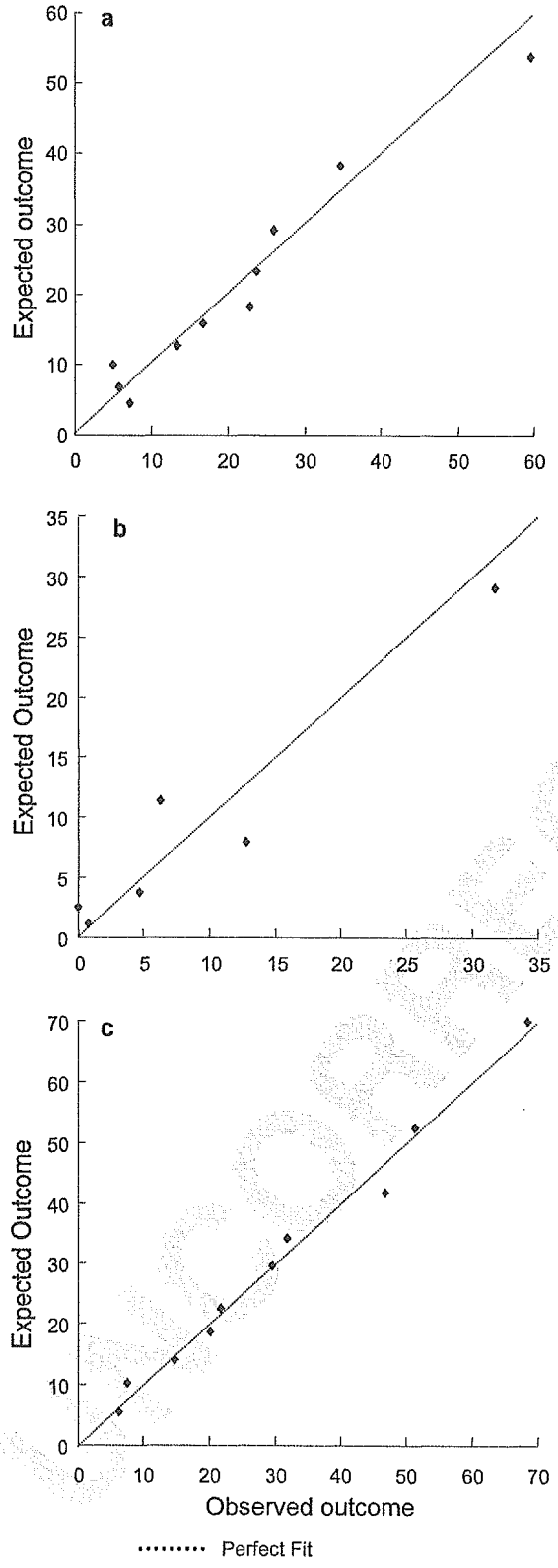

Validation

We conducted jackknife cross validation for the three prediction rules. The areas under the ROC curves for each validation of true bacteremia, blood culture positive for gram-negative rods, and in-hospital death were 0.72 ± 0.02, 0.64 ± 0.02, and 0.64 ± 0.02 respectively. These were not significantly different from those of the original cohort.

Discussion

We developed clinical prediction rules for true bacteremia, blood culture positive for gram-negative rods, and in-hospital death using the data at the time of blood withdrawal for culture. The true bacteremia prediction rule resulted in the categorization of the patients into five groups with risk probabilities ranging from 7 to 60%. Likewise, for the gram-negative rod prediction rule there were four groups with risk probabilities ranging from 1 to 32%, and for the in-hospital death prediction rule five groups with risk probabilities ranging from 7 to 56%.

Our prediction rules were based on the data of vital signs, medical conditions, and laboratory findings. Without medical computing systems, all predictors were usually available for patients undergoing blood cultures, and there were reports that showed the usefulness of some of these clinical data in predicting bacteremia (Bone 1987; Mellors *et al.* 1987; Bates *et al.* 1990; Leibovici *et al.* 1990; Jaimes *et al.* 2004). However, the purpose of these previous prediction rules was 'interpretation' of blood culture results to make clinical judgement whether the results were true or owing to contamination (Mellors *et al.* 1987; Bates *et al.* 1990, 1992, 1997; Leibovici *et al.* 1990), or predicting only for bacteremia (Jaimes *et al.* 2004). On the other hand, the purpose of our clinical prediction rules was 'prediction' for true

Figure 3 Observed vs. expected incidence of true bacteremia (a), gram-negative rods (b), and in-hospital death (c). Scatterplots allowing for visual assessment of the linearity of the increase in event rates across risk groups (a–c). The straight, diagonal broken lines represent perfect calibration and deviations from this line represent over-prediction or under-prediction of actual risk.

13

bacteremia, blood culture positive for gram-negative rods, and in-hospital death using the data at the time of blood withdrawal for culture. In terms of in-hospital death, we used all death irrespective of causes and timing of death because death owing to bacteremia was difficult to clearly distinguish from that owing to other causes in clinical situations.

