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Risk factors for breakthrough invasive fungal infection during secondary prophylaxis

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***Background*: Intensive chemotherapy with severe neutropenia is associated with invasive fungal infections (IFIs) leading to high mortality rates. During leukaemia induction chemotherapy, IFI often prohibited further curative treatment, thus predisposing for leukaemia relapse. Continuing myelosuppressive chemotherapy after diagnosis of IFI has become feasible with the now expanding arsenal of safe and effective antifungals. Secondary prophylaxis of IFI is widely administered, but reliable data on outcome and risk factors for recurrent IFI during subsequent chemotherapy are not available. This study determines risk factors for recurrent IFI in leukaemia patients.**

***Methods*: From 25 European cancer centres, 166 consecutive patients with acute myelogenous leukaemia (AML) and a recent history of proven or probable pulmonary IFI were included. Patients were followed for recurrence or breakthrough IFI during the subsequent chemotherapy cycle.**

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Results: Of the 166 patients included, 69 (41.6%) were female, the median age was 53 years (range 2–81) the and 3 (1.8%) were <16 years. Recurrent IFI occurred in 26 patients (15.7%). Multiple logistic regressions yielded predisposing factors: duration of neutropenia [per additional day; odds ratio (OR) 1.043, confidence interval (CI) 1.008–1.078], high-dose cytarabine (OR 3.920, CI 1.120–12.706), number of antibiotics (per antibiotic; OR 1.504, CI 1.089–2.086), partial response as outcome of prior IFI (OR 4.037, CI 1.301–12.524) and newly diagnosed AML (OR 3.823, CI 0.953–15.340). Usage of high efficiency particulate air filter appeared protective (OR 0.198, CI 0.036–1.089).

***Conclusions*: Duration of neutropenia, high-dose cytarabine, prior antibiotic therapy and a partial response to the first IFI therapy were risk factors for recurrent IFI and should be considered in AML patients with prior pulmonary IFI undergoing further chemotherapy.**

Keywords: antifungal prophylaxis, polyenes, triazoles, echinocandins

Introduction

Invasive fungal infections (IFIs) are a major threat to patients treated for acute leukaemia. Patients undergoing remission induction therapy are considered to be at high risk for IFI. Invasive aspergillosis is the most prevalent among these infections.[1] First-line antifungal treatment fails in ~50%;[2–7] and IFIs are associated with a high mortality.[8] In addition, treatment of proven or probable IFI is long-lasting and requires administration of antifungals after the end of neutropenia to prevent an early relapse of the infection.[9–11] Besides concerns of exacerbations of the IFI, it is well known that some antifungals show an unfavourable safety profile, often resulting in either early cessation or postponement of antineoplastic therapy that bears the risk of relapse.[12]

Primary antifungal prophylaxis looks promising in haematological cancer patients and has been examined in numerous trials.[1] A reduction in the incidence and mortality of IFI was shown in patients undergoing induction chemotherapy for acute leukaemia or myelodysplastic syndromes and recipients of allogeneic bone marrow or stem cell transplantation. These benefits were achieved under primary prophylaxis with fluconazole or, recently, posaconazole.[13–17]

Survivors of IFI undergoing further myelosuppressive chemotherapy are exposed to a substantial risk of relapsed infection. Although this is well known, reliable prospective evaluations elucidating this risk are not yet available. The risk of IFI relapse has been addressed in patients undergoing allogeneic stem cell transplantation. The only risk factor that can be determined early after transplantation is the duration of neutropenia following the conditioning regimen.[18] A number of risk factors that do occur in the transplant setting only have been determined by retrospective studies for the time after engraftment.[18,19]

To analyse the use of secondary antifungal prophylaxis in haematological patients, a case registry was established for patients with proven or probable IFI undergoing subsequent chemotherapy-induced neutropenia. This database was analysed regarding regimens applied for prophylaxis of second IFI to characterize prior IFI and other aspects that may help identify risk factors for recurrent fungal infections.

