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Candida spp. bloodstream infection: influence of antifungal treatment on outcome

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Objectives: To assess the influence of new antifungal treatments on candidaemia outcome.

Methods: Candidaemia episodes prospectively collected through a blood culture surveillance programme in a single institution. The study was divided into two periods of time, 1994–2003 (A) and 2004–2008 (B), according to the introduction of echinocandin treatment. Non-conditional logistic regression methods with mortality as the dependent variable were used.

Results: Four hundred and thirty-three (3%) candidaemias out of 15 628 bloodstream infection episodes were analysed. *Candida albicans* was the most frequent species (211; 49%). Mortality was noted in 132 cases (30%). A total of 262 and 171 candidaemias were reported in period A and B, respectively. There were 94 deaths in period A (36%) and 38 in period B (22%, $P=0.03$). Treatment in period A was amphotericin B in 89 patients (41 dead, 46%) and fluconazole in 151 (41 dead, 27%, $P=0.003$). In period B, 113 patients received a triazole (26 dead, 23%), 30 an echinocandin (3 dead, 10%, $P=0.08$) and 9 (0 dead) were treated with combined therapy (echinocandin and triazole). Mortality was higher in period A (94 dead, 36%) than in period B (38 dead, 27%), $P=0.03$. Independent risk factors associated with mortality in period B were: age, chronic renal failure, ultimately or rapidly fatal prognosis of underlying disease and shock. Echinocandin alone or in combination therapy was associated with better outcome (odds ratio=0.22, 95% confidence interval=0.06–0.81, $P=0.02$).

Conclusions: In patients with candidaemia, echinocandin therapy results in a better outcome.

Keywords: candidaemia, mortality, echinocandins, triazoles

Introduction

Invasive candidiasis is an important cause of complications and death in hospitalized patients. Amphotericin B has served as standard treatment for five decades, but toxic effects often limit its use. Fluconazole has a role in the treatment of candidaemia in patients without neutropenia.[1] However, some *Candida* species such as *Candida krusei* or *Candida glabrata* are frequently resistant to fluconazole. This fact and the fungistatic activity of triazoles constitute the main limitations of fluconazole as first-line therapy in candidaemia. After the studies of Mora Duarte *et al.*,[2] Reboli *et al.*[3] and Kuse *et al.*,[4] echinocandins have emerged as important agents for the treatment of invasive candidiasis. Echinocandin activity is fungicidal and its spectrum includes all of the *Candida* spp. Recently, guidelines for the management of patients with invasive candidiasis and mucosal candidiasis recommended fluconazole or an echinocandin as initial therapy for most adult patients.[5]

We conducted the present study with the aim of analysing the influence of antifungal treatment on the outcome of *Candida* spp. bloodstream infection in a single institution during two time periods: before and after the introduction of echinocandin in clinical practice.

Patients and methods

Setting and data collection

The setting was the Hospital Clínic in Barcelona, a 700-bed university tertiary centre that provides specialized and broad medical, surgical and intensive care for an urban population of 500 000 people. A blood culture surveillance programme was conducted from January 1991.

Briefly, an infectious diseases specialist and a microbiologist review the charts of patients with positive blood cultures. According to the clinical context and the results of the blood culture, organism identification and susceptibilities, they recommended a specific antimicrobial therapy. Patients were observed from candidaemia diagnosis until 30 days of follow-up, death or discharge. Data regarding the episode of candidaemia are thus collected prospectively and entered in a database designed specifically for the blood culture surveillance programme.

Study design and inclusion criteria

The type of study was an analysis of cases of monomicrobial *Candida* spp. bloodstream infections prospectively collected through the previously described blood culture surveillance programme from January 1994 to December 2008. The Ethics Committee of the hospital approved the study.