To predict in-hospital death, several prediction rules were suggested. Acute Physiology and Chronic Health Evaluation II, Simplified Acute Physiology Score, and Mortality Probability Models II predicted for in-hospital death using age, vital signs, Glasgow coma scale, pulmonary artery pressure, urinary output, laboratory tests (blood gas, sodium, potassium, creatinine, urea, bilirubin, bicarbonate, prothrombin time, hematocrit, WBC), type of admission, and comorbidity such as infection, vasoactive drugs, cardiopulmonary resuscitation, mechanical ventilation, and nonelective surgery (Knaus *et al.* 1985; Le Gall *et al.* 1993; Lemeshow *et al.* 1993). On the other hand, our prediction rules could simultaneously estimate the likelihood of bacteremia as well as in-hospital death based on the similar predictors.

Our clinical prediction rules are thus expected to be used for clinical decision regarding the use of antibiotics and other management before the results of blood culture become available. For examples, if the likelihood of true bacteremia is very low, antibiotics can be withheld until the results become available. On the other hand, positivity of gram-negative rods is highly likely, antibiotics covering gram-negative rods can be started immediately after blood withdrawal for culture. By using the estimated mortality at the time of blood culture, a doctor can inform the patient and his family about the prognosis more rationally. Prediction rules such as these are also useful in educating doctors, residents, and medical students to make proper clinical decisions in an explicit way.

Although the process of assigning risk points, as shown in Table 4 and Fig. 1, may appear a bit cumbersome for busy doctors to use manually, current information technology will undoubtedly resolve such concerns (Bates & Gawande 2003). All the risk factors used for clinical prediction, such as patient characteristics, physical examination results, and laboratory results are easily incorporated with computerized systems. In fact, many hospitals already employ computerized doctor ordering entry, which can incorporate clinical decision rules based on clinical data in real time (Kaushal *et al.* 2003; Wrobel 2003). There was a report that by using a computerized decision support system, doctors changed 28% of their treatment decisions (Wang *et al.* 2000). Mullett *et al.* (2004) also reported that a computerized antimicrobial decision support programme based on past patient demographic data, and culture results had improved the rate of effectiveness of empiric antimicrobial therapy for bacteremia patients by 20%. Our study extended their findings to clinical prediction rules for true bacteremia, blood culture positive for gram-negative rods, and in-hospital death.

There are several limitations to our study. First, only one set of blood culture was done in half of the patients in our study. To minimize possible misclassification bias, we conducted scrupulous reviews of the cases by two doctor reviewers. Although the reviewers judged the results of blood culture independently and agreement between reviewers was used for definition of true bacteremia, the high proportion of S. aureus (17.2%) in the contamination could be due to the lack of two sets of blood culture for this organism. However, the contamination rate in our study (41%) was similar to that (47%) in a previous report (19), indicating that current data were acceptable. Second, the proportion of missing data were as high as 25% (LDH). However, it is common to have missing data in clinical setting, and the relationship between missing status and patient characteristics or outcomes were not statistically significant. Third, as shown in Fig. 3, the performance of the prediction rule for gram-negative rods was not as good as that for other two prediction rules. This is mainly due to small sample size, leaving some concern about reliability. Finally, we used here jackknife cross validation technique. Previous studies were prospective in design and utilized other patient cohort for validation (Bates *et al.* 1990, 1992, 1997). Prospective validation will be necessary for our prediction rules in the future.

In conclusion, we developed clinical prediction rules for true bacteremia, blood culture positive for gram-negative rods, and in-hospital death using the clinical data from medical computing system at the time of blood withdrawal for culture. These clinical prediction rules may well be useful in making rational clinical decisions before blood culture results

become available, and can be incorporated with computerized system after prospective validation.

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Cost-effectiveness analysis of antifungal treatment for patients on chemotherapy

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Cost-effectiveness analysis of antifungal treatment for patients on chemotherapy

Invasive fungal infections are fatal complications for patients on chemotherapy, and antifungal prophylactic treatment has been commonly recommended. Because its clinical and economic impact is not well known, we evaluated cost-effectiveness of anti-fungal treatment for patients who were neutropoenic as a result of chemotherapy. We constructed a hypothetical cohort of 40-year-old patients with acute myelogenic leukemia to evaluate years of life survived (YLS), costs (US$), and incremental cost-effectiveness ratio (US$/YLS). The following treatment strategies for fungal infections were compared: (1) prophylactic fluconazole strategy: oral fluconazole administration concurrently with chemotherapy; (2) empirical amphotericin B strategy: empirical intravenous amphotericin B administration at the point where fever is detected; and (3) no prophylaxis strategy: intravenous micafangin administration at the point where fungal infections is diagnosed. Baseline analyses showed that prophylactic fluconazole strategy involved higher costs but also longer YLSs (25 900 US$ and 24.08 YLS). The incremental cost-effectiveness ratio of prophylactic fluconazole strategy was 625 US$/YLS compared to no prophylaxis strategy, and 652 US$/YLS compared to empirical amphotericin B strategy. Baseline result was found to be robust through sensitivity analyses. Our study showed that concurrent administration of oral fluconazole during induction chemotherapy appears to ensure clinical benefits together with acceptable cost-effectiveness.

