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Galactomannan-guided preemptive vs. empirical antifungals in the persistently febrile neutropenic patient: a prospective randomized study☆

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SUMMARY

Background: Patients with neutropenic fever after 4–7 days of broad-spectrum antibiotics are given antifungals empirically. This strategy may lead to over-treatment.
Methods: Patients with hematological malignancies undergoing intensive chemotherapy or hematopoietic stem cell transplantation were randomized to two arms. Patients in the 'preemptive' arm had regular galactomannan (GM) assays, and received caspofungin, amphotericin or voriconazole (CAV) for persistent febrile neutropenia if they had two positive GM results, or a positive GM result and a computed tomography (CT) of the thorax suggestive of invasive pulmonary aspergillosis (IPA). Patients in the 'empirical' arm received CAV in accordance with established guidelines.
Results: Of 27 episodes in the preemptive arm, two cases of IPA were picked up by monitoring. In six episodes, CAV was started despite persistently negative GM readings. One additional patient received CAV for a false-positive GM. Of 25 episodes in the empirical arm, CAV was started empirically in 10, one of whom had CT features of IPA. By intent-to-treat and evaluable-episode analyses, respectively, the preemptive approach saved 11% and 14% of patients from empirical antifungals. Twelve-week survival was 85.2% in the preemptive arm and 84% in the empirical arm.
Conclusions: A preemptive approach may reduce empirical antifungal use without compromising survival in persistently febrile neutropenic patients.

1. Introduction

Invasive mold infections (IMIs) cause morbidity and mortality in patients rendered neutropenic by chemotherapy.[1] The risk of an IMI rises with the depth and duration of neutropenia.[2] Diagnosing an IMI is difficult, so the use of empirical antifungals for persistent fever in neutropenia has become the standard of care.[2,3] This is supported by two pivotal studies demonstrating the benefits of empirical amphotericin deoxycholate (AmB) in neutropenic patients who remain febrile after several days of broad-spectrum antibiotics.[4,5] These two studies form the basis of current international recommendations on the management of febrile neutropenia.[3]

Despite their lasting influence on practice, the two pivotal studies, however, were "underpowered, used antifungal prophylaxis of dubious value, and did not prove their primary hypothesis",[6] views echoed by other authorities.[7] The empirical use of antifungals may lead to over-treatment.[8–10] Doubt has been cast on the efficacy of empirical antifungals in febrile neutropenia, enough to "justify the demand" for an alternative approach using new laboratory techniques.[10]

A new strategy, variously named 'preemptive' and 'presumptive' antifungal therapy, has emerged as an alternative to empirical antifungals in the management of persistent fever in neutropenia. In this strategy, antifungals are initiated only upon identification of a laboratory marker of fungal infection, perhaps in combination with radiological signs. This strategy is modeled on the popular preemptive strategy against cytomegalovirus infection in solid-organ and hematopoietic stem cell transplantation (HSCT).[11] Such a strategy is dependent on improved diagnostics, a situation now upon us with the advent of the galactomannan (GM) and beta-D-glucan (BDG) assays.[12,13] This situation is akin to the development

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of the cytomegalovirus (CMV) pp65 antigenemia and CMV PCR assays in the 1990s.

We have also not been completely satisfied with our prophylactic regimen, as we still see a rather high rate of breakthrough IMI (unpublished observations), and a high rate of use of the broad-spectrum antifungal agents. With these in mind, we hypothesized that serial screening of GM in patients with hematological malignancies at risk of invasive aspergillosis (IA) and receiving effective anti-candidal prophylaxis, would obviate the need for empirical broad-spectrum antifungal therapy.

2. Design and methods

2.1. Objectives

The primary aim of the study was to determine if serial GM monitoring, on a background of effective anti-candidal prophylaxis, obviated the need for empirical broad-spectrum antifungal treatment in high-risk patients with hematological diseases and HSCT recipients. The primary end-point was the use of a broad-spectrum antifungal agent, either caspofungin (CAS), amphotericin B (AmB), liposomal amphotericin (LAmB) or voriconazole (VCZ).