Microbiological methods

Between 1994 and 1997, blood samples were processed by the BACTEC NR-730 system (Becton-Dickinson Microbiology Systems) and maintained routinely for 7 days. Since 1998, we have used the BACTEC 9240 system (Becton-Dickinson Microbiology Systems) with an incubation period of 5 days. Isolates were identified by standard techniques including commercialized methods when they were available (Api 20 C AUX, bioMérieux; Auxacolor, Bio-Rad; and Chromagar plates, Becton Dickinson). MICs were determined by a microdilution method using the recommendations stated in the CLSI documents published since 1997 (M27-A–M27-A3).[6]

Patient characteristics

The following data were obtained for all patients: age, sex, pre-existing co-morbidities, prognosis of the underlying disease, prior antimicrobial therapy, prior surgery (within the last month), current administration of ≥20 mg of corticosteroids every day, source of candidaemia, leucocyte count, origin of the infection (community acquired or nosocomial, including last conventional hospitalization or outpatient visit), length of hospitalization before diagnosis of candidaemia, intensive care unit (ICU) admission, need for mechanical ventilation, empirical and definitive antifungal treatment, presence of shock and mortality.

Definition of terms

Significant candidaemia was defined as one or more blood cultures positive for *Candida* spp. and clinically apparent signs and symptoms of sepsis (as described previously).[7] An episode of candidaemia was considered to be nosocomial if it took place ≥72 h after admission, or if the patient had been hospitalized within 2 weeks before the current admission or had received long-term healthcare (healthcare related); otherwise, the candidaemia was considered to be community acquired. The source of infection was determined by a senior infectious disease specialist, who considered the patient's medical history, physical examination and the results of other microbiological tests and complementary imaging exploration. An intravenous catheter was considered to be the source of candidaemia when, in the absence of any other clinically apparent focus, any of the following criteria was present: local inflammatory signs or suppuration at the insertion site or a positive culture of the catheter tip where the same *Candida* spp. as that isolated in peripheral blood was grown. From January 2000, the following criterion was included in the definition of a catheter-related bloodstream infection: at least 2 h earlier the same microorganism growth in catheter-drawn as venepuncture-drawn blood culture.[8,9] An abdominal source was defined when candidaemia was simultaneous with peritonitis or with *Candida* spp. isolate in an abdominal drainage. When no focal infection could be demonstrated, the source was categorized as unknown.

Co-morbidity was defined as a disease or therapy that could predispose patients to infection, alter defence mechanisms or cause functional impairment, such as the following: diabetes; liver cirrhosis; renal failure; alcoholism (>100 g of alcohol every day); users of injected drugs; active neoplastic disease; severe chronic obstructive pulmonary disease; severe cardiac disease with symptomatic heart failure; severe dementia; and administration of immunosuppressive drugs (≥20 mg of corticosteroids every day on a regular basis). Prognosis of the underlying

Table 1. Description of *Candida* spp. bloodstream episodes included in the study (1994–2008), *N*=433

	n (%)
Age in years (mean±SD)	57±19
Male gender	219 (51)
Co-morbidity	
haematological cancer	92 (21)
solid organ cancer	92 (21)
diabetes mellitus	61 (14)
IMV	60 (14)
neutropenia	59 (14)
liver cirrhosis	42 (10)
HIV infection	36 (8)
chronic renal insufficiency	28 (6)
SOT	21 (5)
HSCT	20 (5)
Prognosis of underlying disease ultimately or rapidly fatal	244 (56)
Origin of bacteraemia nosocomially acquired[a]	399 (92)
Corticosteroids	128 (30)
Central venous catheterization	289 (67)
Parenteral nutrition	95 (22)
Candidaemia source	
unknown source	237 (55)
catheter-related bloodstream infection	150 (35)
abdominal focus	20 (5)
Shock	70 (16)
Mortality	132 (30)
Candida spp.	
C. albicans	211 (49)
C. parapsilosis	77 (18)
C. tropicalis	62 (14)
C. glabrata	50 (12)
C. krusei	20 (5)
other *Candida* spp.[b]	13 (3)

IMV, invasive mechanical ventilation; SOT, solid organ transplantation; HSCT, haematopoietic stem cell transplantation.
[a]Nosocomially acquired includes healthcare-related infection.
[b]Other *Candida* spp.: *C. lusitaniae*, *n*=5; *C. kefyr*, *n*=3; *C. rugosa*, *n*=2; and *C. guilliermondii*, *n*=3.

disease was classified, according to the criteria of McCabe and Jackson, as rapidly fatal (when death was expected within ≤3 months), ultimately fatal (when death was expected within a period of >3 months but <5 years) and non-fatal (when life expectancy was ≥5 years).[10]

Antifungal treatment, either empirical or definitive (before or after the microbiological results and susceptibilities were known, respectively), was considered appropriate if at least one of the antifungal drugs involved had *in vitro* activity against a *Candida* spp. isolate and the dose and route of administration were adequate. Shock was defined as a systolic pressure of <90 mmHg that was unresponsive to fluid treatment or required vasoactive drug therapy.[7] Death was considered related to the bloodstream infection if it occurred before the resolution of symptoms or signs or within 7 days of the onset of candidaemia, and if there was no other explanation; otherwise, death within 30 days of the onset of candidaemia was considered unrelated to the episode.