Patients and methods

Patients

From October 2001 to July 2004, patients were enrolled in a case registry. Eligibility criteria included: (i) history of proven or probable pulmonary IFI during the recent neutropenic (absolute neutrophil count $<500/mm^3$) episode; (ii) acute myelogenous leukaemia (AML); (iii) a current neutropenic episode of at least 3 days. Exclusion criteria: patients receiving allogeneic transplantation and patients with a history of possible IFI were not eligible. Fungal infections were diagnosed according to the criteria used by the investigators of the European Organization for Research and Treatment of Cancer (EORTC) and the Mycology Study Group (MSG).[2] The study was approved by the Ethics Committee of the Cologne University Medical System.

Data collection instruments

A multilingual case record form was accessible through the internet and anonymized data entry and electronic transfer into a relational database were used.[20] Information on enrolled patients concerning age, sex, underlying malignancy as well as treatment results and any chemotherapy postponement attributable to IFI were obtained. In addition, details regarding first IFI (including fungal species, organs involved, treatment regimens and outcome), duration of neutropenia plus details of secondary antifungal prophylaxis regarding dosage, duration and efficacy of prophylaxis, treatment results of underlying malignancy, survival and cause of death, respectively, were collected and entered in the database. In the case of recurrent IFI, additional data were obtained on fungal species and organ involvement as well as treatment outcome. A plausibility control was done for all data received and queries were issued when necessary for further clarification.

Statistical analysis

For each single potential risk factor for recurrent IFI, a separate logistic regression was calculated. For this purpose, all categorical variables were split into dichotomy variables to test the influence of every single category. Those factors with a coefficient significantly different from zero (P value of the likelihood ratio ≤ 0.05) were entered into a forward stepwise multiple logistic regression model to identify the combination of risk factors that might be associated with IFI.

Results

Data were collected from 25 cancer centres from six European countries. A total of 166 adult and paediatric patients with a diagnosis of previous IFI were enrolled and analysed (Figure 1). Sixty-nine (41.6%) were female. Median age was 53 years (range 2–81), and 3 (1.8%) were below 16 years (Table 1). A

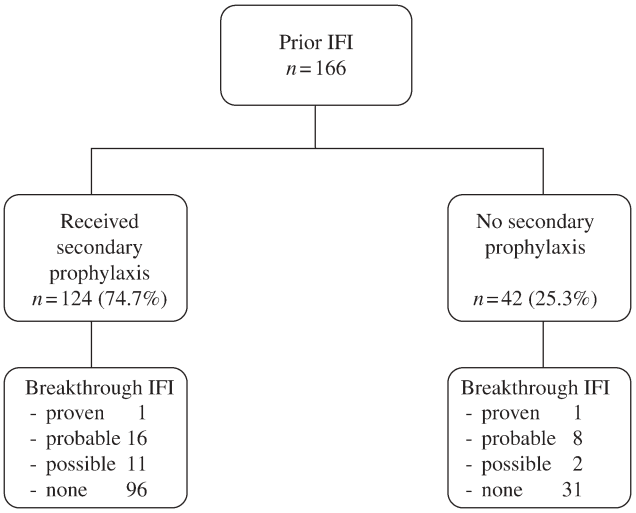

Figure 1. Level of diagnostic certainty and number of breakthrough IFIs in patients with or without secondary prophylaxis.

second IFI was diagnosed in 26 patients (15.7%). These second episodes of IFI were proven in two cases only and probable IFI in the remaining 24 patients. The same organ was involved in 88.5% of the patients (Table 2).

Findings prior to the observation period

Antifungal treatment regimens during prior IFI are demonstrated in Table 3. Surgical resection for the fungal infection had been applied in 14.5% of the patients. Treatment of the underlying disease was delayed in 51.2% of the patients due to treatment of preceding IFI. Pulmonary aspergillosis had been identified in 114 patients (68.7%), whereas in 41 (24.7%) patients, diagnosis was based on radiographic results without microbiological proof of infection (Table 3). Almost 90% had pulmonary involvement as the only site without dissemination. Less than half of the patients (40.4%) responded completely to the treatment of the preceding IFI. Immediately prior to the observation period with a secondary antifungal prophylaxis, complete response of the AML had been documented in 102 patients (61.4%, Table 3).