2.2. Study population and design

This prospective, randomized, non-blinded study was undertaken from 14 June 2006 to 15 October 2007 in the Department of Haematology, Singapore General Hospital, a 1600-bed tertiary institution. Patients could be included if they met any of the inclusion criteria and had none of the exclusion criteria (Table 1). All patients undergoing intensive chemotherapy received oral ciprofloxacin 500 mg twice daily. All patients also received oral itraconazole (ITC) (syrup formulation 200 mg three times a day for a week, followed by capsule formulation 200 mg twice daily until the absolute neutrophil count (ANC) rose above 0.5×10^9 cells/l).

While in hospital, patients were examined daily. Fever led to a repeat physical examination, as well as a chest radiograph (CXR), and multiple sets of blood cultures. Sputum cultures, urine cultures, and a stool test for *Clostridium difficile* cytotoxin could be ordered at the physician's discretion. Broad-spectrum antibiotics were started in accordance with international and departmental guidelines.[3,14]

Patients fulfilling the inclusion criteria and giving informed consent were randomized by block randomization of 4.The randomization list was generated by the statistician. The study coordinator enrolled the patients according to this list. Those randomized to the preemptive arm underwent serial GM monitoring twice a week. The study coordinator informed the primary hematology team of the patient's inclusion in the study and the arm into which the patient was randomized, and documented this in the case records. A positive GM index (GMI), available the next day, triggered an immediate repeat, as well as an urgent computed tomography (CT) scan of the thorax. A second consecutive positive GMI, or a single positive GMI plus a highly suggestive CT thorax[15] would lead to the commencement of CAS, AmB, LAmB, or VCZ. Otherwise, GM monitoring was continued. The control arm (henceforth called the 'empirical' arm) was provided with the standard of care in accordance with international and departmental guidelines.[3,14] Details of the study program are shown in Figure 1.

The hematologists managed their patients in the usual manner. They were free to commence antifungal therapy even if the patient had persistently negative GM readings, though educational efforts were made throughout the study period to encourage compliance with the study protocol. When physicians insisted on starting caspofungin, amphotericin or voriconazole (CAV), the study end-point was considered to have been reached, and GM monitoring stopped. However, if an IMI was not 'probable' or 'proven' by study criteria, the patient was eligible for randomization again in the next cycle of chemotherapy. An infectious diseases (ID) consult could be requested in the usual manner, and the patient would be seen by the ID physician on-call. Managing hematologists could also order CT scans as they saw fit, regardless of the GMI. All scans were read real-time by radiologists on duty at the time the scans were performed. However, for data analysis and manuscript preparation, all CT scans were reviewed by two of the investigators, BHT and FKC.

2.3. Ethical considerations

The study protocol was approved by the hospital's institutional review board and funded by the local National Medical Research Council (NMRC; grant 0984/2005).

The study was terminated when the GM assay became a routine service offering from the microbiology laboratories of our own hospital. Clinicians began to order it frequently. The