Table 2. Univariate and multivariate analysis of factors associated with mortality in candidaemia episodes (period A: 1994–2003)

	Univariate analysis			Multivariate analysis	
	alive *n*=168	dead *n*=94 (36%)	*P*	OR (95% CI)	*P*
Age in years (mean±SD)	53±20	59±19	0.007	1.02 (1.0–1.10)	0.05
Male gender	69 (41%)	39 (42%)	0.5	—	
Co-morbidity					
haematological cancer	42 (25%)	27 (29%)	0.2	—	
solid organ cancer	27 (16%)	19 (20%)	0.2	—	
diabetes mellitus	20 (12%)	14 (15%)	0.3	—	
neutropenia	25 (15%)	18 (19%)	0.2	—	
IMV	10 (6%)	19 (20%)	0.001	—	
liver cirrhosis	10 (6%)	14 (15%)	0.008	3.83 (1.28–11.42)	0.02
HIV infection	13 (8%)	8 (9%)	0.5	—	
chronic renal insufficiency	7 (4%)	8 (9%)	0.04	—	
SOT	10 (6%)	6 (6%)	0.6	—	
HSCT	10 (6%)	6 (6%)	0.5	—	
Prognosis of underlying disease ultimately or rapidly fatal	91 (54%)	68 (72%)	<0.001	3.54 (2.62–5.43)	0.001
Origin of bacteraemia nosocomially acquired[a]	153 (91%)	86 (92%)	0.3	—	
Corticosteroids	50 (30%)	33 (35%)	0.2	—	
Central venous catheterization	79 (47%)	52 (55%)	0.5	—	
Parenteral nutrition	37 (22%)	17 (18%)	0.2	—	
Candidaemia source					
unknown source	89 (53%)	52 (55%)	0.3	—	
catheter-related bloodstream infection	69 (41%)	24 (25%)	0.001	0.30 (0.14–0.63)	0.002
abdominal focus	7 (4%)	9 (10%)	0.03	—	
Shock	12 (7%)	40 (43%)	<0.001	6.11 (2.49–15.0)	<0.001
Candida spp.					
C. albicans	76 (45%)	42 (45%)	0.5	—	
C. parapsilosis	37 (22%)	14 (15%)	0.1	—	
C. tropicalis	27 (16%)	15 (16%)	0.5	—	
C. glabrata	17 (10%)	11 (12%)	0.3	—	
C. krusei	5 (3%)	7 (7%)	0.1	—	
Antifungal definitive therapy					
amphotericin B	48 (28%)	41 (44%)	0.003	—	
fluconazole	110 (65%)	41 (44%)	0.001	0.31 (0.16—0.60)	0.001
fluconazole plus amphotericin B	6 (4%)	3 (3%)	0.3	—	
without antifungal treatment	4 (2%)	9 (10%)	0.2	—	

IMV, invasive mechanical ventilation; SOT, solid organ transplantation; HSCT, haematopoietic stem cell transplantation.
[a]Nosocomially acquired includes healthcare-related infection.

Follow-up

Patients were observed from the diagnosis of candidaemia until 30 days afterwards, until death in hospital or until discharge.

Statistical analysis

Statistical analyses were carried out using the program SPSS (version 14.0; SPSS, Chicago, IL, USA). Continuous variables are expressed as

Table 3. Univariate and multivariate analysis of factors associated with mortality in candidaemia episodes (period B: 2004–2008)