Keywords: antifungal prophylaxis; amphotericin B; cost-effectiveness analysis; fluconazole; fungal infection; chemotherapy.

INTRODUCTION

Invasive fungal infections are fatal conditions for neutropoenic patients so that early diagnosis and treatment are always critical and challenging. Because the clinical manifestations of such patients resemble bacterial infections which are more common febrile states, specific and rapid diagnosis modalities are not available. Physicians therefore continually face clinical dilemmas, such as 'Should we administer antifungal prophylaxis at the time of chemotherapy?', 'Should we administer antifungal agents as soon as fungal infections are suspected?', or 'Should we wait for the fungal test results and then start antifungal agents?

In daily practice, many patients are given antifungal agents prophylactically when chemotherapy is started or empirically when persistent fever is observed (Hughes *et al.* 2002). Given the high mortality rate of invasive fungal infections, prophylactic or empirical treatment seems safer compared with using any antifungal treatment after laboratory test results strongly suggestive of fungal infections. Several studies have compared the efficacy of treatment with empirical amphotericin B and administration

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of fluconazole prophylaxis (Bodey *et al.* 1994; Anaissie *et al.* 1996; Viscoli *et al.* 1996; Malik *et al.* 1998; Winston *et al.* 2000; Wolff *et al.* 2000), and have come out in favour of fluconazole in terms of reduced adverse effects, incidence of fungal infections, and mortality from fungal infections.

However, the clinical benefits and economic impact of fluconazole prophylaxis have not yet been fully clarified. To explore these issues, we conducted cost-effectiveness analyses for a comparison of efficacy and costs among three strategies, oral fluconazole prophylaxis, empirical amphotericin B administration and absence of antifungal prophylaxis.

METHODS

Target population and treatment strategies

The target population consisted of 40 years-old patients who were diagnosed as acute myeloid leukaemia defined as French-American-British types M0 to M7 (Cheson *et al.* 1990). Induction therapy consisted of enocitabine, BH-AC (200 mg/m^2 by means of 3-h infusion) for 10 days, mercaptopurine, 6-MP (70 mg/m^2 orally) with 300 mg/day of allopurinol for 10 days and daunorubicin hydrochloride, DMDNR (40 mg/m^2 intravenously) from days 1–4 (Miyawaki *et al.* 1999). According to the literature concerning this chemotherapy regimen, the white blood count (WBC) nadir was reported to be $395.6 \pm 262.3/mm^3$ and the period of WBC $\leq 1000/mm^3$ 17.2 ± 9.2 days (Miyawaki *et al.* 1999).

We compared three antifungal treatment strategies for the patients in terms of different timing and agents of antifungal treatment. The first is the prophylactic fluconazole strategy, in which the patient receives 400 mg of fluconazole daily orally concurrently with the start of chemotherapy. The second is the empirical amphotericin B strategy, in which the patient is given intravenous amphotericin B when persistent fever of 38 degree centigrade or higher is observed for 48 h or more upon administration of an appropriate broad-spectrum antibiotic therapy and in the absence of any obvious source of fever, such as resistant bacterial infection abscess or infection with atypical micro-organisms (EORTC International Antimicrobial Therapy Cooperative Group 1989; Walsh *et al.* 1991). The third is the no-prophylaxis strategy, in which a patient is administered micafangin (MCFG) intravenously when fungal culture results strongly suggest fungal infections without any preceding administration of antifungal agents (Fromtling 2002). The time frame was set at the period between the start of induction chemotherapy for acute myeloid leukaemia (AML) and the time of complete remission or death.

Parameter estimates

We searched the MEDLINE database between January 1966 and September 2003 for English-language reports with the key words 'fungal infection', 'haematological malignancy', 'fluconazole', 'Amphotericin B', 'antifungal', 'neutropenia', 'immunocompromized', and 'leukaemia'. The retrieved articles were limited to clinical trials as indicated by publication type. We also reviewed bibliographies of retrieved articles and the 'UpToDate' electronic textbook for additional studies (UpToDate 2004). We excluded studies if (1) the patients underwent bone marrow transplantation; (2) the amount administered of an agent investigated was not comparable to that of the agent investigated in our study (e.g. 50 mg of fluconazole); (3) the clinical outcomes were not recorded accurately; and (4) the patients were not in between 35 and 45 years old.