Prophylaxis or observation during subsequent AML chemotherapy

During the observation period, 42 individuals (25.3%) received no secondary antifungal prophylaxis. Among the 124 individuals with prophylaxis, the majority (105 patients, 63.3%) received only one antifungal drug without further change. These were itraconazole ($n = 50$), voriconazole ($n = 24$), colloidal amphotericin B ($n = 17$), liposomal amphotericin B ($n = 10$) and caspofungin ($n = 4$) (Table 4). The median duration of neutropenia during subsequent chemotherapy cycles was 16 days.

Risk factor analysis

In the univariate analysis, the rates of breakthrough IFI did not differ between the subgroups with or without antifungal prophylaxis. Patients with a second episode of IFI had a substantially longer median neutropenia when compared with those with no further IFI (26.5 versus 14 days; $P = 0.001$, OR 1.043 per additional day, CI 1.008–1.078) (Table 5). High-dose cytarabine was administered in 67 patients (40.4%). Patients receiving high-dose cytarabine had a higher risk of developing a second episode of IFI (17/26, 65.4%, $P = 0.005$). The risk of a second IFI also increased in patients who received parenteral nutrition ($P = 0.004$) or received a high number of antibiotics ($P = 0.019$). Partial response of prior IFI ($P = 0.026$) and treatment of recently diagnosed AML ($P = 0.016$) were associated with a higher risk of second IFI as well. Those 49 individuals treated under protected environmental conditions [high efficiency particulate air (HEPA)-filtered facilities] during prior IFI were less likely to develop a recurrent IFI (3 patients with IFI out of 49 with HEPA, $P = 0.029$).

Three of 26 (11.5%) patients with a second episode of IFI died during the observation period (1 patient with partial response of a second episode of IFI who died of cerebral ischaemia and 3 patients with progressive secondary IFI of whom 1 died of hepatic failure and 2 of pneumonia). In contrast, only 7 of 140 patients (5%) without a second episode of IFI died.

Discussion

This study yielded data on the widespread use of secondary prophylaxis of IFI in patients with AML.

Our analysis comprised 166 patients undergoing subsequent antineoplastic treatment after a first episode of proven or probable IFI. Although patients with newly diagnosed AML will develop IFIs in 4% to 6%,[1] the rate is ~3-fold higher in patients pre-treated for AML. As 15.7% of the study population developed a probable or proven IFI, our data underline that there is a substantial rate of second IFI. The high rate of second IFI

Table 1. Patient characteristics

Characteristic	All patients ($n = 166$)	No or possible second IFI ($n = 140$)	Proven or probable second IFI ($n = 26$)	P value of likelihood ratio
Female, *n* (%)	69 (41.6%)	59 (85.5%)	10 (14.5%)	0.727
Age in years, median (min–max)	53 (2–81)	53 (2–81)	44.5 (27–69)	0.526
Weight in kg, median (min–max)	73 (16–105)	73 (16–105)	74 (50–101)	0.941

IFI, invasive fungal infection.

Table 2. Disease pattern and outcome in patients with proven or probable breakthrough IFIs

