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Economic Comparison of an Empirical Versus Diagnostic-Driven Strategy for Treating Invasive Fungal Disease in Immunocompromised Patients

Rosemary Barnes, MD[1]; Stephanie Earnshaw, PhD[2]; Raoul Herbrecht, MD[3]; Orla Morrissey, MB, BCh[4]; Monica Slavin, MB, BS, MD[5]; Eric Bow, MSc, MD, D. Bacteriol[6]; Cheryl McDade[2]; Claudie Charbonneau, MSc, PhD[7]; David Weinstein, MSc[7]; Michal Kantecki, MD[7]; Haran Schlamm, MD[8]; and Johan Maertens, MD, PhD[9]

[1]Cardiff University, University Hospital of Wales, Cardiff, United Kingdom; [2]RTI Health Solutions, Research Triangle Park, North Carolina, USA; [3]Hôpital de Hautepierre, Strasbourg, France; [4]Department of Infectious Diseases, Alfred Health and Monash University, Melbourne, Victoria, Australia; [5]Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, Victoria, Australia; [6]CancerCare Manitoba and the University of Manitoba, Winnipeg, Manitoba, Canada; [7]Pfizer International Operations, Paris, France; [8]Pfizer Inc, New York, New York, USA; and [9]Universitaire Ziekenhuizen Leuven, Campus Gasthuisberg, Leuven, Belgium

ABSTRACT

Purpose: Patients with persistent or recurrent neutropenic fevers at risk of invasive fungal disease (IFD) are treated empirically with antifungal therapy (AFT). Early treatment using a diagnostic-driven (DD) strategy may reduce clinical and economic burdens. We compared costs and outcomes of both strategies from a UK perspective.

Methods: An empirical strategy with conventional amphotericin B deoxycholate (C-AmB), liposomal amphotericin B (L-AmB), or caspofungin was compared with a DD strategy (initiated based on positive ELISA results for galactomannan antigen) and/or positive results for *Aspergillus* species on polymerase chain reaction assay) using C-AmB, voriconazole, or L-AmB in a decision-analytic model. Rates of IFD incidence, overall mortality, and IFD-related mortality in adults expected to be neutropenic for ≥10 days were obtained. The empirical strategy was assumed to identify 30% of IFD and targeted AFT to improve survival by a hazard ratio of 0.589. AFT-specific adverse events were obtained from a summary of product characteristics. Resource use was obtained, and costs were estimated by using standard UK costing sources. All costs are presented in 2012 British pounds sterling.

Findings: Total costs were 32% lower for the DD strategy (£1561.29) versus the empirical strategy (£2301.93) due to a reduced incidence of adverse events and decreased use of AFT. Administration of AFT was reduced by 41% (DD strategy, 74 of 1000; empirical strategy, 125 of 1000), with similar survival rates.

Implications: This study suggests that a DD strategy is likely to be cost-saving versus empirical treatment for immunocompromised patients with persistent or recurrent neutropenic fevers. (*Clin Ther*. 2015;▮:▮▮▮–▮▮▮) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

Key words: antifungal therapy, aspergillosis, cost benefit, fungal infection.

INTRODUCTION

Invasive fungal disease (IFD) is associated with high mortality rates in severely immunocompromised patients, such as those undergoing intensive chemotherapy or stem cell transplantation.[1] IFD results in increased hospital and intensive care unit costs, with pharmacy expenditures (including antifungal treatment) the main cost driver.[2]

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Because IFD is life-threatening, empirical therapy is commonly used in at-risk patients.[3] With this strategy, patients are treated for suspected IFD when they present with persistent or recurrent neutropenic fevers that are unresponsive to broad-spectrum antibacterial therapy for 72 to 96 hours. Conventional amphotericin B deoxycholate (C-AmB), liposomal amphotericin B (L-AmB), and caspofungin are currently the only antifungal agents licensed for empirical treatment in the setting of persistent or recurrent neutropenic fevers. Empirical treatment can be costly, however,[4–6] with the potential for overtreatment of nonfungal fever, resulting in increased toxicity and treatment-related costs.[7]

Early use of diagnostic assays in a diagnostic-driven (DD) therapy strategy is 1 way to potentially identify patients with invasive aspergillosis (IA) more accurately and, consequently, to better select treatments for these patients. In addition, earlier diagnosis and targeted therapy may reduce costs and improve outcomes by eliminating unnecessary toxic treatment. Several studies have helped us to better understand the clinical impact of a DD strategy compared with a standard empirical strategy.[7–12] However, these studies do not highlight the economic impact of a DD therapy strategy.

In the present study, we examined the impact on costs and outcomes that may occur in neutropenic patients with a suspected IFD caused by *Aspergillus* species when treated by using either a typical empirical strategy with antifungal therapy administered to all patients or an early-treatment DD strategy with more targeted antifungal therapy.

PATIENTS AND METHODS

A decision-analytic model was developed to examine the costs and outcomes associated with the standard empirical strategy, in which all patients with persistent or recurrent neutropenic fevers were treated with C-AmB, L-AmB, or caspofungin, compared with a DD strategy, in which selected patients were treated with C-AmB, L-AmB, or voriconazole. Antifungal agents were chosen based on the indications listed in the summaries of product characteristics as well as expert feedback.

The model was developed from a UK perspective and included a time horizon of 5 months.[13] All costs are presented in 2012 British pounds sterling. Costs and outcomes were not discounted because the time horizon was <1 year.