The clinical outcomes for the antifungal agents examined were rated in terms of probability of fungal infections, adverse effects, mortality, life expectancy (LE) and costs (Table 1). All clinical outcomes were expressed as weighted means for the baseline values (Morimoto *et al.* 2002). The fungal infections were defined as either invasive fungal or systemic fungal infections which required the presence of fungus in the blood, pulmonary tissues or secretions, sinuses, soft tissues, or other organs in association with symptoms and signs of fungal infections that can not be explained by other pathogens (Ascioglu *et al.* 2002). Adverse effects included any symptoms attributable to antifungal medications such as gastrointestinal symptoms, skin eruption, renal dysfunction, toxicity and electrolyte imbalance. Adverse events were considered when patients were withdrawn from the study because of the above-mentioned symptoms.

Disease-free survival was defined as the time from the first complete remission to the date of relapse or death from any cause. Relapse was defined as a recurrence of AML after the first complete remission. The LE with AML was calculated from the disease-specific survival data by using the declining exponential approximation of life expectancy method (Beck *et al.* 1982). Background mortality for the model was based on the data of general population mortality for 2002 published by the Ministry of Health, Labour, and Welfare of Japan, and adjusted for age and sex. The probability ranges for the sensitivity analyses were determined on the basis of the variances reported in the literature or of expert opinions when such variances were not reported in the literature.

Table 1. Model parameters: base-case values and ranges used in sensitivity analyses

Probability variable	Baseline value	Range for sensitivity analyses		Data sources
		Lower	Upper	
(a) Clinical outcomes				
Prophylactic fluconazole strategy				
Probability of fungal infection	0.076	0.023	0.089	Schaffner and Schaffner (1995)
Probability of adverse effect	0.019	0.023	0.032	Winston *et al.* (1993)
Death from fungal infection	0.238	0.091	1.000	Chandrasekar and Gatny (1994)
				Egger *et al.* (1995)
Empiric amphotericin B strategy				
Probability of adverse effect	0.147	0.000	0.667	Stein *et al.* (1982)
Death from fungal infection	0.269	0.000	0.300	Walsh *et al.* (1999)
				Walsh *et al.* (1991)
				EORTC International Antimicrobial Therapy Cooperative Group (1989)
				Malik *et al.* (1998)
				Anaissie *et al.* (1996)
				Bodey *et al.* (1994)
				Viscoli *et al.* (1996)
				Wolff *et al.* (2000)
No prophylaxis strategy				
Probability of fungal infection	0.157	0.028	0.205	Schaffner and Schaffner (1995)
Death from fungal infection	0.285	0.148	1.000	Winston *et al.* (1993)
				Chandrasekar and Gatny (1994)
				Slavin *et al.* (1995)
				Rotstein *et al.* (1999)
Micafungin sodium (MCFG)				
Death from fungal infection	0.238	0.000	1.000	Assumption
Complete remission	0.606	0.358	0.700	Zittoun *et al.* (1995)
Death	0.059	0.052	0.071	Cassileth *et al.* (1998)
(b) Life Expectancies (years)				
Life Expectancy with AML	3.4	2.9	3.8	Miyawaki *et al.* (1999)
Life expectancy without AML	39	33	43	
(c) Costs (US$*)				
Hospitalization	5 093	3 644	5 914	Hospital Sources
Medical procedures (including chemotherapy)	7 542	5 394	10 600	
Laboratory services	1 404	749	1 729	
Medication (excluding antifungals)	1 053	283	3 536	
Nutrition	733	518	972	
Transfusions	8 608	1 338	16 211	
Total of fixed cost	24 433	11 924	38 962	
Antifungal drugs				
Oral fluconazole	884	737	1 202	
Empiric amphotericin B	112	94	140	
No prophylaxis	0	0	0	
MCFG	870	444	1 295	
Cost associated with death from any cause	6 596	2 195	16 119	

*US$ indicates dollar in the US (1US$ = 120Yen, March 2003); Baseline value and range for sensitivity analyses are based on weighted average.
AML, acute myeloid leukaemia.

Because MCFG was only recently introduced and its efficacy has not been well clearly established, we made a few assumptions related to its clinical outcomes. Based on the fairly good performance of MCFG as suggested in one report (Fromtling 2002), we assumed that no adverse effect would occur and mortality from the fungal infections would be equivalent to that observed as a result of oral fluconazole prophylaxis. Because of this relative uncertainty, the range for sensitivity analyses was set between 0 and 1.