Table 1
Study inclusion and exclusion criteria

Inclusion criteria
Patients were eligible if they were at least 12 years of age or older, with a Karnofsky score $\geq$70%, and if they had any of the following conditions:
(1) Newly diagnosed or relapsed acute leukemia or high-risk MDS receiving induction or salvage chemotherapy with expected duration of neutropenia (ANC $<0.5 \times 10^9$/l) of at least 10 days
(2) SAA receiving chemotherapy or immunosuppressive therapy using antithymocyte globulin
(3) Receiving allogeneic/autologous HSCT using myeloablative conditioning regimens
(4) Consolidation regimens HyperCVAD type B or HIDAC with expected duration of neutropenia (ANC $<0.5 \times 10^9$/l) of at least 10 days
Exclusion criteria
(1) Patients who were HIV-infected
(2) Patients with uncontrolled bacteremia or active pulmonary infection at the time of randomization
(3) Patients with pre-existing proven and probable invasive fungal infections, according to standardized definitions (see Case definitions and classification, Ascioglu et al., 2002[15])
(4) Patients receiving concomitant piperacillin/tazobactam or amoxicillin–clavulanate
(5) Patients on palliative chemotherapy
(6) Patients with history of allergy to triazoles
(7) Patients with prior history of anaphylactic reaction to AmB
(8) Patients with serum levels of AST, ALT, ALP, or bilirubin more than 5 times the upper limit of normal or renal impairment with calculated creatinine clearance <30 ml/min
(9) Patients with expected life-expectancy <72 h

MDS, myelodysplastic syndrome; ANC, absolute neutrophil count; SAA, severe aplastic anemia; HSCT, hematopoietic stem cell transplant; AmB, amphotericin B; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