Population

Patients were assumed to be aged ≥ 18 years with hematologic malignancies, undergoing chemotherapy or autologous/allogeneic hematopoietic stem cell transplantation, and expected to be severely neutropenic (neutrophil count $<0.5 \times 10^9$ cells/L) for ≥ 10 days.[7–12] Patients could not have had a diagnosis of proven or probable IFD or have received treatment with an investigational antifungal agent in the previous 6 months.

Comparators

DD Strategy

Patients began antifungal therapy when they were suspected of having an IFD based on characteristic lesions on computed tomography scan, *Aspergillus* species colonization, and/or positive ELISA results for galactomannan antigen (GM) and/or positive results for *Aspergillus* species on polymerase chain reaction (PCR) assay. Patients were treated with C-AmB, L-AmB, or voriconazole.

Empirical Strategy

Patients began antifungal therapy when they had persistent or recurrent neutropenic fevers that failed to defervesce despite broad-spectrum antibacterial therapy for 72 to 96 hours, with no IFD identified. Patients were treated with C-AmB, L-AmB, or caspofungin.

Model Structure

The decision model (Figures 1A–1C) was designed as a standard decision tree, with chance nodes representing the probability of occurrence of each event and decision nodes representing decision points. Patients at risk for IFD, such as those with IA, were entered into the model and were assigned to each strategy as soon as they became neutropenic. At baseline for treatment of initial neutropenic fevers, patients underwent a standard diagnostic evaluation, which included blood cultures, urine cultures, body site–specific microbiologic cultures, serum biochemistry, and hematology studies. After the standard diagnostic evaluation, initial empirical broad-spectrum antibacterial therapy was initiated. Thereafter, other monitoring and microbiologic tests were performed, as

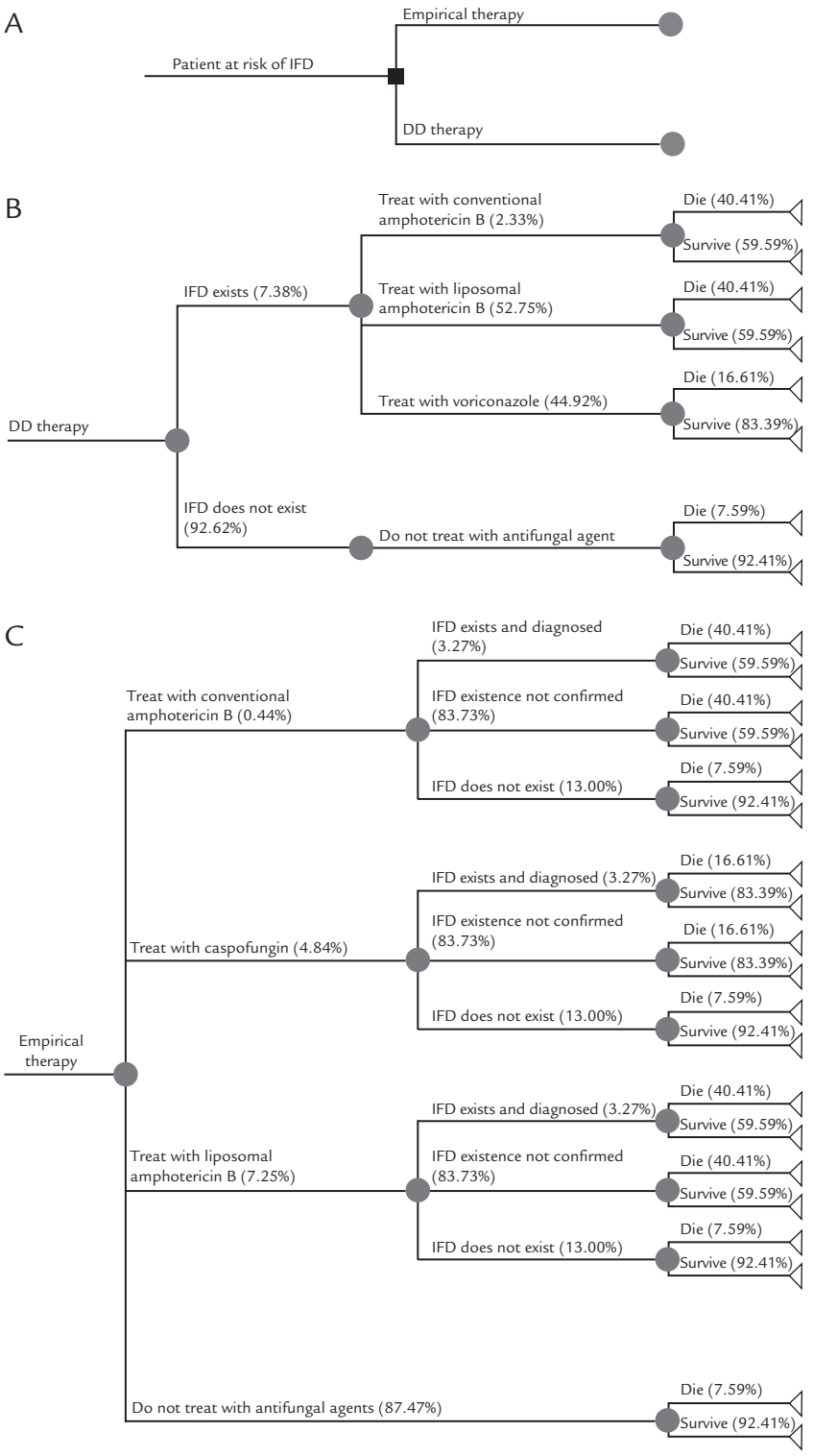

Figure 1. Model structure showing (A) overall structure, (B) diagnostic-driven (DD) strategy decision tree, and (C) empirical strategy decision tree with point estimates. Chance nodes (circles) represent the probability of occurrence of each event, and decision nodes (squares) represent decision points. IFD = invasive fungal disease.

clinically appropriate, during the episode of neutropenic fevers.