Costs

Costs were retrieved from the hospital claims of 30 inpatients at a teaching hospital in Japan. Future costs and benefits were not discounted because of the short time

frame of our model. Costs for hospitalization, medical procedures, laboratory, medications other than antifungal agents, nutrition, transfusions, and antifungal agents were examined. We retrieved the costs associated with death based on those of deceased patients and calculated the weighted average of all the costs paid during the final week before death. Because the reimbursement rate is universally regulated by the government in Japan, we used the current charges to estimate the cost of drugs and supplies. Costs of antifungal agents were estimated by multiplying the daily costs by duration of therapy as reported in the literature (Walsh *et al.* 1991; Winston *et al.* 1993; Chandrasekar & Gatny 1994; Egger *et al.* 1995; Schaffner & Schaffner 1995; Slavin *et al.* 1995; Malik *et al.* 1998; Rotstein *et al.* 1999; Walsh *et al.* 1999). The fixed costs were calculated by summation of hospitalization, medical procedures (including chemotherapy), laboratory services, medication (excluding antifungals), nutrition, and transfusions; and we confirmed that these costs were comparable with those reported in cost studies for AML conducted in western countries (Uyl-de Groot *et al.* 1998; Berman *et al.* 2002). The fixed costs did not take into account the duration associated with treatment course.

Baseline analysis and sensitivity analyses

To evaluate cost-effectiveness, we separately assessed the years of life saved (YLS) and costs associated with different antifungal strategies in AML patients on chemotherapy (Sox *et al.* 1988). The incremental cost-effectiveness (CE) ratio (US$/YLS) of the first effective strategy with the longest LE to that of the second was calculated by dividing additional cost (US$) by additional benefit (YLS). Sensitivity analyses were performed to evaluate the potential effects of the ranges of parameter estimates on the results. The DATA software program, version 4.0 (TreeAge Software, Inc, Williamstown, MA) was used for all analyses.

RESULTS

Parameter estimates

The clinical probabilities were obtained from randomized controlled trial reports (Meunier *et al.* 1991; Rozenberg-Arska *et al.* 1991; Winston *et al.* 1993; Chandrasekar & Gatny 1994; Menichetti *et al.* 1994; Egger *et al.* 1995; Schaffner & Schaffner 1995; Slavin *et al.* 1995; Rotstein *et al.* 1999) with regards to age and AML as an underlying disease. These probabilities were then used for 'prophylactic fluconazole strategy' and 'no prophylaxis strategy'. On the other hand, for empirical amphotericin B strategy, both reports of nonrandomized clinical trials and reviews were used (Stein *et al.* 1982; EORTC International Antimicrobial Therapy Cooperative Group 1989; Walsh *et al.* 1991; Bodey *et al.* 1994; Anaissie *et al.* 1996; Viscoli *et al.* 1996; Malik *et al.* 1998; Walsh *et al.* 1999; Winston *et al.* 2000; Wolff *et al.* 2000) because no literature on randomized clinical trials was available. The probability estimates and LE of complete remission from induction therapy, recurrence of disease, and death were retrieved from chemotherapy literature (Zittoun *et al.* 1995; Cassileth *et al.* 1998; Miyawaki *et al.* 1999). (Table 1)

On average, the probability of fungal infections was relatively small at 0.076 when oral fluconazole was administered prophylactically, but it increased to 0.157 if antifungal prophylaxis was not given. The probability of adverse effect associated with intravenous amphotericin B was more likely to occur compared to oral fluconazole. Mortality was almost comparable among three strategies once fungal infections occur (0.238 for oral fluconazole prophylaxis, 0.269 for empirical amphotericin B administration, and 0.285 for no prophylaxis or empirical antifungal administration).

Baseline analysis

Based on the baseline estimates of parameters, prophylactic fluconazole strategy appeared to be the best strategy in terms of effectiveness (24.08 YLS) compared to empiricl amphotericin B strategy (23.16 YLS) and no prophylaxis strategy (23.12 YLS). However, in terms of costs, prophylactic fluconazole strategy was more expensive ($25 900) than the other two strategies ($25 400). Thus, incremental cost-effectiveness ratio of prophylactic fluconazole strategy was 625 US$/YLS when compared to no prophylaxis strategy, and 652 US$/YLS in comparison with empirical amphotericin B strategy. (Table 2)

Sensitivity analyses

Influential parameters that changed indications for the optimal strategy toward empirical amphotericin B strategy were the probability of fungal infections in the no prophylaxis strategy and mortality from fungal infections in the case of prophylactic fluconazole strategy. If the incidence of fungal infections in the absence of prophylaxis decreased, the incremental CE ratio of the prophylactic fluconazole strategy increased up to 141 940 US$/YLS and this strategy was finally dominated by the empirical amphotericin B strategy when the probability became less than 0.028 ($24 921 vs. 24.58 YLS). When mortality from fungal infections with the prophylactic fluconazole strategy increased, the incremental cost-effectiveness ratio

Table 2. Cost-effectiveness of three strategies of antifungal treatment in a AML patient

Strategy	Cost per patient, US$	Incremental costs, US$	Mean life expectancy, years	Incremental effectiveness, YLS	Incremental cost-effectiveness ratio
No prophylaxis	25 400		23.12		
Empiric amphotericin B	25 400	0	23.16	0.04	
Prophylactic fluconazole	25 900	600	24.08	0.92	652

The difference in cost divided by the difference in life expectancy for each strategy compared with the next best strategy.
YLS, Years of Life Survived; AML, acute myeloid leukaemia.