Prior IFI				Secondary prophylaxis		Second IFI				
pathogen	organs involved	diagnostic certainty	outcome	regimen (mg)	days until breakthrough	pathogen	organs involved	diagnostic certainty	outcome	Overall outcome
Aspergillus sp.	lung	probable	PR	—	—	*Aspergillus* sp.	oesophagus	proven	PR	survived
Aspergillus fumigatus	lung	proven	PR	itraconazole 400 capsule	79	*A. fumigatus*	lung	proven	PR	survived
Aspergillus sp.	lung	probable	PR	itraconazole 400 oral solution	53	*Aspergillus* sp.	lung, spleen	probable	PR	survived
Aspergillus sp.	lung, liver	probable	PR	—	—	*Aspergillus* sp.	lung	probable	PR	survived
Aspergillus sp.	lung	probable	PR	amphotericin B, deoxycholate 0.97/kg	25	*Aspergillus* sp.	lung	probable	PD	survived
Aspergillus sp.	lung	probable	PR	itraconazole 200–400 capsule	38	*Aspergillus* sp.	lung	probable	PR	survived
Aspergillus sp.	lung	proven	SD	itraconazole 400 capsule	33	*Aspergillus* sp.	lung	probable	CR	survived
A. fumigatus	lung	probable	PR	fluconazole 200 iv	27	*Candida* sp.	liver	probable	SD	survived
Mucor sp.	lung	proven	PR	amphotericin B, liposomal 1.0–3.8/kg, amphotericin B, deoxycholate 0.4–0.7/kg	67	not specified[a]	lung	probable	PR	survived
Not specified[a]	lung	probable	CR	—	—	not specified[a]	lung	probable	PD	died
Not specified[a]	lung	probable	PR	amphotericin B, deoxycholate 0.7–1.0/kg	57	not specified[a]	lung	probable	CR	survived
Not specified[a]	lung	probable	PR	amphotericin B, deoxycholate 1.0/kg	23	not specified[a]	liver	probable	PR	survived
Aspergillus sp.	lung	probable	CR	amphotericin B, deoxycholate 0.98/kg	19	*Aspergillus* sp.	lung	probable	PD	died
Aspergillus sp.	lung	probable	PR	amphotericin B, deoxycholate 0.42/kg	14	*Aspergillus* sp.	lung	probable	SD	survived
Not specified[a]	lung	probable	PR	itraconazole 600 oral solution	147	not specified[a]	lung, spinal cord	probable	PR	survived
Aspergillus sp.	lung	probable	PR	fluconazole 400 po/iv	6	*Aspergillus* sp.	lung	probable	PR	survived
Aspergillus sp.	lung	probable	CR	fluconazole 400	16	*Aspergillus* sp.	lung	probable	CR	survived
Not specified[a]	lung	probable	PR	voriconazole 400 po	17	not specified[a]	lung	probable	PD	died
Aspergillus sp.	lung	probable	CR	fluconazole 400 oral solution	28	*Aspergillus* sp.	lung	probable	CR	survived
Not specified[a]	lung	probable	PR	voriconazole 400 po	36	not specified[a]	lung	probable	PR	survived
Aspergillus sp.	lung	probable	PR	amphotericin B, deoxycholate 0.91/kg	41	*Aspergillus* sp.	lung	probable	PR	survived
Not specified[a]	lung	probable	PR	—	—	not specified[a]	lung	probable	PR	survived
Not specified[a]	lung	probable	CR	—	—	*Aspergillus* sp.	lung	probable	PR	survived
Aspergillus sp.	lung	probable	PR	itraconazole 400 oral solution	76	*Aspergillus* sp.	lung	probable	PD	survived
A. fumigatus	lung	proven	SD	itraconazole 200 iv	20	*Aspergillus* sp.	lung	probable	PR	survived
Aspergillus sp.	lung	probable	PR	itraconazole 200 capsules (12 days), amphotericin B, deoxycholate 0.89/kg (20 days), voriconazole 200 iv (20 days), fluconazole 200 iv (5 days)	57	*Aspergillus* sp.	lung	probable	PR	survived

IFI, invasive fungal infection; PR, partial response; PD, progressive disease; CR, complete response; SD, stable disease.
[a]Based on imaging studies.

Table 3. Findings during prior IFI, *P* values of single logistic regression analysis