Once persistent or recurrent neutropenic fevers were established, a decision was made to manage them according to the patient's assigned strategy. Patients in the DD strategy group were treated similarly to patients in the empirical strategy group except the former received antifungal prophylaxis with fluconazole, and additional health care resources (eg, GM-ELISA and PCR testing) were used to diagnose IFD. It was assumed that the DD strategy and the empirical strategy were initiated at the same time.

In the DD strategy (Figure 1B), an IFD was diagnosed on the basis of clinical and biomarker findings. As a result, patients with a probable or possible diagnosis of IA were treated with appropriate antifungal agents. Patients without a probable or possible diagnosis were not treated with antifungal agents. However, the model structure allowed patients without a confirmed diagnosis of IFD to receive antifungal treatment at the discretion of the clinician while awaiting the outcome of other investigations if an IFD was strongly suspected on clinical grounds. After treatment or no treatment, patients either survived or died (based on the epidemiologic and clinical data obtained from the published literature).

In the empirical strategy (Figure 1C), patients were treated with antifungal agents on the basis of persistent or recurrent fevers, regardless of whether the IFD was confirmed to exist. A portion of patients may have had proven or probable IFD, another portion of patients may definitely not have had an IFD, and the remainder of patients may have had an IFD but never had its existence confirmed. After treatment or no treatment, patients either survived or died (based on the epidemiologic and clinical data taken from the published literature).

Model Inputs

Incidence

To estimate the costs and outcomes associated with each treatment strategy, the incidence of IFD within a particular clinical setting was required. Within the model, the incidence of IFD was assumed to be 10.9% (95% CI, 9–13), based on a population of patients treated with myelosuppressive chemotherapy for hematologic malignancies or autologous stem cell transplantation in a German tertiary care center.[14]

Clinical Success

Clinical success in the model was assumed to be successful treatment of an IFD and survival of the patient. Ideally, mortality data would be obtained from head-to-head clinical studies. However, available clinical studies have limitations; for example, patients were treated with random mixtures of antifungal agents, and antifungal treatment in the DD strategy was delayed based on study criteria, which may have affected mortality. Furthermore, comparative clinical studies of patients receiving empirical therapy versus DD therapy reported very high overall survival rates for both arms,[8,9,11] which made it difficult to estimate the true impact of the treatment strategy on survival.

As a result of these limitations, data from epidemiologic studies were obtained. Mortality was estimated from observations derived from neutropenic patients with hematologic malignancies or who were receiving autologous stem cell transplantation in a German tertiary care center between 2002 and 2006; overall mortality was 10.7% (95% CI, 9–13) and IFD-related mortality was 28.6% (95% CI, 19–39).[13] Assuming that patients without an IFD would not die because of this disease, we assumed that patients with an IFD would have an increase in mortality of 28.6%. Given this assumption, the overall mortality was adjusted to be specific for patients with an IFD (36.2%) and for patients without an IFD (7.6%). The specific mortality values and the calculations are presented in Figures 1B and 1C and Supplemental Table I (as given in the online version at http://dx.doi.org/10.1016/j.clinthera.2015.03.021).

Hahn-Ast et al[13] also estimated the impact of using nonpolyene antifungal agents (defined as voriconazole and caspofungin) on overall survival. They performed a multivariate analysis for overall survival in patients with IFD and reported that the use of these novel antifungal agents was associated with a significant improvement in overall survival (hazard ratio, 0.589 [95% CI, 0.362–0.959]; $P = 0.033$). Using these data, the IFD-related and non–IFD-related mortality rates were adjusted to be specific for patients receiving amphotericin-based agents and patients on novel antifungal agents (Supplemental Table I, given in the online version at http://dx.doi.org/10.1016/j.clinthera.2015.03.021).

Other assumptions made for clinical success and mortality were that treatment with antifungal agents benefited only those patients with an IFD. Instances of IFD identified by using the DD strategy, but not

diagnosed in the empirical strategy, were assumed to occur among patients treated with antifungal agents in the empirical strategy arm; GM-ELISA and PCR tests were assumed to have a sensitivity of 67.7%[15]; and the empirical strategy only identified 29% to 31% of the IFD confirmed by using the DD strategy.[8,11]

Adverse Events

Adverse events (AEs) in the model were those that occurred in ≥10% of patients in the empirical trials[16–18] and that were deemed to be most resource intensive. As recommended by the key opinion leaders (R. Barnes, R. Herbrecht, O. Morrissey, M. Slavin, E. Bow, J. Maertens, and C. Cordonnier, personal communications, October and November 2012), the AEs were limited to nephrotoxicity, tachycardia, and hypertension. To normalize the percentages to a common population, the percentage of patients experiencing AEs during receipt of caspofungin, voriconazole, or amphotericin B was estimated by applying the absolute difference in AEs seen between each antifungal agent and L-AmB within the respective trials to the pooled AE percentages derived for L-AmB. The proportions of patients experiencing the AEs associated with each antifungal agent are presented in Table I.[16,18]

Resource Use and Costs

Health care resources and costs considered in the model were general health care resources used to manage each treatment strategy, antifungal treatment costs, and costs to treat AEs.

