis; **CEA** = cost-effectiveness analysis; **CUA** = cost-utility analysis; **HSCT** = haematopoietic stem cell transplantation; **IC** = incremental cost; **IFI** = invasive fungal infections; **IV** = intravenous; **LYG** = life-year gained; **MDS** = myelodysplastic syndrome; **PO** = oral; **tx** = treatment.

or expert opinion) used for obtaining model probabilities.

Nomura et al.[30] evaluated the cost effectiveness of fluconazole prophylaxis compared with empirical treatment with amphotericin B and no prophylaxis (i.e. only directive antifungal treatment when infection is diagnosed). They performed a literature survey limited to clinical trials in order to obtain the clinical parameter values used in the decision tree. Furthermore, resource use and

Table II. Study design and main results of full economic evaluations on antifungal prophylaxis in immunocompromised patients (pts) treated for haematological malignancies. All studies were conducted from a healthcare payer perspective

Study, year of values, currency	Analysis [time horizon]	Source of efficacy/ effectiveness data	Cost components	Source of cost data	Results
Schaffner and Schaffner,[28] 1993, $US	Pt-level (prospective study) [neutropenic period]	RCT	Prophylactic agents; LOS; microbiological and radiological studies; antifungal and antibacterial treatments	Resource use estimated in RCT; prices obtained from the hospital administration or pharmacy	Net benefit = $US3811 (average cost per pt: fluconazole = $US35 440, placebo: $US31 559); difference was not statistically significant
Wakerly et al.,[29] 1994–5, £	Model [neutropenic period]	Literature survey and clinical interviews conducted in nine UK hospitals	LOS; prophylactic agents; diagnostic procedures; labour costs; treatment costs	Resource use based on the literature and clinical interviews; unit costs extracted from national sources	All strategies involving prophylaxis are less costly options than the 'no prophylaxis' strategy; the most favourable strategy depends on the pt group and the data source used
Nomura et al.,[30] 1993, $US	Model [lifetime]	Literature survey limited to clinical trials; background mortality obtained from Japanese database	Prophylactic agents; LOS; medical procedures; medications other than antifungals; transfusions; antifungal treatments	Costs retrieved from hospital claims of inpatients at a teaching hospital in Japan together with the current national reimbursement charges	Fluconazole vs empirical AmB = $US652 per LYG Fluconazole vs no prophylaxis and no empirical treatment = $US625 per LYG
Penack et al.,[31] NS, €	Pt level (retrospective study) [neutropenic period]	Prospective, randomized, nonstratified and unblinded trial	Prophylactic agents; diagnostic procedures; therapeutic procedures; antifungal and antibacterial treatment	Resource use data retrospectively gathered for individual pts; unit costs extracted from national sources	Net benefit[a] = €1094 (95% CI 2242, −53; p = 0.061); probability of positive net benefit = 97.4%
de Vries et al.,[32] 2004, €	Model [neutropenic period]	Meta-analyses including RCTs	Prophylactic agents; LOS; diagnostic procedures; antifungal treatment	Resource use obtained from Dutch databases and expert opinion; unit costs extracted from national databases	For both Netherlands and Germany, itraconazole dominated fluconazole and no prophylaxis with regard to the IC per IFI averted; probability of itraconazole being dominant vs fluconazole: ≈98% in both countries
Sohn et al.,[33] 2007, W	Model [lifetime]	Randomized, double-blind, head-to-head, multicentre study	Prophylactic agents; LOS; laboratory/imaging; empirical therapy; antifungal treatment; treatment side effects	Derived from a previously published economic evaluation of antifungal treatment in Korea, which extracted costs from national health insurance databases	Micafungin dominated fluconazole with regard to the IC per LYG; micafungin resulted in 4.8 LYG and savings of W95 511 000 per 100 pts vs fluconazole
Schonfeld et al.,[34] 2006, $US	Pt level (estimated costs applied to individual pts in RCT) [treatment period + 4 wk post-treatment]	Randomized, double-blind, head-to-head, multicentre study	Prophylactic agents; total hospital costs	Unit costs prophylactic drugs extracted from national sources; hospital costs due to IFIs extracted from the literature	Micafungin dominated fluconazole with regard to the IC per treatment success; probability of micafungin being dominant: 55.5%