Table 3. Sensitivity analyses

		Sensitivity analysis				
Variable	Base-case values	Sensitivity analysis values	Strategy with the longest life expectancy (US$ and years)	Strategy with the second longest life expectancy	The effectiveness of fluconazole strategy (years)	Incremental Cost-Effectiveness Ratio of fluconazole, $/YLS
Probability of fungal infection						
No prophylaxis	0.157					
		0.028	Amphotericin B ($24 921 and 24.58 years)	No prophylaxis	24.11	Dominated by amphotericin B
		0.205	Fluconazole ($25 539 and 22.62 years)	Amphotericin B	–	283
Death from fungal infection						
Prophylactic fluconazole	0.238					
		0.091	Fluconazole ($25 902 and 24.29 years)	Amphotericin B	–	468
		1.000	Amphotericin B ($25 371 and 23.15 years)	No prophylaxis	23.00	Dominated by amphotericin B

YLS, Years of Life Survived.

also increased and the strategy was finally dominated by the empirical amphotericin B strategy when the mortality was 100% ($25 371 vs. 23.15 YLS). (Table 3)

DISCUSSION

Based on currently available data, our analyses indicate that oral fluconazole prophylaxis could be the antifungal treatment strategy of choice compared to empirical amphotericin B or no prophylaxis for patients undergoing chemotherapy. Patients treated with oral fluconazole prophylaxis can be expected to achieve 0.9-year longer LE with an acceptable increase of treatment costs of US$600.

A meta-analysis reviewing 24 trials with 2758 randomized patients reported that no survival benefit was gained from antifungal prophylaxes, and that oral fluconazole prophylaxis or empirical amphotericin B therapy had no effect on mortality of cancer patients who manifested neutropoenia (Gotzsche & Johansen 1997). On the other hand, our study demonstrated that both prophylactic fluconazole strategy and empirical amphotericin B strategy provided longer YLS than no prophylactic strategy. This difference is mainly due to the assumption that in the case of the no prophylaxis strategy antifungal agents would not be administered until fungal culture was found to be positive, and that the resultant delay of antifungal treatment resulted in higher mortality. However, the control group in meta-analysis might receive some antifungal agent. The longer YLS with acceptable incremental costs which can be expected with the prophylactic oral fluconazole strategy indicates that it should be considered for AML patients who undergo chemotherapy as well as for other patients who are at high risk of prolonged neutropoenia and subsequent fungal infections.

Empirical administration of amphotericin B has been used as a standard antifungal therapy for persistently febrile neutrocytopenic patients (UpToDate 2004; Pizzo *et al.* 1982; EORTC International Antimicrobial Therapy Cooperative Group 1989). Studies have suggested that up to one-third of febrile neutropoenic patients who did not respond to a 1-week course of antibiotic therapy had systemic fungal infections that, in most cases, are caused by Candida or Aspergillus species (Pizzo *et al.* 1982; EORTC International Antimicrobial Therapy Cooperative Group 1989). Although the information on the diversity of fungal pathogens was not incorporated in the present study, sensitivity analyses have showed that indicators for the best strategy could be changed toward empirical amphotericin B strategy when mortality from fungal infections with oral fluconazole prophylaxis is assumed to be high. Hence, at institutions at which mould infections such as Aspergillus species and drug-resistant Candida species are fre-

quently encountered, empirical amphotericin B strategy would be preferable. Sensitivity analyses have also suggested that the prophylactic fluconazole strategy could be dominated by the empirical amphotericin B strategy when the incidence of fungal infections without prophylaxis is assumed to be at its lowest. Because the cost of amphotericin B is lower than that of fluconazole, empirical amphotericin B strategy could be a cost-effective strategy in settings where fungal infections are less likely to occur.

Our results must be interpreted within the limitations inherent to cost-effectiveness analyses using the hypothetical cohort model. First, the probability of invasive infections may have been underestimated in our study because fungal infections are difficult to diagnose and, the treatments frequently precede the diagnosis in the actual clinical settings associated with the published studies. To assess the magnitude of such influence, sensitivity analyses were carefully conducted and showed that oral fluconazole prophylaxis was consistently the best strategy irrespective of the incidence of fungal infections and with an acceptable incremental range between US$ 403 and US$ 615. The exception was the case where the probability of fungal infections was rare even though no antifungal prophylaxis was provided.

Second, we assumed that fungal infections could be effectively controlled by MCFG without further treatments. Evidence to date suggests good tolerability of MCFG but the efficacy of this relatively new drug has not yet been established (Fromtling 2002). Thus, this assumption may change in real settings. However, sensitivity analysis also showed that no matter in which direction (i.e. up or down) the mortality of patients with fungal infections treated with MCFG administration changed, prophylactic fluconazole strategy proved to be consistently the best strategy with acceptable cost-effectiveness ratio.