Characteristic, no. of patients	All patients ($n = 166$)	No or possible second IFI ($n = 140$)	Proven or probable second IFI ($n = 26$)	*P* value of likelihood ratio
First-line treatment				
itraconazole	5 (3.0%)	2 (1.4%)	3 (11.5%)	**0.006**
voriconazole	12 (7.2%)	11 (7.9%)	1 (3.8%)	0.468
fluconazole	2 (1.2%)	1 (0.7%)	1 (3.8%)	0.179
amphotericin B, deoxycholate	41 (24.7%)	31 (22.1%)	10 (38.5%)	0.076
amphotericin B, liposomal	9 (5.4%)	9 (6.4%)	0 (0.0%)	0.184
amphotericin B, lipid complex	1 (0.6%)	1 (0.7%)	0 (0.0%)	0.666
caspofungin	2 (1.2%)	2 (1.4%)	0 (0.0%)	0.540
sequential treatment of first IFI with different antifungals	93 (56.0%)	82 (58.6%)	11 (42.3%)	0.125
not assessed	1 (0.6%)	1 (0.7%)	0 (0.0%)	–
Status of underlying disease during prior IFI				
newly diagnosed AML	106 (63.9%)	84 (60.0%)	22 (84.6%)	**0.016**
relapse	13 (7.8%)	12 (8.6%)	1 (3.8%)	0.410
complete response	37 (22.3%)	35 (25.0%)	2 (7.7%)	0.051
partial response	5 (3.0%)	4 (2.9%)	1 (3.8%)	0.786
progressive disease	5 (3.0%)	5 (3.6%)	0 (0.0%)	0.328
Outcome of prior IFI				
complete response	67 (40.4%)	62 (44.3%)	5 (19.2%)	**0.017**
partial response	88 (53.0%)	69 (49.3%)	19 (73.1%)	**0.026**
stable disease	10 (6.0%)	8 (5.7%)	2 (7.7%)	0.697
progressive disease	1 (0.6%)	1 (0.7%)	0 (0.0%)	0.666
Isolation status				
reverse isolation	75 (45.2%)	62 (44.3%)	13 (50.0%)	0.591
HEPA	49 (29.5%)	46 (32.9%)	3 (11.5%)	**0.029**
no isolation	40 (24.1%)	31 (22.1%)	9 (34.6%)	0.172
not assessed	2 (1.2%)	1 (0.7%)	1 (3.8%)	–
Status of underlying disease immediately prior to subsequent neutropenia				
complete response	102 (61.4%)	93 (91.2%)	9 (8.8%)	**0.002**
partial response	17 (10.2%)	15 (88.2%)	2 (11.8%)	0.641
stable disease	6 (3.6%)	4 (66.7%)	2 (33.3%)	0.225
progressive disease	21 (12.7%)	15 (71.4%)	6 (28.6%)	0.082
relapse	17 (10.2%)	11 (64.7%)	6 (35.3%)	**0.019**
not assessed	3 (1.8%)	2 (66.7%)	1 (33.3%)	–

IFI, invasive fungal infection; AML, acute myelogenous leukaemia; HEPA, high efficiency particulate air filter.
P values result from single logistic regression analysis.
A longer version of this table is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

underlines the need of prophylaxis in the setting of subsequent chemotherapy.

This study focused on patients with AML with pulmonary fungal infection. The strength of our study lies in its investigation of a homogeneous patient population. Data were collected in a multicentre registry with the absolute number of IFI events being relatively low with respect to the number of potential risk factors under study. Although we report the by far largest sample in patients being under observation for second IFI in AML, the observed risk factors still warrant confirmation.[21] A weakness of our study is the observational design; however, as there is no general acceptance of secondary antifungal prophylaxis in AML right now, this large study could be performed at best in a multinational case registry. Despite these limitations, we were able to document data, which should be corroborated by further investigations.

The low rate of complete response of prior IFI ~40% is in line with the data reported from clinical trials.[2,22] Due to the low number of children in the case registry, further data collection in the paediatric population is urgently required. However, most children suffer from acute lymphoblastic leukaemia and thus have a different risk profile for IFI.

Itraconazole was the most frequently used prophylactic agent. We believe that the frequent itraconazole use was due to a longer licensing in the European countries, although the use of newer antifungals increased during the observation period.[23,24]

In the univariate analysis, we observed seven factors that influenced the occurrence of a second episode of IFI. These were duration of neutropenia, use of high-dose cytarabine, number of antibiotics, itraconazole as first antifungal during prior IFI, partial response of prior IFI, and newly diagnosed

Table 4. Findings during observation period, i.e. subsequent chemotherapy induced neutropenia