Continued next page

Table II. Contd

Study, year of values, currency	Analysis [time horizon]	Source of efficacy/ effectiveness data	Cost components	Source of cost data	Results
Stam et al.,[35] 2006, €	Model [lifetime]	Treatment efficacy from RCT; AML and MDS survival and QOL estimates extracted from the literature	Prophylactic agents; LOS; diagnostic procedures; monitoring; treatment side effects; outpatient care	Data on length of prophylaxis obtained from RCT; drug acquisition costs obtained from national databases; Dutch costs related to an IFI obtained from the literature	Posaconazole dominated standard azole treatment with regard to the IC per QALY gained; posaconazole resulted in 0.08 QALYs gained and savings of €183 per pt vs standard azole treatment; estimated probability of posaconazole being cost effective at a WTP threshold of €20 000 per QALY gained: 90%
Collins et al.,[36] 2006, $US	Model [during treatment and 100 d[b]]	RCT	Prophylactic agents; inpatient costs (i.e. room charges, radiology, operating room, drugs, laboratory tests, supplies, therapy and all other charges)	Unit costs prophylactic drugs extracted from national sources; hospital costs due to IFIs extracted from literature	Posaconazole dominated standard azole treatment with regard to the IC per IFI avoided; posaconazole resulted in 6% more IFIs averted and savings of $US2507 per person vs standard azole treatment during the treatment phase; estimated probability of posaconazole being dominant during the treatment phase: 78.8%
O'Sullivan et al.,[37] 2006, $US	Model [lifetime]	RCT	Prophylactic agents; inpatient costs attributable to an IFI (one parameter containing all costs)	Unit costs prophylactic agents from national databases and manufacturer; costs attributable to an IFI extracted from unpublished healthcare cost data	Posaconazole dominated standard azole treatment with regard to the IC per LYG; posaconazole resulted in 0.07 LYG and savings of $US600 per pt vs standard azole treatment; estimated probability of posaconazole being dominant: 73%
Greiner et al.,[38] 2006, CHF	Model [lifetime]	RCT	Prophylactic agents; inpatient costs attributable to an IFI; outpatient costs (consultations, antifungal treatment)	Unit costs prophylactic agents from national databases; costs attributable to an IFI extracted from local statistics, literature reviews and expert opinion	Posaconazole dominated standard azole treatment with regard to the IC per LYG; posaconazole resulted in 0.016 LYG and savings of CHF1118 per pt vs standard azole treatment; estimated probability of posaconazole being dominant: 73.4%

a Here, net benefit was defined as: net costs no prophylaxis minus net costs L-AmB.

b Two separate analyses were performed.

AmB = amphotericin B; **AML** = acute myeloid leukaemia; **CHF** = Swiss franc; **dominated** = more effective and less costly; **IC** = incremental cost; **IFI** = invasive fungal infections; **LOS** = length of stay; **LYG** = life-year gained; **MDS** = myelodysplastic syndrome; **NS** = not specified; **QOL** = quality of life; **RCT** = randomized controlled trial; **W** = Korean won; **WTP** = willingness to pay.

costs were retrieved from hospital claims together with Japanese reimbursement charges. They concluded that fluconazole prophylaxis appears to ensure clinical benefits with acceptable cost effectiveness.