	Univariate analysis			Multivariate analysis	
	alive $n=133$	dead $n=38$ (22%)	P	OR (95% CI)	P
Age in years (mean ± SD)	59 ± 17	70 ± 11	<0.001	1.07 (1.03–1.12)	0.001
Male gender	82 (62%)	29 (76%)	0.07	—	
Co-morbidity					
haematological cancer	23 (17%)	—	—	—	
solid-organ cancer	31 (23%)	15 (40%)	0.04	—	
IMV	18 (14%)	13 (34%)	0.005	—	
diabetes mellitus	18 (14%)	9 (24%)	0.1	—	
neutropenia	15 (11%)	1 (1%)	0.1	—	
liver cirrhosis	12 (9%)	6 (16%)	0.2	—	
HIV infection	13 (10%)	2 (5%)	0.4	—	
chronic renal insufficiency	6 (5%)	7 (18%)	0.01	8.27 (2.17–31.5)	0.002
SOT	5 (4%)	—	—	—	
HSCT	4 (3%)	—	—	—	
Prognosis of underlying disease ultimately or rapidly fatal	59 (44%)	26 (68%)	<0.001	3.74 (2.32–5.89)	0.001
Origin of bacteraemia nosocomially acquired[a]	122 (92%)	38 (100%)	0.1	—	
Corticosteroids	32 (24%)	13 (34%)	0.1	—	
Central venous catheterization	121 (92%)	37 (97%)	0.2	—	
Parenteral nutrition	29 (22%)	12 (32%)	0.2	—	
Candidaemia source					
unknown source	76 (57%)	20 (53%)	0.3	—	
catheter-related bloodstream infection	45 (34%)	12 (32%)	0.5	—	
abdominal focus	1 (1%)	3 (8%)	0.04	—	
Shock	8 (6%)	10 (27%)	0.001	6.54 (2.21–19.4)	0.001
Candida spp.					
C. albicans	69 (52%)	24 (63%)	0.1	—	
C. parapsilosis	24 (18%)	2 (5%)	0.03	—	
C. tropicalis	14 (11%)	6 (16%)	0.3	—	
C. glabrata	16 (12%)	6 (16%)	0.4	—	
C. krusei	8 (6%)	—	—	—	
Antifungal definitive therapy					
amphotericin B[b]	5 (4%)	—	—	—	
triazole	87 (65%)	26 (68%)	0.2	—	
echinocandin	27 (20%)	3 (8%)	0.08	0.41 (0.13–1.12)	0.07
triazole plus echinocandin	9 (7%)	—	—	—	
triazole plus amphotericin B	—	1 (3%)	—	—	
amphotericin B plus echinocandin	2 (2%)	—	—	—	
without antifungal treatment	3 (2%)	8 (21%)	0.1	—	

IMV, invasive mechanical ventilation; SOT, solid organ transplantation; HSCT, haematopoietic stem cell transplantation.
[a]Nosocomially acquired includes healthcare-related infection.
[b]Amphotericin B deoxycholate, $n=2$; amphotericin B lipidic formulation, $n=3$.

mean ± SD or median (range) according to their homogeneity. Categorical variables were compared using the χ^2 test or Fisher's exact test (when necessary). The quantitative variables were compared using the Student–Fisher *t*-test or analysis of variance (ANOVA). Non-parametric tests were used when the application conditions were not applicable. Statistical significance was defined as a two-tailed *P* value <0.05.

Variables with $P \leq 0.2$ in the univariate analysis were further analysed by using a stepwise non-conditional (logistic regression) multivariate analysis to find out the independent factors associated with mortality. For analysis purposes, we considered related and unrelated mortality (within 30 days of bloodstream infection) together and the time of study was divided into two periods according to the introduction of echinocandin in clinical practice (period A, 1994–2003; and period B, 2004–2008).

Results

During the 15 years of study, 433 monomicrobial *Candida* spp. bloodstream infections out of 15628 (3%) positive blood culture episodes were reported. Table 1 shows the epidemiological and clinical characteristics of candidaemia episodes included in the study. Haematological neoplasm and solid organ cancer were the most frequent co-morbidities. There were 399 (92%) cases of nosocomial acquisition. Unknown focus and catheter related were the most frequent candidaemia sources (55% and 35%, respectively). A total of 262 (61%) candidaemia episodes were registered in the first period of study (period A: 1994–2003) whereas 171 (39%) episodes were included in the second period (period B: 2004–2008). Mortality was noted in 132 cases (30%) in the whole series. There were 94 (36%) deaths in period A and 38 (22%) deaths in period B ($P=0.03$). *Candida albicans* was the most frequent species (211; 49% of cases), followed by *Candida parapsilosis* (77; 18%), *Candida tropicalis* (62; 14%), *C. glabrata* (50; 12%), *C. krusei* (20; 5%) and other species (13; 3%).