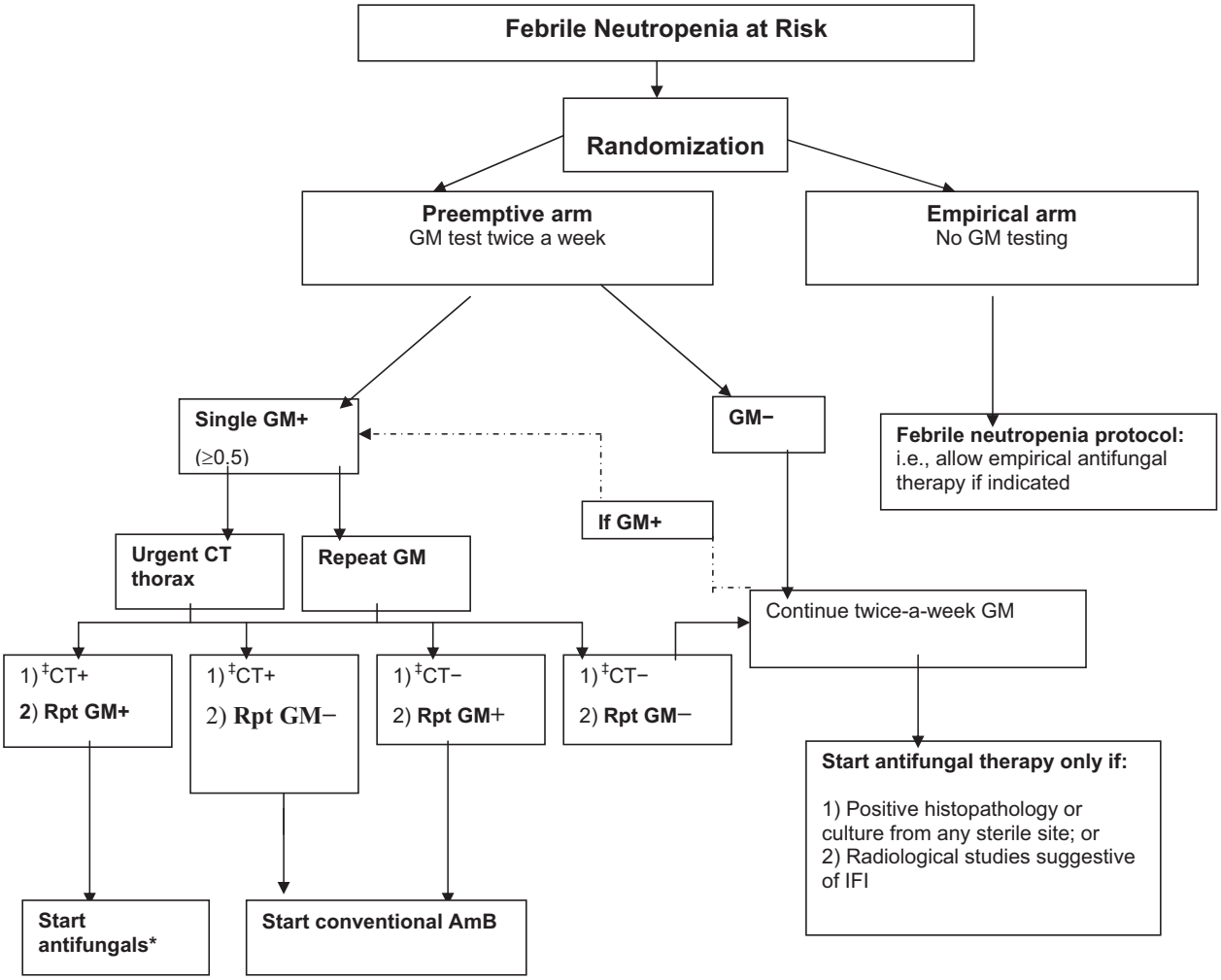

Figure 1. Study flow chart (GM, galactomannan; IFI, invasive fungal infections; CT, computed tomography; ‡CT+ denotes CT findings suggestive of invasive pulmonary aspergillosis; ‡CT− denotes CT findings not suggestive of invasive pulmonary aspergillosis; *drug choices include voriconazole, caspofungin, and lipid formulations of amphotericin).

investigators found it impossible to distinguish those in the preemptive from those in the empirical arm, and hence terminated the study.

2.4. Antigen detection

The GM assay was performed using the Platelia Aspergillus EIA (BioRad, France), a one-stage immunoenzymatic sandwich microplate assay that detects GM in human serum. The assay uses the rat monoclonal antibodies EBA-2, directed against Aspergillus GM. The monoclonal antibodies are used to coat the wells of the microplates for capturing the antigen and for detection of the antigen bound to the sensitized microplate.

Serum samples were heat-treated in the presence of ethylenediaminetetraacetic acid (EDTA) in order to dissociate immune complexes and to precipitate serum proteins that could possibly interfere with the test. The treated serum samples and conjugate were added to the wells coated with monoclonal antibodies and incubated. A monoclonal antibody–GM–monoclonal antibody/peroxidase complex is formed in the presence of GM antigen. The strips were washed to remove any unbound material. Next, the substrate solution was added. This reacts with the complexes bound to the well to form a blue color reaction, if the complexes are bound. The enzyme reaction was stopped by the addition of acid (with color change from blue to yellow). The absorbance of samples and controls was determined with a spectrophotometer set at 450 and 620 nm wavelength.

To exclude false-positives due to contamination in the testing process, only sterilized consumables were used. Samples testing positive were retested from the original specimen tube as well, to confirm a positive result.

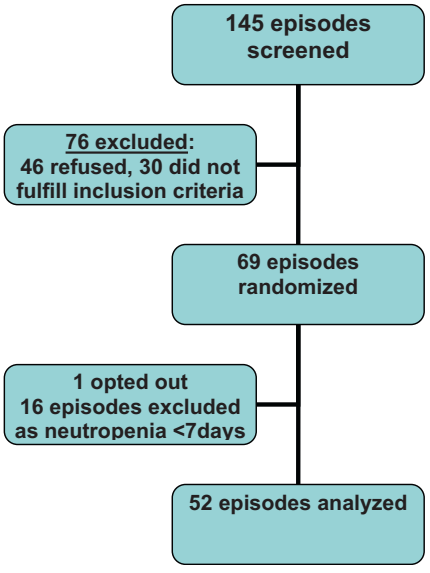

Figure 2. Flow diagram depicting passage of participants through study.

In this study, a GMI of ≥0.5 was considered positive.

2.5. Case definition and classification

Treatment episodes were classified as proven IA, probable IA or possible IA, based on the definitions of the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC-IFIG/MSG).[15]

'Broad-spectrum antifungal agent' in this article refers to CAS or AmB or LAmB or VCZ. The use of any of these agents is abbreviated as the use of CAV.