The cost benefit of low-dose L-AmB prophylaxis was assessed by Penack et al.[31] Data on resource use were retrospectively gathered for patients who recently were included in a randomized controlled trial (RCT) comparing L-AmB with no prophylaxis. Costs associated with medication and diagnostic tests were valued using German market prices and the German cost catalogue for hospital-based procedures, respectively. The authors concluded that the use of L-AmB prophylaxis in high-risk patients could result in significant cost savings compared with no prophylaxis.

de Vries et al.[32] designed a decision analytic model to assess the cost effectiveness of itraconazole compared with both fluconazole and no prophylaxis for the prevention of IFIs. Effectiveness measures for the different strategies in terms of the risk of acquiring an IFI were extracted from previously published meta-analyses. Furthermore, estimates of medical resource use due to an IFI were obtained from a retrospective cohort study and expert opinions. Subsequently, national unit costs were linked to these resources. de Vries et al.[32] concluded that itraconazole was likely to result in improved outcomes and lower costs compared with fluconazole and no prophylaxis in both the Netherlands and Germany.

The cost effectiveness of prophylaxis with micafungin versus fluconazole was estimated by Sohn et al.[33] and Schonfeld et al.[34] They both used efficacy data obtained from a large RCT.[39] Schonfeld et al.[34] performed the analysis for the US situation, while Sohn et al.[33] used the Korean national health insurance perspective. The former used published literature to directly obtain US cost estimates associated with the different clinical outcomes in order to estimate the cost per treatment success after linking those cost estimates to the individual clinical outcomes in the clinical trial. On the other hand, Sohn et al.[33] constructed a decision analytic model that included Korean data on costs and life expectancy to assess the costs per life-year gained (LYG). Although both studies[33,34] evaluated the cost effectiveness for two different countries and used different outcome measures (i.e. costs per treatment success and costs per LYG), they both estimated micafungin to be the dominant strategy (i.e. more effective and cost saving).

Finally, Stam et al.,[35] Collins et al.,[36] O'Sullivan et al.[37] and Greiner et al.[38] assessed the cost effectiveness of posaconazole for prophylactic treatment in comparison with standard azole prophylactic treatment. All four based their analysis on an RCT conducted by Cornely et al.,[40] where, in the comparator arm 81% of the patients received fluconazole and 19% received itraconazole. Furthermore, all four designed a decision analytic model in order to include data from several data sources. Unlike Collins et al.,[36] who considered the incremental cost per IFI avoided, Stam et al.,[35] O'Sullivan at al.[37] and Greiner et al.[38] extended their decision analytic models with a Markov model to allow estimation of QALYs gained[35] or LYG.[37,38] Although the analyses were conducted for different countries and used different outcome measures, the conclusions drawn by the four different papers were similar; they all concluded that posaconazole is likely to be a cost-effective alternative relative to fluconazole or itraconazole, and may result in cost savings.

3. Comparison of Studies

As shown in table I and described in the previous sections, the economic evaluations examined a wide variety of treatment options in different patient populations. The cost benefit or cost effectiveness of antifungal prophylaxis with amphotericin B, fluconazole, itraconazole, micafungin and posaconazole have all been estimated.[28-39] Furthermore, a diversity of comparators were included in these economic analyses. The antifungals that have already been on the market for a considerable number of years now (i.e. fluconazole, amphotericin B and itraconazole) were all compared with no prophylaxis.[28-32] In addition to the comparison with no prophylaxis, two studies explicitly compared fluconazole prophylaxis with oral polyenes and empirical treatment with amphotericin B,

respectively.[29,30] Until a few years ago, 'no prophylaxis' was the standard strategy (i.e. existing care) in many institutions. Consequently, the no prophylaxis strategy was an appropriate comparator at that time. However, as antifungal prophylaxis is currently recommended and used in many institutions for patients at high risk of infection, new prophylactic agents should no longer be compared only with no prophylaxis.[18,19] The recently introduced prophylactic agents micafungin and posaconazole have been compared with fluconazole and 'standard azole treatment' (fluconazole or itraconazole), respectively.[33-38]