Table 2 shows univariate and multivariate analysis of factors associated with mortality in period A candidaemia episodes. Age, liver cirrhosis, chronic renal insufficiency, ultimately or rapidly fatal prognosis of underlying disease, abdominal focus, invasive mechanical ventilation (IMV) and shock were associated with mortality in univariate analysis. Thirteen cases (5%) did not receive antifungal therapy. Nine out of these 13 cases died in the first 24 h following candidaemia isolation whereas the remaining 4 patients survived after central venous catheter removal. One hundred and fifty-one (58%) patients received fluconazole as antifungal therapy and 89 (34%) cases were treated with amphotericin B. There were 41 deaths anong the patients treated with fluconazole (27%) and 41 (46%) among the patients treated with amphotericin B ($P=0.003$). In multivariate analysis, independent risk factors associated with mortality in period A were: age, liver cirrhosis, ultimately or rapidly fatal prognosis of underlying disease and shock. Catheter-related bloodstream infection [odds ratio (OR) = 0.30, 95% confidence interval (CI) = 0.14–0.63, $P=0.002$] and the use of fluconazole as definitive antifungal therapy (OR = 0.31, 95% CI = 0.16–0.60, $P=0.001$) were significantly associated with a better outcome.

Table 3 shows univariate and multivariate analysis of factors associated with mortality in period B candidaemia episodes. Age, solid organ cancer, chronic renal insufficiency, ultimately or rapidly fatal prognosis of underlying disease, abdominal focus, IMV and shock were characteristics associated with mortality in univariate analysis. Eleven cases (6%) did not receive antifungal therapy for reasons similar to those previously described (eight patients died 24 h after the candidaemia episode). One hundred and thirteen patients received a triazole (26 dead, 23%), 30 an echinocandin (21 caspofungin, 9 anidulafungin, 3 dead, 10%, $P=0.08$) and 9 (0 dead) were treated with combined therapy (echinocandin and triazole). Table 4 shows the main clinical characteristics of the patients according to therapy

Table 4. Comparison of patients who received monotherapy with triazole or echinocandin

	Monotherapy with triazole $n=113$	Monotherapy with echinocandin $n=30$	*P*
Age in years (mean ± SD)	63 ± 16	56 ± 21	0.2
Male gender	86 (76%)	24 (80%)	0.3
Co-morbidity			
haematological cancer	14 (12%)	8 (27%)	0.1
solid organ cancer	33 (29%)	7 (23%)	0.3
IMV	20 (18%)	6 (20%)	0.5
diabetes mellitus	14 (12%)	6 (20%)	0.2
neutropenia	7 (6%)	5 (17%)	0.1
liver cirrhosis	13 (12%)	1 (3%)	0.3
chronic renal insufficiency	10 (9%)	3 (10%)	0.5
SOT	5 (4%)	—	—
HSCT	—	4 (13%)	—
Prognosis of underlying disease ultimately or rapidly fatal	61 (54%)	14 (47%)	0.2
Origin of bacteraemia nosocomially acquired[a]	110 (97%)	30 (100%)	0.5
Corticosteroids	32 (28%)	6 (20%)	0.3
Candidaemia source			
unknown source	55 (49%)	13 (43%)	0.3
catheter-related bloodstream infection	38 (34%)	8 (27%)	0.2
Shock	8 (7%)	3 (10%)	0.2
Mortality	26 (23%)	3 (10%)	0.08
Candida spp.			
C. albicans	71 (63%)	9 (30%)	0.01
C. parapsilosis	16 (14%)	6 (20%)	0.2
C. tropicalis	13 (12%)	4 (13%)	0.5
C. glabrata	12 (11%)	6 (20%)	0.3
C. krusei	2 (2%)	3 (10%)	0.2

IMV, invasive mechanical ventilation; SOT, solid organ transplantation; HSCT, haematopoietic stem cell transplantation.
[a]Nosocomially acquired includes healthcare-related infection.