2.6. Statistical analysis

Patients with probable or proven IA were not eligible for subsequent inclusion; otherwise patients could be included more than once. Hence analysis was performed according to treatment episodes.

Because the duration of neutropenia did not always turn out as anticipated, treatment episodes were eventually included for analyses only if there had been neutropenia of at least 7 days' duration.

In the intent-to-treat (ITT) analysis, all episodes that ended with CAV were included, regardless of the reason for CAV. In the evaluable-episode (EE) analysis, patients who were put on CAV because they had probable/proven IA, or a positive GM not amounting to proven/probable IA, were excluded.

Fisher's exact or Chi-square tests were used for categorical variables. The Student's *t*-test was used for comparison of continuous variables. A *p*-value of ≤0.05 was considered significant. Survival analysis was done by the method of Kaplan–Meier. All statistical analyses were performed using SPSS software (version 13 for Windows; IBM–SPSS, Chicago, IL, USA).

This study was registered at Clinicaltrials.gov NCT00361517.

3. Results

One hundred and twenty-five patients, representing 145 potentially eligible episodes, were screened. Eventually, 47 patients, representing 52 episodes, were randomized (Figure 2).

The characteristics of the treatment episodes are shown in Table 2.

Table 2
Characteristics of treatment episodes

	Preemptive arm	Empirical arm	*p*-Value
No. of episodes	27	25	
Age (years)			0.84
Mean	41.41	42.24	
Median	44	45	
Range	17–67	16–77	
Sex			0.73
Male	16	16	
Female	11	9	
Underlying disorder			0.58
AML	11	14	
ALL	5	6	
MDS	1	0	
SAA	1	0	
Allo-HSCT	5	2	
Auto-HSCT	4	3	
Duration neutropenia(days)			0.07
Mean	18	13	
Median	16	10	
Range	7–41	7–31	
Median duration antifungal prophylaxis (days)	19	19	0.63
Broad-spectrum antifungal used	9	11	0.17
Voriconazole	1	1	
Caspofungin	3	0	
Amphotericin B	5	10	

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; SAA, severe aplastic anemia; Allo-HSCT, allogeneic hematopoietic stem cell transplant; Auto-HSCT, autologous hematopoietic stem cell transplant.

Of the 27 episodes in the preemptive arm, the primary endpoint was reached in nine (33.3%). Two were diagnosed as proven/probable cases as a result of a positive GM result triggering further evaluation (Table 3). One other patient received CAS for what was eventually classified as a false-positive GM (P4E1, Table 4). There were seven instances of false-positive GM readings in the preemptive arm (Table 4). Of these, only one received CAV (P4E1, Table 4). Of the remaining 24 episodes in this arm, CAV was started empirically in six, despite persistently negative GM readings. The details of these six patients are shown in Table 5. One patient in the preemptive arm (P1E3) received an antifungal late in his third enrolment despite negative GM results. At this point he had skin nodules. However, of note he had had positive GM readings in his previous episodes, but his physician was not

Table 3
Proven/probable invasive mold infections picked up by galactomannan monitoring

Case, age (years)	Underlying disease	Type of chemotherapy	GMI/day of neutropenia	Mode of diagnosis
P5E2, 44	CML	Allogeneic HSCT	1.3/day 46 post-HSCT	Probable, CT findings
P13E1, 36	ALL	Induction	1.4/day 16	Proven, CT and histopathology

GMI, galactomannan index; CML, chronic myelogenous leukemia; ALL, acute lymphoblastic leukemia; HSCT, hematopoietic stem cell transplant; CT, computed tomography.