The economic evaluations were performed for different patient populations at risk for acquiring IFIs (table I). For simplicity, these patients are often roughly divided into the following two categories: (i) patients with haematological malignancies treated with chemotherapy; and (ii) patients undergoing an HSCT (i.e. bone marrow transplantation). Six studies[28,30,35-38] focused on immunocompromised patients treated with chemotherapy, two studies[33,34] focused only on patients undergoing a bone marrow transplantation and three studies included both patient groups.[29,31,32] However, only one of those stratified and performed separate analyses for the two groups.[29] It is important to note that one should be cautious when combining different patient groups, as the underlying disease has an important influence on baseline IFI incidence rates. Therefore, we strongly discourage the generalization of pharmacoeconomic results from one patient group to another. We will extensively elaborate on the influence of IFI incidence rates on the cost effectiveness of prophylactic regimens in section 5.

The included economic evaluations did not only look at different prophylactic agents and different patient populations, they also differed considerably with respect to evaluation type, time horizon and efficacy and cost data included. In general, there are two main approaches for data collection and analysis in economic evaluations.[41] One could perform an analysis using patient-level data, which are usually gathered alongside clinical trials, or using decision analytic modelling, where data are drawn from a number of sources. Three of the 11 economic evaluations used patient-level data to estimate the cost effectiveness.[28,31,32] When using patient-level data, one would ideally collect prospective data on efficacy and resource use simultaneously alongside an RCT, as Schaffner and Schaffner[28] did in their cost-benefit analysis. However, Penack et al.[31] collected the economic data retrospectively for the patients included in an RCT, while Schonfeld et al.[34] obtained cost estimates from the literature and linked those to the individual clinical outcomes assessed in an RCT. The other economic evaluations all designed a decision analytic model to bring evidence on treatment effectiveness and costs from a range of sources together.[29,30,32,33,35-38] Most of these modelling studies obtained efficacy data only from one RCT.[33-38] However, de Vries et al.[32] performed a formal meta-analysis, which is generally accepted as the highest level of evidence, to estimate the efficacy of different prophylactic treatment modalities.

The appropriate time horizon for an economic evaluation should be the period over which the costs and/or the effects (i.e. treatment effects and adverse effects) of the treatment options being compared might differ.[41] In the case of antifungal prophylaxis, the appropriate time horizon refers to the period a patient is at risk of an IFI and receives prophylactic or directed treatment. Most of the selected evaluations used this time horizon, by estimating costs and effects that occurred during the neutropenic period while on treatment.[28,29,31,32,34,36] Some also included a post-treatment period of a few weeks in their time horizon.[34,36] However, for a more generic cost-effectiveness measure, such as costs per LYG, one should take a time horizon that reflects a patient's entire lifetime. Five cost-effectiveness analyses included background survival probabilities in their models in order to estimate differences in mean survival rates between different treatment strategies, taking the underlying disease into account.[30,33,35,37,38] Stam et al.[35] also included morbidity in the form of utilities in their analyses and assessed the costs per QALY gained. However, no quality of life loss as a result of an IFI was included; only utilities of the underlying condition were taken into account.[35] Although one would ideally include both, to our knowledge no quality weights associated with IFIs have yet

been published in the literature. This certainly is an area for further research.

According to national guidelines, costs and effects that will be incurred in the future should be discounted because of time preferences.[41] In view of the fact that costs related to antifungal prophylaxis and IFIs (i.e. treatment, diagnostic procedures and length of stay) will be incurred within the first year following the start of prophylactic treatment, discounting on costs is redundant here. This obviously also applies for effects (e.g. the number of IFIs) that occur within the first year. However, if the cost per LYG or QALY gained is the cost-effectiveness measure of interest, life-years or QALYS should be appropriately discounted. Although Stam et al.[35] applied annual discount rates of 1.5% for QALYs, and O'Sullivan et al.[37] and Greiner et al.[38] applied annual discount rates of 3% for life-years, Nomura et al.[30] and Sohn et al.[33] did not discount future life-years. Greiner et al.[38] and O'Suliivan et al.[37] did mention that they discounted with a 3% rate; however, the costs used in their analysis do not necessitate discounting.