Third, our cost data were obtained at Japanese clinical settings. Although our data were comparable with those of cost studies for AML conducted in western countries (Uyl-de Groot *et al.* 1998; Berman *et al.* 2002), our results may not be applicable to other countries because the medical insurance system is not comparable. Nevertheless, a study investigating cost-effectiveness of antifungals in acquired immune deficiency syndromes (AIDS) patients reported that, when the CD4 count became less than 200/mm^3, the costs of fluconazole prophylaxis against AIDS-related primary systemic fungal infections increased to $40 500 and life expectancy to 28.42 months, resulting in a ratio of $240 000 per YLS (Scharfstein *et al.* 1997). Our results, on the other hand, showed that incremental ratios for the prophylactic fluconazole strategy were 625 US$/YLS, which makes it highly cost-effective.

Fourth, our study was conducted in a relatively short time and can thus not be evaluated in the long run. However, fungal infections for neutropoenic patients represent a critical condition so that short-term prognosis and cost should be emphasized.

In conclusion, because invasive fungal infections cannot be diagnosed rapidly with currently available diagnostic modalities and thus result in high mortality without prompt treatment for patients on chemotherapy, the use of oral fluconazole as prophylaxis could well be a useful and cost-effective intervention.

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Experience with Oseltamivir for Infants Younger Than 1 Year Old in Japan

To the Editors:

Influenza is a self-limiting disease, but it rarely causes acute encephalopathy with a reported mortality of 31.8%.[1,2] Among patients with influenza-associated encephalopathy, 81.8% were younger than 5 years old, with the peak incidence among 1-year-olds.[2] Roche Laboratory, Inc. issued an alert in 2003 that oseltamivir should not be used in infants younger than 1 year old, because an animal study showed that mortality occurred in oseltamivir-treated infant rats in which the concentration of oseltamivir in the brain was 1500 times higher than that of adults rats.[3]

Because of the high incidence of encephalopathy in Japan, Japanese physicians have frequently prescribed oseltamivir for children,[4] and the Japanese share of worldwide oseltamivir use was 50.3% in 2002. We retrospectively collected data of 103 consecutive infants younger than 1 year old treated with oseltamivir for influenza at 2 general hospitals in Japan between November 2002 and March 2003 (Table 1). Follow-up chart review and telephone interviews were conducted to determine mortality and encephalopathy, defined as altered mental status within 1 week of the appearance of influenza-like symptoms without evidence of meningitis, myelitis or febrile convulsion, because encephalopathy develops within 1 week after febrile events.[1] In infants whose health status after 1 week was not known by chart review or telephone interview, we sent follow-up letters asking about their status. Hospital review committees approved the protocol of this study, and informed consent was waived. Three (2.9%) infants received influenza vaccination during the study season. Although the follow-up data for an 11-month-old boy were not obtained, none of the remaining 102 infants died or developed encephalopathy.

TABLE 1. Infants Younger Than 1 Year Old Who Received Oseltamivir

Variables	N or Mean	% or 95% Confidence Intervals
Male	54	53
Age (mo)	7.5	6.9–8.0
Weight (kg)	8.1	7.8–8.4
Ambulatory	102	99
Hospitalization	1	1
Temperature (°C)	38.9	38.7–39.0
Oseltamivir		
Duration (days)	3.9	3.7–4.2
Dose (mg/kg)	4.0	3.9–4.2
Antibiotics		
Used	22	21.4
Not used	81	78.6

In Japan, the annual incidence of influenza-like illness for 2000 was reported as 26,250 per 100,000 children 0–4 years of age,[4] with the mortality from influenza-associated encephalopathy 0.271 per 100,000 children.[5] Based on these figures, the mortality from influenza-associated encephalopathy is assumed to be 0.00001 in the infected children 0–4 years of age. If the infant whose follow-up data were not available had died or developed encephalopathy, the mortality would be 0.0097 (95% confidence interval, 0.0017–0.053). However, because the hospitals in our study have active emergency rooms in the respective communities, we believe this case is very unlikely.

After the alert by Roche Laboratories, Inc., the use of oseltamivir in infants younger than 1 year old came to be considered contraindicated. Because there has been no human evidence of fatality risk for infants younger than 1 year old and such infants are more susceptible to influenza-associated encephalopathy than older children,[2] the Japan Pediatric Association asked the Ministry of Health, Labor and Welfare of Japan on February 2, 2004 whether the Ministry would allow the use of oseltamivir in infants younger than 1 year old. The Ministry replied that oseltamivir could be used in such infants with detailed informed consent. However, practicing pediatricians were still confused about its use because of the lack of clinical data, and our findings provide preliminary evidence in support of the use of oseltamivir.

There are several limitations to this study: (1) our study was retrospectively conducted, but no prospective studies could be conducted after the alert because of ethical concerns; (2) our study sample was not large enough to reach definite conclusions. However, it takes a long time to collect data large enough to definitively assess such rare events; (3) some infants might not have influenza, because no formal diagnostic criteria were used. However, oseltamivir is frequently prescribed based on the physician's judgment, so that our data are likely to reflect actual practice.