General health care resource costs in the model were estimated by using a micro-costing approach. Specifically, resource use for general diagnosis and treatment within an empirical therapy or DD strategy was initially estimated from the published literature[7,8,11,12] and then reviewed by the key opinion leaders (R. Barnes, O. Morrissey, M. Slavin, and J. Maertens, personal communications, November 2012). Patients in the DD strategy used health care resources in a manner similar to those treated via the empirical strategy, except that patients in the DD strategy were also screened for *Aspergillus* species until they recovered from neutropenia. The health care resources, percentages of patients expected to receive resources, and the mean number of resources patients were expected to use during the treatment strategy are presented in Table II.[19]

Antifungal agent use for each treatment strategy was obtained from the specific product characteristics[14,20–23] and reviewed by the key opinion leaders (R. Barnes, O. Morrissey, M. Slavin, and J. Maertens, personal communications, November 2012). Costing of antifungal agents depended on patient weight. The average patient weight, used to calculate the average unit cost, was estimated as the average weight of men and women in England in 2010 (84.6 kg and 71.2 kg, respectively).[24] The model considered treatment from the point of infection, and antifungal prophylaxis before initiation of empirical therapy was not included. Patients treated with the DD strategy were assumed

Table I. Proportion of patients receiving antifungal agents who experienced adverse events (AEs) and the costs of the AEs.

	Antifungal Agent				
AE	C-AmB	Caspofungin	L-AmB	Voriconazole	Cost per AE (£)
Hypertension*	9.6%	0.6%	0.6%	0.6%	110.77
Nephrotoxicity†	27.1%	3.2%	12.1%	11.5%	88.12
Tachycardia*	10.8%	0.6%	0.6%	0.6%	165.34

C-AmB = conventional amphotericin B; L-AmB = liposomal amphotericin B.
*Hypertension and tachycardia were only reported in the study by Walsh et al.[1] The difference between C-AmB and L-AmB is estimated.
†Defined as a doubling of the serum creatinine level or an increase of at least 88.4 μmol/L if elevated at baseline.[16,18]

Table II. General resource use according to treatment strategy and unit costs.

Resource	Proportion of Patients Using Resource (%)		Mean No. of Resources Used		
	DD	Empirical	DD	Empirical	Unit Cost (£)
Neutrophil count tests	100.0	100.0	17.9	17.9	3.05
Chest radiograph	83.3	83.3	4.2	4.2	58.57
Blood cultures	98.3	98.3	7.4	11.5	3.05
Urine cultures	73.3	75.0	11.9	3.0	1.26
Nasal, pharyngeal, and rectal swab	100.0	100.0	9.5	9.5	1.26
CT scan	70.0	65.0	1.0	1.0	61.00
Abdominal echography	21.7	8.3	1.0	1.0	50.47
Bronchoscopy	25.0	18.0	1.0	1.0	583.48
Bronchoalveolar lavage	25.0	18.0	1.0	1.0	583.48
Cytomegalovirus PCR	60.0	60.0	14.3	14.3	1.23
Nonfungal molecular tests*	20.0	20.0	14.3	14.3	1.23
Lung biopsy	2.0	2.0	1.0	1.0	646.68
Transbronchial biopsy	4.0	4.0	1.0	1.0	646.68
Skin biopsy	4.0	4.0	1.0	1.0	146.72
Galactomannan antigenemia screening†	100.0	–	7.4	–	3.05
Aspergillus PCR test	100.0	–	4.0	–	1.23

DD = diagnostic-driven; CT = computerized tomography; PCR = polymerase chain reaction.
Costs were obtained from standard UK costing sources.[1]
*Molecular tests included human herpes virus 6 PCR, herpes PCR, and adenovirus PCR.
†Galactomannan screening costs are provided as a kit of 96 tests. The cost of a single assay is estimated to be £3.05 (ie, £292.80 per kit/96 tests per kit).

to receive antifungal prophylaxis with fluconazole 400 mg/d for 18 days.[8] Mold-active antifungal prophylaxis was not administered to patients in either strategy. Antifungal therapy dosing details, unit costs, and administration costs are presented in Table III.[14,19–23,25]

For costing AEs (Table I), the key opinion leaders outlined typical treatment that would be associated with each AE (R. Barnes, O. Morrissey, M. Slavin, and J. Maertens, personal communications, November 2012). Treatment algorithms for each AE are presented in Supplemental Tables II and III (as given in the online version at http://dx.doi.org/10.1016/j.clinthera.2015.03.021).[19,26]

Model Calculations

For each treatment strategy, we derived the number of patients treated with antifungal drug therapy, the number of diagnosed IFD, the number of deaths, and costs. The incremental cost per death avoided was calculated as:

$$= \frac{(\text{total cost of DD strategy} - \text{total cost of empirical strategy})}{(\text{number of survivors in DD strategy} - \text{number of survivors in empirical strategy})}$$

Sensitivity Analyses

To test the robustness of model assumptions and parameters, the effect of changing parameters in both

Table III. Distribution of antifungal agents administered in patients who received antifungal therapy, duration of use, dosing, administration time, and unit costs.