All relevant direct medical costs associated with both antifungal prophylaxis and the diagnosis and treatment of IFIs should ideally be included in economic evaluations concerning antifungal prophylaxis. Except one,[31] all of the studies reviewed in this article more or less covered these key components.[28-30,32-38] Although Penack et al.[31] performed a separate analysis comparing length of stay in different care units, they did not include costs related to an increase in length of stay due to an IFI in their cost-benefit analysis. This is a fundamental flaw, as these hospitalization costs are indicated as a main determinant of the total direct medical costs.[14]

In all studies, costs of prophylactic drug use were obtained by multiplying days on prophylactic treatment by national unit costs. Estimates of direct medical costs associated with an IFI (i.e. diagnostic procedures, treatment and length of stay) were obtained through a variety of methods in the different studies.[41] As mentioned earlier in this section, in their cost-benefit analyses Schaffner and Schaffner[28] prospectively and Penack et al.[31] retrospectively gathered patient data on resource use from a single RCT. Subsequently, in order to obtain individual cost estimates, resource use was valued by using national unit costs.[28,31] In modelling studies, one wants to link a mean cost estimate to every disease state. Nomura et al.[30] and Sohn et al.[33] directly obtained cost estimates from hospital claims and national health insurance databases, respectively. The latter, moreover, included additional medical costs obtained from the literature for costs not available in the Korean national health insurance database. Furthermore, the three studies performed in the US[34,36,37] based their cost estimates on case-control studies where incremental hospitalization costs due to an IFI were estimated by comparing the costs in a group of patients who experienced an IFI (cases) with a group of patients who did not (controls). Obviously, patients were matched on underlying conditions. This is potentially the most appropriate way, as long as the matching procedure has been done correctly, to estimate the incremental costs as all differences in resource use or costs between two groups are able to be included. Schonfeld et al.[34] and Collins et al.[36] extracted their cost estimates from a published cost-of-illness study,[14] while O'Sullivan et al.[37] performed the cost estimation themselves by using unpublished data. Note that Schonfeld et al.[34] did not design a model for estimating cost effectiveness, but linked the cost estimates to individual patient outcomes in order to perform an analysis on patient-level data. Another way of obtaining cost estimates when data on resource use or costs are lacking for a specific situation (e.g. country) is to derive resource use estimates from clinical expert opinions and subsequently value these by using national unit costs. Four studies (partly) based their resource use estimates on expert opinions.[29,32,35,38] Wakerly et al.[29] performed two separate analyses in which they used either literature sources or expert opinions to obtain estimates of resource use. Stam et al.[35] combined estimates of short-term resource use obtained from clinical trial data with long-term resource use estimates from expert opinions. Besides length of hospital stay, de Vries et al.[32] also derived resource use estimates from clinical experts. They conducted a case-control study to estimate the

increased length of stay due to an IFI by using hospital data.[32] Greiner et al.[38] also combined clinical trial data with literature sources and expert opinion in order to define estimates of resource use.

Although not always explicitly stated, all the included cost-benefit and cost-effectiveness studies were performed from a healthcare payer's perspective (table II). This means that possible benefits/costs due to production gains/losses were not taken into account.[41] Recent international guidelines for pharmacoeconomic research[42] indicate that the societal perspective should be preferred. However, we believe that the omission of indirect costs due to productivity losses is legitimized in this situation as these seriously ill patients are probably already absent from work because of their underlying disease. In other words, as these indirect costs will not be substantial, the healthcare perspective matches the societal perspective in these patients.