In conclusion, no association was found between oseltamivir and mortality or encephalopathy in infants younger than 1 year old.

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Increased CD36 Expression in Vertically Human Immunodeficiency Virus-Infected Children Unrelated to Antiretroviral Therapy

To the Editors:

CD36 is a multifunctional transmembrane glycoprotein with a wide tissue distribution. In adipose tissue and skeletal muscle, CD36 is essential for long chain fatty acid recognition and transport, and its genetic deficiency can result in insulin resistance and dyslipidemia.[1] On macrophages, the major role of CD36 is the specific uptake of oxidized low density lipoproteins that leads to foam cell formation and the genesis of atherosclerotic lesions.[2]

An early and marked down-regulation of CD36 on monocytes, induced by protease inhibitors (PI), has been suggested to represent a possible cause for insulin resistance and dyslipidemia occurring in human immunodeficiency virus (HIV)-infected patients.[3] In contrast, a recent study described a PI-driven up-regulation of CD36 leading to accumulation of sterols in macrophages, suggesting a potential proatherogenic effect of PI.[4]

The pediatric population represents an unique opportunity to study the effects of HIV infection and antiretroviral therapy on the emergence of cardiovascular disease, in the absence of confounding behavioral factors.

The aim of our study was to define CD36 expression on circulating monocytes from vertically HIV-1-infected children and age-matched healthy controls.

CD36 antigen expression was measured by means of flow cytometry in 47 consecutively enrolled HIV-infected children (4–18 years of age) and in 38 age-matched healthy controls (mean age, 10 years; range, 2–17; 13 boys and 25 girls). The level of expression of CD36 on monocytes ($CD14^+$) was measured as mean fluorescence intensity channel (MFI) of the $CD36^+$ peak on a logarithmic scale.

Overall CD36 expression was higher in HIV-infected children (MFI 4.1 ± 0.9) than in controls (MFI 3.7 ± 0.7) ($P < 0.05$). Of the 47 HIV-infected patients: 10 were naive to antiretroviral therapy; 24 patients were receiving a PI-based regimen; 13 were receiving a nonnucleosidic reverse transcriptase inhibitor-based regimen. No difference in CD36 expression was observed between patients assuming antiretroviral therapy (independently from the different regimen) and naive patients. On multivariate analysis, no significant correlations were observed between CD36 MFI and age, gender, weight, HIV RNA, CD4 absolute count, CD4%, CD4:CD8 ratio, triglycerides, cholesterol and glucose (Table 1).

Thus in this pediatric population, the only variable significantly associated with increased expression of CD36 was HIV infection itself. The difference between HIV-infected children and controls, although statistically significant, is slight, but these data confirm the trend observed in an adult population where CD36 overexpression in HIV-positive patients was more evident.[5]

The biologic consequence of CD36 increased expression cannot be easily inferred; nevertheless as autopsy findings of coronary disease were described in young HIV-infected patients even before the advent of highly active antiretroviral treatment,[6] evidences exist of a potential deleterious effect of HIV itself on vascular function, and the assumption of a possible role of CD36 up-regulation, in the genesis of atherosclerosis, should be taken into account.

In agreement with data obtained from an adult population, we did not observe any change in CD36 expression caused by antiretroviral therapy.

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TABLE 1. Features of HIV-Infected Children Stratified According to Antiretroviral Regimens

	Untreated (10)	PI (24)	NNRTI (13)
CD36 MFI	4 ± 0.9*	4 ± 1.1	4.4 ± 0.9
Age (yr)	12 ± 5	12 ± 4	13 ± 4
Gender (M/F)	4/6	7/17	3/10
Weight (kg)	38 ± 19	37 ± 16	47 ± 17
Glucose (mg/dL)	79 ± 9	79 ± 6	84 ± 13
Triglycerides (mg/dL)	70 ± 28	116 ± 86	101 ± 51
Cholesterol (mg/dL)	138 ± 25	174 ± 27	158 ± 35
LDL cholesterol (mg/dL)	80 ± 16	100 ± 29	82 ± 22
$CD4^+$ cells/mm^3	653 ± 235	722 ± 394	1008 ± 317
$CD4^+$ (%)	29 ± 11	30 ± 12	37 ± 7
CD4:CD8	0.8 ± 0.4	0.9 ± 0.5	1.2 ± 0.3
HIV RNA log copies/mL	4.3 ± 4.3	3.9 ± 0.5	1.7 ± 0.7

*Mean ± SD.

Untreated, naive for antiretroviral therapy; PI, patients receiving 1 or 2 PIs plus 2 nucleosidic reverse transcriptase inhibitors (NRTI); NNRTI, patients receiving 1 nonnucleosidic reverse transcriptase inhibitor plus 2 NRTI; LDL, low density lipoprotein.

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