Antifungal Agent	DD Strategy		Empirical Strategy		Dosage	Unit Cost (£)	Administration Time (h)*
	% Using	Duration (d)	% Using	Duration (d)			
C-AmB	2.3	21.0	3.5	21.0	1.0 mg/kg/d	7.76	3.0
Caspofungin	NA	NA	38.7	28.0	70-mg loading dose on day 1; maintenance dose of 50 mg QD	Day 1: 416.78 Post day 1: 327.67	1.0
L-AmB	52.7	23.3	57.8	23.3	3 mg/kg/d	483.45	2.0
Voriconazole	44.9	30.3	NA	NA	6 mg/kg every 12 h loading dose on day 1; maintenance dose of 4 mg/kg BID on days 2–7; 200 mg oral BID on day 8+	Day 1: 385.70 Post day 1: 231.42 Post day 7: 78.77	1.5 from day 1 to 7
Fluconazole†	100	18.0	NA	NA	400 mg QD	1.42	0 (oral agent)

DD = diagnostic-driven; C-AmB = conventional amphotericin B; NA = not applicable; QD = once daily; L-AmB = liposomal amphotericin B.
Sources include the British National Formulary[19] and Summaries of Product Characteristics.[14,20–22]
*Day ward nurse hourly wage was assumed to be £85.00.[25]
†Fluconazole was used only as a prophylactic treatment.

1-way and probabilistic sensitivity analyses were examined. Parameters analyzed in 1-way sensitivity analyses included the incidence of IFD, overall and IFD mortality, overall survival hazard ratio, GM-ELISA/PCR test sensitivity, unit costs and probability of AEs, percentage of patients receiving each antifungal agent, duration of antifungal therapy, percentage of patients using each resource, and number of resources used for each antifungal agent within each strategy. The effects of varying individual parameters were examined by using plausible ranges of values from the literature, 95% CIs, or by varying estimates by ±20%. Sensitivity results for each input were ranked from most sensitive to least sensitive and were plotted on a tornado diagram.

In addition to 1-way sensitivity analyses, probabilistic sensitivity analyses (second-order Monte Carlo simulation) were also performed. The parameters varied in these analyses and were similar to those in the 1-way sensitivity analyses. We assumed that parameter estimates followed a γ distribution for the following parameters: overall survival hazard ratio, unit costs, duration of antifungal therapy, and number of resources used for each antifungal agent within each strategy. A β distribution was assumed for the incidence of IFD, overall and IFD mortality, GM-ELISA/PCR test sensitivity, probability of AEs, and percentage of patients using each resource. A Dirichlet distribution was assumed for the percentage of patients receiving each antifungal agent within each strategy. Analyses were run 10,000 times to capture stability in the results for each relevant scenario. Scatter plots were developed to represent uncertainty, and cost-effectiveness acceptability curves were created.

RESULTS

Baseline Findings

The number of confirmed IFD in the DD strategy (74 of 1000 at-risk patients) was more than the number of confirmed IFD in the empirical strategy (33 of 1000 at-risk patients). However, the DD strategy was associated with a smaller number of patients who were given antifungal treatment compared with the empirical strategy (74 of 1000 vs 125 of 1000 at-risk patients, respectively). Survival among patients in the DD and empirical strategies were similar: 90.8% and 89.8% of patients, respectively.

Although patients treated according to a DD strategy versus an empirical strategy incurred greater

Table IV. Baseline results of costs and outcomes of diagnostic-driven (DD) and empirical strategies.

Model Outcome	DD Approach	Empirical Approach
Total costs, £ per patient	1561.29	2301.93
Antifungal treatment costs	799.21	1678.06
Antifungal agent AE costs	0.96	1.34
GM and PCR costs	27.46	0
Other medical costs*	733.66	622.53
No. of patients treated with antifungal drug therapy (per 1000 patients)	74	125
No. of diagnosed IFD (per 1000 patients)	74	33
No. of deaths (per 1000 patients)	92	102
Probability of survival, %	90.8	89.8

AE = adverse event; GM = galactomannan; PCR = polymerase chain reaction; IFD = invasive fungal disease.
*Higher "other" medical costs were incurred in the DD strategy due to the use of additional health care resources such as computed tomography scans, abdominal echography, bronchoscopy, and bronchoalveolar lavage.

costs due to the use of biomarkers (£27.46 vs £0, respectively), patients treated by using a DD strategy incurred lower overall costs (difference of £740.64) due to the effective use of antifungal agents. As a result, the DD-based treatment strategy was cost-saving (ie, costs were less, the strategy prevented more deaths). The baseline results are presented in Table IV.

Sensitivity Analysis

Figure 2 illustrates the sensitivity of the incremental cost per death avoided for the DD strategy versus the empirical strategy. Compared with the empirical strategy, the resulting incremental cost per death avoided was most sensitive to changes in GM-ELISA test sensitivity. Specifically, the DD strategy remained less costly and more effective in preventing death when GM-ELISA test sensitivity approached its lower limit. Results were somewhat sensitive to changes in the relative increase in the number of patients treated in the empirical versus DD strategy, incidence of IFD, and the duration of treatment with L-AmB in the empirical arm. However, despite changes in these parameters within their plausible ranges, the DD strategy was still cost-saving. Changes in all other parameters did not affect the results (ie, the DD strategy remained less costly while avoiding more deaths than the empirical strategy).