Table 4
False-positive galactomannan readings—details

	Case	GM index	Repeat index	CT thorax	CAV used?	Alternative diagnosis	Outcome
1a	P4E1	1.2	0.2	Normal	No	*Escherichia coli* bacteremia	Alive
1b	P4E1	1.2	None	Normal	CAS	*Stenotrophomonas maltophilia* bacteremia	Alive
2	P5E1	0.7	0.5	Normal	No	False-positive (see text)	Alive
3	P6E1	0.5	0.2	No significant abnormality	No	False-positive	Alive
4a	P1E2	1.3	0.1	Normal	No	False-positive (see case reports)	Alive
4b	P1E2	0.6	0.8	Not done	No	False-positive (see case reports)	Alive
5	P8E1	0.5	0.2	Consolidation in RUL	No	*Pseudomonas aeruginosa* bacteremia and pneumonia	Alive
6	P9E1	0.6	0.2	Atelectasis	No	False-positive	Alive

GM, galactomannan; CT, computed tomography; CAV, caspofungin, amphotericin or voriconazole; CAS, caspofungin; RUL, right upper lobe.

Table 5
Patients started on CAV in the preemptive arm despite a persistently negative galactomannan index (GMI)

Episode	Underlying illness/chemotherapy	Neutropenic fever *prior* to CAV (days)	Duration of CAV (days)	Alternative diagnosis	CT thorax finding	Outcome
P1E3	ALL/salvage	8	32	Classified as failure of monitoring	Ground-glass changes (see case reports, failure)	Alive (eventually died outside monitoring period)
P2E2	ALL/HSCT	9	33	Possibly engraftment syndrome (see case reports)	Pneumonitis, pericardial effusion (see case reports)	Died outside monitoring period
P3E1	AML/salvage	10	11	None at the point of starting CAV. Pre-terminal blood cultures yielded *Fusarium sp* (see case reports)	Multiple lung nodules, with several areas of consolidation	Died outside monitoring period
P10E1	AML/mobilization	6	3	*Stenotrophomonas maltophilia* bacteremia	Resolving consolidation from pneumonia in previous episode of neutropenia	Alive
P11E1	AML/re-induction	18	20	*Escherichia coli* bacteremia	Bilateral pleural effusions	Alive
P12E1	AML	4	1	Communication error. AmB started, then stopped when lab informed ward of error	Not done	Alive

CAV, caspofungin, amphotericin or voriconazole; CT, computed tomography; ALL, acute lymphoblastic leukemia; HSCT, hematopoietic stem cell transplant; AML, acute myeloid leukemia; AmB, amphotericin B.

Table 6
Risk of being started on caspofungin, amphotericin or voriconazole

Preemptive arm		Empirical arm		*p*-Value
ITT: total No. of recipients of CAV/total in arm	9[a]/27	Total No. of recipients of CAV/total in arm	11/25	0.57
EE: No. of empirical recipients of CAV/No. without proven/probable	6/24[b]	No. of empirical recipients of CAV/No. without proven/probable	9/23[c]	0.36
No. of appropriate recipients of CAV according to monitoring protocol	3/27	No. of recipients of definitive antifungal treatment	2/25	1.00

ITT, intent-to-treat analysis; EE, evaluable-episode analysis; CAV, caspofungin, amphotericin or voriconazole.
[a] Includes one who received it because of a false-positive galactomannan assay (see Table 5).
[b] See Table 4 for details.
[c] Of the two patients with proven/probable invasive fungal infection, one received AmB empirically (see text) and the other received it because of a clinical sign (see Supplementary Material).

keen on treatment as he appeared well (for details, please see Case 1 in the Supplementary Material). Hence, in the ITT analysis, the risk of being started on CAV in the preemptive arm was 33.3% (9/27). In the EE analysis, the risk of being started on CAV for patients randomized to the preemptive arm was 25% (6/24).