Characteristic, no. of patients	All patients ($n = 166$)	No or possible second IFI ($n = 140$)	Proven or probable second IFI ($n = 26$)	*P* value of likelihood ratio
First prophylactic regimen				
no prophylaxis given	42 (25.3%)	33 (78.6%)	9 (21.4%)	0.234
itraconazole	50 (30.1%)	43 (86%)	7 (14%)	0.699
voriconazole	24 (14.5%)	22 (91.7%)	2 (8.3%)	0.285
amphotericin B, deoxycholate	17 (10.2%)	12 (70.6%)	5 (29.4%)	0.100
amphotericin B, liposomal	10 (6.0%)	9 (90%)	1 (10%)	0.611
caspofungin	4 (2.4%)	4 (100%)	0 (0.0%)	0.383
sequential prophylaxis with different antifungals	19 (11.4%)	17 (89.5%)	2 (10.5%)	0.513
Exposed to construction work	69 (41.6%)	58 (84.1%)	11 (15.9%)	0.933
Central venous catheter	137 (82.5%)	113 (82.5%)	24 (17.5%)	0.153
Mucositis	21 (12.7%)	15 (71.4%)	6 (28.6%)	0.082
Diabetes mellitus	4 (2.4%)	4 (100%)	0 (0.0%)	0.383
Total parenteral nutrition	35 (21.1%)	24 (68.6%)	11 (31.4%)	**0.004**
Purine analogues	16 (9.6%)	11 (68.75%)	5 (31.25%)	0.071
Corticosteroids	3 (1.8%)	3 (100%)	0 (0.0%)	0.451
Therapeutic monoclonal antibodies	0 (0.0%)	0 (0.0%)	0 (0.0%)	—
High-dose cytarabine	67 (40.4%)	50 (74.6%)	17 (25.4%)	**0.005**
Duration of neutropenia (days), median (min–max)	16 (3–91)	14 (3–91)	26.5 (7–63)	**0.001**
Number of antibiotics administered, median (min–max)	3 (0–8)	3 (0–8)	4 (0–7)	**0.019**
Autologous transplantation	6 (3.6%)	5 (83.3%)	1 (16.7%)	0.945
Isolation status				
HEPA	50 (30.1%)	46 (92%)	4 (8%)	0.075
reverse isolation	72 (43.4%)	60 (83.3%)	12 (16.7%)	0.755
no isolation	41 (24.7%)	32 (78.0%)	9 (22.0%)	0.202
not assessed	3 (1.8%)	2 (66.7%)	1 (33.3%)	—

IFI, invasive fungal infection; HEPA, high efficiency particulate air filter.
P values result from single logistic regression analysis.

Table 5. Results of forward stepwise multiple logistic regression analysis

Variable	*P* value of Wald statistic	Odds ratio	95% Confidence interval
Factors present during observational period			
duration of neutropenia, per additional day	0.015	1.043	1.008–1.078
high-dose cytarabine	0.023	3.920	1.210–12.706
number of antibiotics, per additional antibiotic	0.014	1.504	1.089–2.086
Factors present during prior IFI			
first therapeutic antifungal is itraconazole	0.002	78.709	5.053–1226.1
HEPA	0.063	0.198	0.036–1.089
therapeutic outcome is 'partial response'	0.016	4.037	1.301–12.524
newly diagnosed AML	0.059	3.823	0.953–15.340

IFI, invasive fungal infection; HEPA, high efficiency particulate air filter; AML, acute myelogenous leukaemia.

AML (Table 5). HEPA during prior IFI seems to protect from further IFI.

Those seven factors that appear to have an impact on second IFI still need to be investigated in prospective controlled studies. It remains unanswered why the therapeutic use of itraconazole for prior IFI may be a risk factor for a second IFI. However, the number of patients with first-line itraconazole treatment for prior IFI was small as reflected by the vast confidence interval. HEPA filtration has been reported to protect patients from a first episode of invasive aspergillosis. An influence of HEPA

conditions on a lower risk of a second episode of IFI is a new observation. It may be speculated that the reduction in the fungal burden by HEPA filtration may protect the patient for some time even after leaving this environment.

Our observations are of particular importance because we pointed out that lack of antifungal prophylaxis was not a risk factor for a second episode of IFI in AML patients undergoing subsequent chemotherapy cycles.[25] This observation is unexpected and contradicts the rationale of administering antifungal prophylaxis in these patients.[19]

Due to the focus on AML and the exclusion of allogeneic stem cell recipients, only a few patients treated with corticosteroids were identified. Therefore, steroids could not be confirmed as a predisposing factor for IFIs, as shown elsewhere.[26,27] Active underlying disease was present in a high proportion of patients, but could not be demonstrated as a risk factor as reported in allogeneic transplant settings.[28,29]

In conclusion, we identified risk factors predisposing AML patients for a second IFI. These were newly diagnosed AML at the time of prior IFI, partial response of prior IFI, use of high-dose cytarabine treatment, duration of neutropenia, and number of antibiotics used. HEPA filtration during prior IFI was found to be a factor rendering a second episode of IFI less likely.

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Transparency declarations

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Supplementary data

A longer version of Table 3 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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