Figure 3 shows the resulting scatter plot of a DD strategy compared with an empirical strategy. In this analysis, assuming that the distribution of antifungal treatment in the different strategies does not change, the DD strategy was found to be less costly while preventing more deaths (ie, runs of the model with results falling within quadrant 4) 90.16% of the time. The incremental cost per death avoided was £30,000 or less (ie, runs of the model with results falling below the dotted diagonal line within quadrant 1 and quadrant 4) 99.24% of the time. Owing to the possible variability in the hazard ratios for overall survival for newer antifungal agents, many of the simulations fell within the second (0.14%) and third (5.91%) quadrants, where the DD strategy was either more costly and less effective in preventing death or less costly but did not prevent enough deaths to be worth the lower cost.

DISCUSSION

In this analysis, we compared the economic impact of using a DD strategy with an empirical strategy for the management of patients with persistent or recurrent neutropenic fevers at risk of IFD. To the best of our knowledge, this study is the first conducted to evaluate the economic impact of a DD strategy on the management of IFD, including suspected IA. According to the results of our analysis, we estimated that ~41% fewer

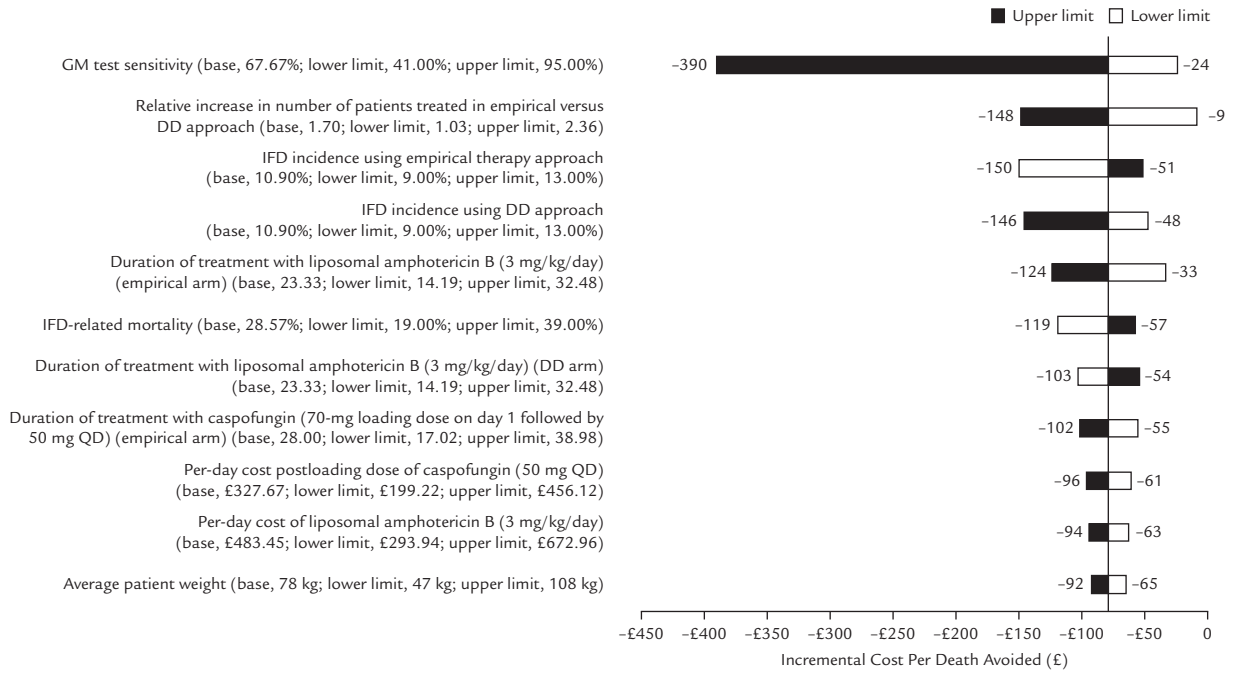

Figure 2. One-way sensitivity analysis: effect of parameter variation on the incremental cost per death avoided for a diagnostic-driven (DD) strategy versus an empirical strategy.
GM = galactomannan; IFD = invasive fungal disease; QD = once daily.

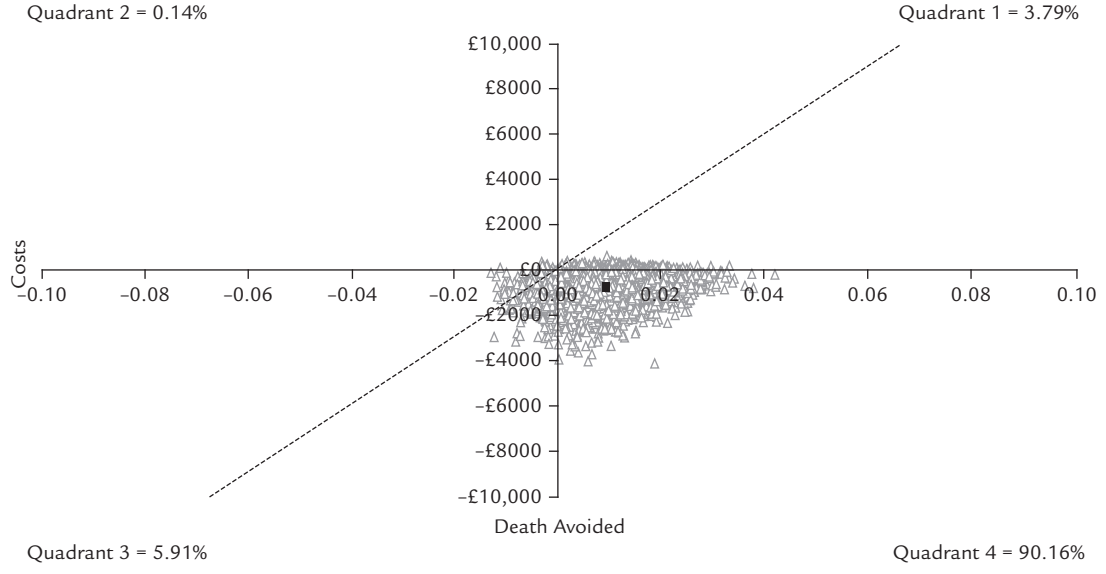

Figure 3. Results of probabilistic sensitivity analysis: incremental cost per death avoided scatter plot of a diagnostic-driven strategy versus an empirical strategy. The dotted diagonal line represents an incremental cost per death avoided of £30,000.