Finally, a sound pharmacoeconomic analysis should always include an assessment of the uncertainty surrounding the economic outcomes that result from the uncertainty in the input parameter values.[41,43,44] This can be done either by using parametric or non-parametric, resampling, methods when economic outcomes are estimated using patient-level data or by using sensitivity analysis when these outcomes are based on a decision theoretic model. The three economic evaluations that were based on patient-level data all report confidence intervals around the estimated cost-benefit[28,31] or cost-effectiveness[34] outcomes. Penack et al.[31] and Schonfeld et al.[34] stated that they used a non-parametric bootstrap method, while Schaffner and Schaffner[28] did not elaborate on the method used. The advantage of non-parametric bootstrapping is that no assumptions of the underlying distribution are made.[45] This makes these methods particularly suitable for estimating confidence intervals around incremental cost-effectiveness ratios, because of the statistical characteristics of this ratio.

Nowadays, probabilistic sensitivity analysis (PSA) is the method of choice in order to handle parameter uncertainty in decision models. For instance, in the UK, the National Institute for Health and Clinical Excellence (NICE) guidelines state that a PSA should be employed to characterize uncertainty.[44] However, three of the modeling studies included in this review lack a PSA and only performed multiple univariate sensitivity analyses to assess the impact on cost effectiveness of changing one variable at a time.[29,30,33] Nevertheless, it is very important to assess the joint uncertainty in all parameters by using PSA, as it is this overall uncertainty that could have important implications for medical decision making. The other five modeling studies indeed include both multiple univariate sensitivity analyses and a PSA.[32,35-38] The quality of the PSA, however, varied among studies. A brief description of the requirements necessary for a valid and relevant PSA is presented in Drummond et al.[41] de Vries et al.[32] presented in detail the method followed for the conduction of the PSA; however, no distributional assumptions regarding the costs of treatment or hospitalization are mentioned. Collins et al.[36] briefly mentioned the conduction of a PSA and did not report any distributional assumptions around the parameter uncertainty. In contrast, the PSA conducted in Stam et al.,[35] Greiner et al.[38] and O'Sullivan et al.[37] are clearly presented and in accordance with the criteria set by Drummond et al.[41]

4. Summary of Results

Two reviews have previously been published that discuss the available evidence on the cost effectiveness of antifungal prophylaxis in susceptible patients.[46,47] In 2004, Dixon et al.[46] not only focused on patients with haematological malignancies but also included many different patient populations, such as HIV/AIDS patients, cancer patients and transplant recipients. They concluded that they were unable to find a coherent body of evidence for any particular patient group and/or indication.[46] Furthermore, they touched on the poor quality of the studies included in their review. However, the two studies[28,29] that also met our inclusion criteria and that were therefore also included in our review, scored above average (i.e. decent quality).

In 2006, Moeremans and Annemans[47] summarized the available evidence of health economic

knowledge of antifungal treatment. As opposed to Dixon et al.,[46] they only included neutropenic patients in their review.[47] With regard to prophylaxis, they concluded that, since 2004, the pharmacoeconomic evidence had not been expanded and, therefore, economic data to support recommendations for prophylactic drug therapies were still lacking at that time.[47] However, as noted in previous sections, most full cost-effectiveness studies on antifungal prophylaxis have been published since 2006.[30-38]

One should bear in mind that the cost benefits or cost effectiveness of antifungal prophylaxis depends considerably on several factors other than the specific prophylactic agent. As wide variations exist in studies regarding patient characteristics, underlying diseases, hospital settings, drug regimens and study methods, it is difficult to find clear evidence of the economic advantages of a single prophylactic agent. Furthermore, one agent could be the most economic strategy under particular circumstances (e.g. specific patient group in a particular country), while it is exceeded by others under different circumstances. Therefore, we strongly advise against indiscriminately generalizing conclusions from economic analyses of antifungal prophylactic drugs. We will extensively ground this with an example in the next section.

However, some general lessons can be learned from the studies included in this review. First, antifungal prophylaxis is potentially a (highly) economically favourable intervention. Four of five studies that compared fluconazole, amphotericin B or itraconazole with no prophylaxis estimated the prophylactic intervention to be cost beneficial,[29,31] cost effective[30] or even cost saving,[32] while the other study[28] did not reveal any statistical difference in economic outcomes (table II). As IFIs are associated with significant mortality and expensive treatment, carefully targeted antifungal prophylaxis could considerably reduce treatment costs and increase life expectancy.[13-15] Obviously, the economic advantages of prophylaxis highly depends on baseline IFI incidence rates.