Of 25 episodes in the empirical arm, 10 patients (40%) were started empirically on CAV, and one patient was started on AmB because of paronychia of the thumb (which turned out to be caused by *Fusarium sp*). One of the 10 patients started empirically on CAV also had a CT thorax with features characteristic of invasive pulmonary aspergillosis (IPA); she also was found to have an elevated GMI, done after recovery of ANC at the discretion of her physician (see Supplementary Material). The other nine patients put empirically on CAV did not have either proven or probable invasive fungal infection (IFI). The risk of being started on CAV was 44% (11/25) by ITT analysis and 39.1% (9/23) by EE analysis, for patients randomized to the empirical arm.

Hence the risk of being put empirically on CAV was greater in the empirical than in the preemptive arm, though the difference was not statistically significant (Table 6). In the ITT analysis, the preemptive approach saved about 11% of patients from empirical antifungals, while in the EE analysis the preemptive approach saved 14% of patients from empirical antifungals, without adverse consequences.

Twelve-week survival was 85.2% in the preemptive arm and 84% in the empirical arm.

4. Discussion

In this study, we demonstrated that holding back antifungals in the persistently febrile neutropenic patient until the GMI was positive was a potentially viable strategy. Such an approach, variously termed 'preemptive' and 'presumptive', represents an alternative to empirical antifungals.[16–18] It is modeled on the successful strategy against CMV in transplantation.[19]

We employed prophylaxis in this study as it is the routine in our department for patients likely to experience prolonged neutropenia. The use of antifungal prophylaxis in febrile neutropenia is supported by international guidelines.[20] We used ITC because of evidence for its efficacy in this setting, as well as a relatively high rate of IA in our institution.[21,22] Though ITC is 'mold-active', our experience, along with that in the literature, suggests that the prophylactic efficacy of ITC in preventing IA is patchy.[23] Glasmacher et al. compared fluconazole against ITC as prophylaxis in neutropenic patients and found that the rates of breakthrough IA were similar in the two arms.[23]

Oshima et al. reviewed their experience with a 'presumptive' strategy in which an antifungal was started only when a GMI or a BDG assay was positive, or when a CT thorax showed nodules.[18] They concluded that the presumptive strategy was safe—the only death was attributed to progression of acute myeloid leukemia.[18] Because of the retrospective nature of this study, a bias cannot be excluded.[16]

The use of diagnostic modalities to trigger antifungals has been shown to reduce the need for their use. In a non-randomized study, Maertens et al. assayed GM daily in at-risk hematological patients, until neutropenia resolved.[9] They also performed CT thorax and bronchoscopy in those at high risk for an IFI. Whereas 35% of the patients would have been started on broad-spectrum antifungals had the investigators adopted the traditional empirical approach, only 7.7% of the patients in this cohort eventually received LAmB.

The 12-week survival was 63%; no case of IA was missed, though one of zygomycosis was.[9]

Cordonnier et al. compared the empirical approach with a preemptive approach.[17] Patients with hematological malignancies (after chemotherapy or an autologous HSCT) who were febrile after 4 days of broad-spectrum antibiotics were started on antifungals if they were randomized to the empirical treatment arm. If they were randomized to the preemptive arm, they would only be started on an antifungal if they developed one of several triggers, such as imaging-documented pneumonia or a positive GM test. GM screening was performed twice a week. Forty-two percent of patients in the empirical arm and 48% of those in the preemptive arm received prophylaxis. Two-week survival was 97% in the empirical arm and 95% in the preemptive arm ($p = 0.31$). The incidence of IFI was significantly higher in the preemptive than in the empirical arm; these included candidiasis in the preemptive arm. (All patients with candidiasis did not receive azole prophylaxis.) The preemptive arm enjoyed statistically significant cost-savings.[17]

Our study also compared the two different approaches to antifungal therapy in febrile neutropenic patients in a randomized manner. It was different from that of Cordonnier et al. because the trigger for antifungal therapy in the preemptive arm was the positive GM assay (± a positive CT thorax), and because all patients were on Candida-active prophylaxis. Like the study of Cordonnier et al., our results suggest that the preemptive approach may reduce the use of broad-spectrum antifungals without compromising survival.