patients would be treated with antifungal agents in a DD strategy compared with an empirical strategy. As a result, we were able to avoid more AEs caused by antifungal treatment in already immunocompromised patients. In addition, survival was found to be similar for both the DD and empirical strategies and was consistent with survival rates reported in published clinical studies,[8,9,12] despite the fact that survival data were derived from a retrospective medical record extraction study.[13]

Overall, given the reduced use of antifungal agents, the total cost of the DD strategy was reportedly lower than that of the empirical strategy, despite the additional costs of GM-ELISA and/or *Aspergillus* species PCR testing. The costs of GM-ELISA and PCR testing were more than offset by lower antifungal treatment costs as a result of more targeted therapy. The findings of this analysis suggest that the DD strategy may be cost-saving for patients who are neutropenic and have persistent or recurrent unexplained fevers.

One key factor of this analysis will affect the overall savings that may be experienced by a given center; that is, the incidence of IFD that occurs within the center's population. This incidence varies not only between centers due to the environment but also depending on the case-mix of the patients within any given center. High-risk patients will have a greater risk of IFD than lower risk patients. The incidence assumed within this study was derived from a population of patients treated with myelosuppressive chemotherapy or autologous stem cell transplantation for hematologic malignancies in a German tertiary care center.[13] Other centers that treat a greater proportion of high-risk patients may derive even greater cost savings from a DD strategy.

Another limitation of this analysis is the exclusion of prophylaxis with the azole posaconazole. Prophylaxis with posaconazole could influence treatment options and cost savings for patients at high risk of IFD but was not considered in this model because the data to support the outcomes were not available.

An important limitation of this analysis is that patients who are at risk for fungal disease are a heterogeneous population. These patients have different underlying conditions that result in large variability in overall mortality rates. As a result, outcomes of the analyses may vary greatly between patient subpopulations. However, sensitivity analyses found that overall mortality was not a large driver of costs. This is in keeping with overall survival being relatively high, as was also seen in the clinical trials of the DD strategy.[8,9,11,12]

Another limitation of this analysis is that the incidence, survival, and efficacy data were not obtained from a single head-to-head clinical trial but were instead obtained from a retrospective cohort study of patients treated with myelosuppressive chemotherapy or autologous stem cell transplantation for hematologic malignancies in a German tertiary care center.[13] A number of clinical studies have assessed the outcomes of the DD and empirical strategies.[7–12] However, it is difficult to draw conclusions about the potential economic impact of the ideal application of these 2 strategies because heterogeneous treatment regimens and DD strategies were used in the clinical studies. In addition, in 1 study, a delay in the use of antifungal agents within the DD strategy occurred due to study inclusion criteria, and this delay may have affected mortality rates.[8] The timing of the implementation of a DD therapy strategy is important because it may determine how effective the strategy will be in providing early treatment compared with an empirical strategy.

A major limitation of the present study was the assumption that the use of a DD strategy would detect IFD, such that treatment for these diseases could occur just as early as empirical treatment. Because DD strategy studies were administered with the criterion that patients must be neutropenic for at least 4 to 5 days, it is unknown whether clinical outcomes for a DD strategy when IFD is identified earlier differ from those of a DD strategy when an IFD is identified later. Additional clinical studies will be important to fully understand the impact of this limitation and whether earlier treatment of IFD improves outcomes.

Overall, untreated IA is associated with high mortality rates.[27] As a result, use of a broad empirical strategy has historically been the standard treatment approach to attempt to alleviate physicians' concerns that some cases of IFD may be missed. Our analysis found that the DD strategy with targeted treatment may be considered a cost-saving alternative to the empirical strategy, while maintaining a similar overall survival rate. Future head-to-head studies collecting economic data will be important to confirm these analyses.

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Profs. Barnes, Herbrecht, Slavin, and Maertens, Drs. Morrissey, Bow, Charbonneau, Kantecki, and Schlamm, Mr. Weinstein contributed to the model design and data extraction and reviewed and approved the manuscript; and Dr. Earnshaw and Ms. McDade designed and developed the model and analysis, obtained data for the analysis, performed analysis, and drafted, reviewed, and approved the manuscript.