Table 5. *Candida* spp. isolates, antifungal treatment and outcome reported in period B

	Fluconazole $n=101$ total/dead (%)	Voriconazole $n=12$ total/dead (%)	Echinocandin $n=30$ total/dead (%)	Triazole + echinocandin $n=9$ total/dead (%)
C. albicans	66/15 (23)	5/1 (20)	9/1 (11)	5/0
C. parapsilosis	13/1 (8)	—	7/1 (14)	1/0
C. tropicalis	13/5 (38)	2/1 (50)	4/0	1/0
C. glabrata	9/2 (22)	3/1 (33)	7/1 (14)	1/0
C. krusei	—	2/0	3/0	1/0

with triazole or echinocandin. In multivariate analysis, independent risk factors associated with mortality in period B were: age, chronic renal insufficiency, an ultimately or rapidly fatal prognosis of underlying disease and shock. Echinocandin use as definitive antifungal monotherapy was associated with a better outcome (OR=0.41, 95% CI=0.13–1.12, $P=0.07$); when echinocandin was used alone or in combined therapeutic regimens the difference was statistically significant (OR=0.22, 95% CI=0.06–0.81, $P=0.02$).

Table 5 shows *Candida* spp. isolates, antifungal treatment and outcome reported in period B.

Discussion

According to our results, the mortality rate of candidaemia episodes has decreased significantly during the study period: from 36% cases in the initial 10 year period to 22% in the last 5 year period. This lower mortality coincides with echinocandin introduction in therapeutics and with decreased use of amphotericin B formulations. In the first time period analysed, the mortality of patients treated with amphotericin B (46%) was higher than the mortality of patients who received fluconazole (27%). This difference was statistically significant in univariate and multivariate analysis. During the second period of study, the mortality of patients treated with a triazole was similar to that in the previous period (23%), whereas the mortality of patients treated with an echinocandin was 10%. Patients receiving echinocandins showed a higher frequency of neutropenia and a lower incidence of *C. albicans* than patients receiving fluconazole. No significant differences were observed in the remaining characteristics of the patients according to therapy. In multivariate analysis, echinocandin use, alone or in combination with a triazole, was an independent factor associated with better outcome. Reboli *et al.*[3] reported that the efficacy of anidulafungin was higher than that of fluconazole in the treatment of invasive candidiasis. It is important to note that the mortality rate reported in the latter study (31.4% in the fluconazole group and 22.8% in the anidulafungin group) was higher than that reported in the present study (23% and 10%, respectively). This discrepancy in mortality rate could be caused by differences in severity of the initial infection or in the characteristics of the patients. Nonetheless, mortality was lower in the group receiving echinocandin treatment in both studies, probably because of its fungicidal and concentration-dependent activity against *Candida* species and its excellent tolerability.[11]

In our study, age, septic shock, liver cirrhosis, ultimately or rapidly fatal prognosis of underlying disease and chronic renal insufficiency were independent risk factors for mortality. Catheter-related candidaemia was associated with a better outcome in the first period of the study. However, this observation was not reproduced in the second period of the study probably because of global reduction of mortality in our series. On the other hand, the number of patients who received an echinocandin was insufficient to analyse efficacy according to different *Candida* species. The mortality of patients with *C. albicans*, *C. tropicalis* or *C. glabrata* infection that received an echinocandin was lower than that observed in cases treated with a triazole. However, 1 patient out of 13 (8%) with *C. parapsilosis* infection treated with fluconazole died compared with 1 out of 7 (14%) treated with an echinocandin.

There are several potential limitations to our study. First, the period of study is 15 years and probably healthcare-related characteristics have changed during the analysed years in addition to the changes in antifungal treatment. However, we divided the study into two periods to carry out a more homogeneous statistical analysis. The second limitation is that antifungal treatment selection was not random as a consequence of design-inherent study characteristics. On the other hand, we do not have data about the initial triazole administration route and its duration, but it was probably parenterally administrated in the majority of cases. The current practice in our hospital is administration of first-line oral triazole only in cases with mild or moderate infection.

In conclusion, the results of the present study showed that patients with candidaemia who were treated with echinocandin have a better outcome than those receiving triazole as monotherapy. These results are coincident with the last Infectious Diseases Society of America (IDSA) guidelines for invasive candidiasis treatment where the Expert Panel favours an echinocandin for patients with moderately severe to severe illness.[5]

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Transparency declarations

Conflicts of interest: none to declare.

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