One shortcoming of our approach is that the GM assay per se is inadequate as the trigger in a preemptive strategy. The CMV pp65 antigenemia assay and the CMV PCR are sensitive and specific enough for a preemptive approach to CMV prevention. Even then 'missed' cases leading physicians to commence anti-CMV agents for treatment purposes are well reported.[24,25] The GM assay will not pick up fusariosis, scedosporiosis, or zygomycosis. The cases of fusariosis seen in this small study suggest that, rare though they are, these are truly emerging pathogens. The GM assay therefore is not failsafe for use as the only trigger for antifungals in a severely immunocompromised and highly vulnerable population.

Apart from its inability to pick up these rarer molds, the GM assay has a rather poor sensitivity—Pfeiffer et al. found the sensitivity to be 71% in a meta-analysis.[26] This figure falls in patients on mold-active prophylaxis.[27] The negative predictive value (a little over 80%) is inadequate for sole use in such a strategy.[28,29] On the other hand, as may be seen from the Supplementary Material, failure to take positive GM results seriously (after ruling out obvious causes of false-positivity) may lead to the diagnosis of IA being missed.

The relative freedom given to managing physicians may be regarded as a flaw. However, it was crucial in allowing the study to be carried out, as at that time no data from a randomized clinical trial existed to support its use. The freedom they were given, however, was used to see how effective the study strategy was in comparison with the more established empirical approach. This strategy of giving flexibility to attending physicians in their compliance with study algorithms has been used before.[30] In a study conceptually similar to ours, a biomarker (procalcitonin) was used to guide the cessation of antibiotics. Primary physicians were allowed to continue antibiotics even when the algorithm advised stopping.[30]

As it was, by evaluable-episode analysis, the proportion of patients in the preemptive arm who received CAV was numerically two-thirds that of patients in the empirical arm, though the difference was not statistically significant. Had the GM assay a better negative predictive value for IA, the attending clinicians might have been less nervous. Segal et al. pointed out that the better the diagnostic tool was at detecting an occult fungal infection early, the more likely physicians would be to "not modify the antifungal regimen for patients with negative screening results".[7] It is possible that our small sample size may have prevented a true difference to be seen.

Nevertheless the results are heartening. Although we randomized study subjects, the patients in the preemptive arm had mean and median periods of neutropenia that were marginally longer than those in the empirical arm ($p = 0.07$). Despite this disadvantage, the preemptive arm did not suffer an increased mortality. The withholding of empirical antifungals may have been balanced by the appropriate initiation of antifungals in two patients whose IPA was picked up by regular GM monitoring.

Unfortunately, we had to terminate the study early. Could we have stopped physicians looking after patients in the empirical arm from ordering GM tests when they became easily available? On ethical grounds alone, we felt that we could not. This was based on the premise that "research is ethically justifiable only if it is.. morally acceptable within the communities within which it is carried out".[31] At the time of our study, no guideline recommended routine regular GM screening in febrile neutropenic patients. Given the high mortality of IA, it was understandable that physicians would want every available tool to diagnose IA early. In 2008, a publication recommended daily GM monitoring in neutropenic patients with persistent fever despite broad-spectrum antibacterials.[32]

In conclusion, this prospective, randomized study showed that, in the setting of effective anti-candidal prophylaxis, CAV may be held off safely in the majority of febrile neutropenic patients, if the GMI is persistently negative. Our study suggests the safety of a preemptive approach to antifungal therapy in persistently febrile neutropenic patients.

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Conflict of interest: Dr Tan has received travel grants from Pfizer. Dr Goh has lectured at symposia organized by MSD and Pfizer. Dr Lin owns stock in Pfizer. Dr Goh has received research funding from Novartis Oncology and Janssen Cilag and honoraria from Novartis Oncology, Janssen Cilag, Celgene, and Bristol Myers Squibb. Dr Kurup has received travel grants from Pfizer.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2011.01.011.

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