CONFLICTS OF INTEREST

Prof. Barnes has received research grants and speaker's fees and served on advisory boards for Astellas, Gilead Sciences, Merck Sharp & Dohme, and Pfizer Inc; Dr. Earnshaw and Ms. McDade are employees of RTI Health Solutions; Prof. Herbrecht has served as a consultant for Astellas, Basilea, Gilead Sciences, Merck Sharp & Dohme, Pfizer Inc, and Schering-Plough and has received research support from Pfizer Inc; Dr. Morrissey has received investigator-initiated grants from, has been a member of advisory boards, and has given lectures for Gilead Sciences, Merck Sharpe & Dohme, and Pfizer Inc; Prof. Slavin has received research grants and speaker's fees and served on advisory boards for Merck, Gilead Sciences, and Pfizer Inc; Dr. Bow has served as a consultant for Amgen, Astellas, Merck Frosst, Pfizer Inc, GLyPharma, and Teva and has received research support from Amgen and Pfizer Inc; Drs. Charbonneau and Kantecki are employees of Pfizer Inc; Mr. Weinstein and Dr. Schlamm were employees of Pfizer Inc during the development of the manuscript; and Prof. Maertens has served as a consultant for Amgen, Astellas, Basilea, Bio-Rad, F2G, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer Inc, and ViroPharma and has received speaker's fees from Astellas, Bio-Rad, Gilead Sciences, Merck, and Pfizer Inc.

SUPPLEMENTAL MATERIAL

Supplemental tables accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clinthera.2015.03.021.

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Address correspondence to: Rosemary Barnes, Department of Medical Microbiology and Infectious Diseases, Institute of Infection and Immunity, School of Medicine, Cardiff University, Health Park, Cardiff CF14 4XN, United Kingdom. E-mail: barnesra@cf.ac.uk

Supplemental Table I. Mortality rates.

Parameter	Model Estimate (%)
Overall mortality	10.7
Mortality with an IFD*	36.2
Mortality without an IFD*	7.6
Mortality if treated with amphotericin agent†	
Mortality with an IFD	40.4
Mortality without an IFD	7.6
Mortality if treated with novel antifungal agent†	
Mortality with an IFD	16.6
Mortality without an IFD	7.6

IFD = invasive fungal disease.

*Mortality with and without an IFD were estimated as overall mortality = incidence of IFD × (X + increased risk of IFD mortality) + percentage of patients without IFD × X, where X is the mortality of patients without IFD. This calculation became 10.7% = 10.9% (X + 28.6%) + (100.0% – 10.9%) × X; thus X = 7.6%. IFD-related mortality was calculated as 36.2% (7.6% + 28.6%).

†Mortality for patients treated with an amphotericin agent is estimated as mortality = percentage of patients on novel antifungal agents × (X × [1 – 0.589]) + percentage of patients on amphotericin-based agents × X, where X is the mortality of patients on amphotericin-based agents. Within Hahn-Ast et al,[13] 15 patients (10 patients on caspofungin and 5 patients on voriconazole) of 84 patients were on novel antifungal agents. Non–IFD-related mortality for patients on amphotericin-based agents and novel antifungal agents was assumed to be the same as the overall mortality without IFD. IFD-related mortality for patients on amphotericin-based agents was 36.2% = (15/84) (1 – 0.589) × X + ((84 – 15)/84) × X; thus X = 40.4%. IFD-related mortality for novel agents was calculated as 16.6% (40.4% × [1 – 0.589]).

Supplemental Table II. Adverse event–related resource use.*

Adverse Event	Resource Use
Hypertension	Treatment is assumed to include nurse monitoring, verapamil, antihypertensive therapy, and dialysis
Nephrotoxicity	Treatment is assumed to include NaCl infusion prophylaxis, daily electrolytes, abdominal ultrasound, and daily urine collection
Tachycardia	Treatment is assumed to include nurse monitoring and ECG

NaCl = sodium chloride.

*Resource uses for treating AEs were provided by clinicians via ECODE Model Resource Use Questionnaire.

Supplemental Table III. Adverse event (AE)-related costs.

AE	Unit Cost (£)	% Using	No. of Resources	Source/Assumptions
Hypertension	110.77			Cost of this AE was estimated by using the average number of resources identified (listed below) by the KOLs and weighted by the number of KOLs identifying each resource below
Hypertension: AE components				
Nursing monitoring	164.00	66.7	2.0	Per hour of patient contact We assumed 2 additional hours of monitoring time
Verapamil	1.73	33.3	1.0	British National Formulary[18]
Antihypertensive therapy	1.03	33.3	1.0	British National Formulary[18]
Dialysis 1%	1.56	33.3	1.0	Hospital hemodialysis or filtration, with access via hemodialysis catheter, for patients aged ≥19 years. This is the average of elective inpatient, elective inpatient excess bed days, nonelective inpatient (long stay), nonelective inpatient (long stay) excess bed days, and nonelective inpatient (short stay)
Nephrotoxicity	88.12			Cost of this AE was estimated by using the average number of resources identified (listed below) by the KOLs and weighted by the number of KOLs identifying each resource below
Nephrotoxicity: AE components				
NaCl infusion prophylaxis	85.40	33.3	1.0	NaCl infusion 1 l (1000 ml)
Daily electrolytes	89.56	33.3	1.0	Direct access: pathology services phlebotomy (electrolytes)
Abdominal ultrasound	51.27	33.3	1.0	Ultrasound scan <20 min
Daily urine collection	38.13	33.3	1.0	Daily urine collection
Tachycardia	165.34			Cost of this AE was estimated by using the average number of resources identified (listed below) by the KOLs and weighted by the number of KOLs identifying each resource below
Tachycardia: AE components				
Nurse monitoring	164.00	66.7	2.0	Per hour of patient contact. We assumed 2 additional hours of monitoring time
ECG	84.01	66.7	2.0	Diagnostic imaging outpatient

KOL = key opinion leader; NaCl = sodium chloride.
Sources: Department of Health[26] and the British National Formulary.[18]