Furthermore, the newer antifungal agents seem to be potentially more cost effective than fluconazole, which is still being used as the prophylactic agent of choice in many institutions. Both itraconazole and micafungin have been estimated as cost saving relative to fluconazole.[32-34] Furthermore, posaconazole has been estimated as cost saving compared with standard azole treatment (i.e. 81% received fluconazole and 19% received itraconazole).[35-38] As mentioned previously, regarding micafungin and posaconazole, it is important to note that the clinical effectiveness measures used in several cost-effectiveness studies were obtained from the same single RCT.[39,40] In other words, differences in incremental cost-effectiveness outcomes between the two studies on micafungin or the four studies on posaconazole originate from different cost estimates or different (country-specific) life expectancies.

Next to the above-mentioned antifungal agents, voriconazole is also often used in practice as an agent for antifungal prophylaxis in immunocompromised patients. However, evidence arising from RCTs that prove its relative effectiveness as a prophylactic agent is not yet publicly available. For that reason, the economic evaluation of prophylaxis with fluconazole is hard to implement. Al-Badriyeh et al.[27] conducted a pharmacoeconomic evaluation of antifungal prophylaxis with voriconazole versus prophylaxis with posaconazole. The authors drew their efficacy and effectiveness data from a targeted retrospective chart review. Their evaluation approach, however, was closer to a cost comparison analysis than a cost-benefit analysis, which precluded the inclusion of this study in our systematic review.

The advantage of itraconazole, micafungin and posaconazole is that they, unlike fluconazole, show activity against *Aspergillus* species.[20] This explains the large potential benefits in terms of cost effectiveness of these newer antifungal agents compared with fluconazole.[32-38] As *Aspergillus* infections are associated with very high mortality rates and are most costly to treat, obviously, these drugs are potentially able to save both more costs and more life-years than fluconazole.[13,14] In other words, the higher investment costs of using the more expensive newer drugs could possibly be totally offset by the averted costs. Furthermore, the increase in the incidence of mould infections further highlights the importance of preventing these *Aspergillus* infections.[11] However, as holds

true for all types of IFIs, it depends on the specific patient group together with the specific hospital setting as to what the exact IFI incidence rate will be and which prophylactic strategy will be most cost effective.

5. General Remarks on the Cost Effectiveness of Antifungal Prophylaxis

As applies for all prevention programmes, the cost effectiveness of antifungal prophylaxis is highly dependent on the baseline IFI incidence rate.[48] The baseline IFI rate refers to the number of cases in a situation where no antifungal prophylaxis is given. Obviously, the higher the baseline IFI incidence rate, the more IFIs and associated mortality, morbidity and costs could be prevented by using prophylaxis. Hence, the baseline incidence rate can have a large impact on the cost effectiveness of antifungal prophylaxis. This effect can also have important implications for medical decision making. In the Netherlands, interventions are considered certainly cost effective if their estimated cost effectiveness is below a threshold of €20 000 per LYG.[49] Although this threshold is informal and not undisputed, it is often used by decision makers. From a pharmacoeconomic point of view, this means that, in the Dutch situation, antifungal prophylaxis with drug A would be considered cost effective versus no prophylaxis if the baseline IFI incidence rate was assumed to be 10% (incremental cost per LYG €2000), while it would not be considered cost effective if the baseline IFI incidence rate was assumed to be 3% (incremental cost per LYG €30 000). This example assumes per-patient costs for antifungal prophylaxis with drug A of €1500 and treatment of IFI of €25 000; assumed clinical outcomes were a life expectancy of 5 years in patients without IFI, a mortality rate in patients with IFI of 50%, and an effectiveness rate of antifungal prophylaxis with drug A of 50%.

