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Factors Associated with Bacteraemia in Febrile, Granulocytopenic Cancer Patients

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The objective of this investigation was to determine factors predictive of bacteraemia at presentation in febrile, granulocytopenic cancer patients in order to estimate the probability of bacteraemia in each patient, and to compare factors associated with a diagnosis of gram-positive or gram-negative bacteraemia. Retrospective analysis of two sets of data (derivation and validation sets) randomly obtained from a large prospective study was conducted in a multicentre study of febrile, granulocytopenic cancer patients admitted for empiric antibacterial therapy. Within the derivation set, prognostic factors (clinical and laboratory data) likely to be associated with a generic diagnosis of bacteraemia and with a specific diagnosis of gram-positive or gram-negative bacteraemia were analysed by means of three backward, stepwise, logistic regression analyses. The predictive probability of bacteraemia was calculated using the logistic equation. The discriminating ability of the model in predicting bacteraemia was evaluated in the derivation and validation sets using receiver-operating characteristic curves. The predictive probability of gram-positive or gram-negative bacteraemia was not calculated. In the derivation set, 157 of 558 episodes (28%) were microbiologically documented bacteraemias. Predicting factors were antifungal prophylaxis, duration of granulocytopenia before fever, platelet count, highest fever, shock and presence and location of initial signs of infection. The variables institution, antibacterial prophylaxis and underlying disease showed borderline associations with bacteraemia. Shock was associated with gram-negative bacteraemia, while signs of infection at catheter site were predictive of gram-positive bacteraemia. Quinolone prophylaxis was negatively associated with gram-negative bacteraemia. When tested in the validation set, the model was poorly predictive, although a small subgroup of episodes (representing only 16% of the total sample size) with low risk of bacteraemia was identified. Factors predictive of bacteraemia can be identified, with discrimination between gram-positive and gram-negative aetiology. Further studies are warranted in order to improve the discriminant ability of the model.
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INTRODUCTION

CLASSICAL TEACHING in infectious disease classifies febrile episodes in granulocytopenic cancer patients according to the presence or absence of a microbiological documentation of infection, and according to any identified site. When granulocytopenic patients become febrile and receive empirical antimicrobial therapy, a microbiological cause for the febrile episode can be demonstrated in only about 30–40% of patients, the majority of whom will have bacteraemia [1–3]. The identification of factors predictive of a specific diagnosis or infection aetiology at initial presentation and the derivation of prediction rules might improve our understanding of this clinical situation, as well as assisting physicians in individualising treatment, deciding whether inpatient or outpatient care is needed, stratifying patients in clinical trials and evaluating the results of therapeutic studies. Using univariate and multivariate methods, we have analysed data prospectively collected at presentation from a large number of episodes of fever and suspected infection in granulocytopenic cancer patients. Our aims were: (1) the identification of possible associations between information available at initial presentation and a subsequent diagnosis of bacteraemia. (2) The derivation of an algorithm based on these data in order to provide an estimate of the probability of bacteraemia. (3) The identification of factors associated specifically with a diagnosis of gram-positive or gram-negative bacteraemia.

PATIENTS AND METHODS

Patients

Demographic information and data on history, symptoms, signs and laboratory tests available at the onset of fever were collected prospectively from febrile and granulocytopenic cancer patients entered in the fifth trial of empirical antibiotic therapy performed by the International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organisation for Research and Treatment of Cancer (EORTC) and by the Clinical Trial Group of the National Cancer Institute of Canada from 1986 to 1988. In this trial, patients were randomised to receive a combination of ceftazidime and amikacin either with or without

vancomycin. The results of this trial have already been published [4].