There are several factors that affect the baseline incidence rate of IFIs and consequently act on the cost effectiveness of antifungal prophylaxis. First, a number of patient-specific risk factors for the development of IFIs have been identified.[3,9] For the major part, these are associated with the underlying disease and accompanying treatment. It is important to note that risk factors can differ depending on the fungus. For example, severe gastrointestinal damage will highly increase the risk of acquiring an invasive *Candida* infection, while this has no impact on the risk of acquiring an *Aspergillus* infection.[3] Obviously, as the probability of acquiring an IFI (i.e. baseline IFI incidence rate) will be higher in high-risk patients, the cost effectiveness of antifungal prophylaxis in high-risk patients will be more favourable than in low-risk patients. Consequently, we strongly discourage generalizing cost-effectiveness results from one patient group to another.

Second, as also applies for several infectious diseases caused by bacteria or viruses, significant geographical differences in the epidemiology of IFIs were found.[3,50] Baseline IFI incidence rates vary not only from region to region, but even from hospital to hospital. Consequently, the use of a particular prophylactic agent in a particular patient population could be cost effective in one country/region, while it will not be cost effective in the same patient population in another country/region. Although the same model structure can often be used for different countries, one should always use specific geographical IFI incidence data to obtain valid cost-effectiveness results.

Finally, the sustained use of antifungal prophylaxis can influence the (geographical) infection patterns of both moulds and yeasts. The successful use of fluconazole has, for example, caused a shift from azole-susceptible species to less susceptible and even azole-resistant ones.[9] These changing patterns in IFIs, together with the local variability in infection rates, can have important consequences for the cost effectiveness of particular prophylactic agents. In our example in the Dutch situation, we estimated the incremental cost effectiveness of antifungal prophylaxis with drug A versus no prophylaxis, but the influence of baseline IFI incidence rates on the incremental cost effectiveness will, of course, also be present if two different prophylactic agents are compared. For example, in areas where IFIs are predominantly caused by *Aspergillus* species, it is evident that the newer antifungal agents (i.e. itraconazole, posaconazole or micafungin) that show activity against

these *Aspergillus* species become pharmacoeconomically more favourable than fluconazole.

In summary, it is important to be aware that the cost effectiveness of a particular antifungal prophylactic agent depends on several crucial aspects. This should be kept in mind when comparing the results of different economic evaluations or when generalizing the results from one patient population or setting to another.

6. Conclusion

Considering the available evidence, antifungal prophylaxis in immunocompromised patients treated for haematological malignancies seems to be an intervention with favourable cost-benefit, cost-effectiveness and cost-saving potential. Furthermore, the newer recently introduced antifungal agents seem to be an attractive alternative to fluconazole from a pharmacoeconomic point of view. However, due to a wide heterogeneity regarding patient characteristics, underlying diseases, hospital settings and study methods in the included economic studies, as well as the lack of 'head-to-head' trials, it is difficult to find clear evidence of the economic advantages of a single prophylactic agent.

In the past years, new antifungal agents such as micafungin and posaconazole have been approved for clinical use.[21] Unfortunately, these drugs have not yet been compared with each other in one single clinical trial. Other antifungals are in different stages of development prior to approval.[5] For example, ravuconazole and isavuconazole are new triazoles that could possibly be used for antifungal prophylaxis in the future.[51] Due to the rapid successive market entry of these antifungal prophylactic strategies, (clinical) trials including all relevant comparator interventions will often be lacking at the time of registration. However, a sound cost-effectiveness analysis including all relevant strategies is required in order to assess which strategy gives best value for money. Therefore, indirect and mixed treatment comparison methods could have great potential for estimating the comparative cost effectiveness of multiple antifungal prophylactic options using evidence from trials that individually do not compare all treatment options.[52] Such a mixed treatment comparison has recently been performed for estimating the cost effectiveness of antifungal treatment for invasive *Candida* infections.[53]

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