Methodology and definitions used in studies performed by the IATCG of the EORTC have been reported elsewhere [2–8]. At the presentation of fever, defined as a single axillary temperature higher than 38.5°C or higher than 38°C in three instances over a 12-h period, patients undergo comprehensive clinical and laboratory evaluations, including chest X-ray, cultures of blood, urine and any other material from clinically relevant sites, and are then randomised for empirical treatment. In the time frame from development of fever to initiation of empiric therapy, at least two blood cultures are recommended, as well as cultures from any clinically relevant site. Each febrile episode is subsequently classified as bacteraemia, microbiologically documented bacterial, viral or fungal infection, mixed infection (i.e. infections with bacterial and non-bacterial pathogens), clinically documented infection, possible infection and non-infectious fever. Episodes of fungaemia are classified among fungal infections. Bacteraemia is defined as the presence of clinical signs and symptoms of infection together with the isolation of a bacterial pathogen from blood. For an episode to be ascribed to coagulase-negative staphylococci, corynebacteria other than the JK group, or other common skin contaminants, at least two sets of positive blood cultures are required, unless the same organism is concomitantly isolated from another infected site. Shock is defined as a systolic blood pressure lower than 90 mmHg (lower than 60 mmHg in children) or a decrease of more than 50 mmHg in a hypertensive patient. Neutropenia is defined as an absolute granulocyte count below 1×10^9/l. All case reports are reviewed by the Data Review Committee of the group, in order to provide uniformity in case evaluation and definition.

For the purpose of the present analysis, all 84 randomised episodes were evaluated, including documented viral or fungal infections, mixed infections and fevers not due to infection, which were originally considered as non-evaluable for the assessment of response to treatment [4]. However, 57 episodes were excluded because of missing data on the duration of granulocytopenia before fever. The remaining 834 episodes of fever developing in 771 patients were divided into two groups, using a computer-generated random procedure. The first group of 558 episodes (67%) was used to derive the multivariate model and to evaluate factors associated either with a diagnosis of gram-positive or of gram-negative bacteraemia (derivation set). The second group of 276 episodes (33%) was used to assess the discriminating ability of the model (validation set). The febrile episode is the unit of analysis of this study and the term "patient" refers to a patient during a single febrile episode.

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Statistical methods

Probability of bacteraemia. In the derivation set, baseline characteristics of patients with a final diagnosis of bacteraemia (either single agent or polymicrobial) were first compared with those of all other patients (including those with microbiologically documented bacterial infections without bacteraemia, viral, fungal and mixed infections, clinically documented infections, possible infections and non-infectious fevers) using the standard χ^2 test for heterogeneity or, when appropriate, the Fisher's exact test or the χ^2 test for trend.

Characteristics evaluated for association with a diagnosis of bacteraemia were sex, age, presence (and type) of an intravenous line at the onset of fever, underlying disease, number of patients randomised by each institution (reflecting the "size" of the institution, since larger institutions are used to enrolling more patients than smaller institutions), administration of antifungal and antibacterial prophylaxis, duration of granulocytopenia before fever, initial granulocyte and platelet counts, highest temperature before inclusion in the study during the last 12 h, presence of shock and, finally, presence and location of an identifiable site of infection at presentation. As shown in Table 1, continuous variables (age, duration of granulocytopenia before fever, granulocyte and platelet counts, highest temperature before inclusion in the study, number of patients randomised by each institution) were categorised according to standard clinical criteria and to the results of previous analyses from our group [2,9,10] and coded as 0,1,2..., etc. These transformed variables were used in all statistical analysis as ordinal variables.

The probability of bacteraemia was then modelled as a function of the abovementioned characteristics using a multivariate logistic regression analysis [11,12]. Starting from the full model with all variables included, non-significant variables were progressively deleted with a step-down procedure based on a likelihood ratio test. Since the aim of this analysis was model building, rather than formal statistical significance testing, relaxed removal and re-entry criteria were used in the step-down procedure ($P>0.15$ and $P\leq 0.10$, respectively). As a measure of the strength of the association between each variable retained in the final model and the probability of bacteraemia, the odds ratio (OR) value, i.e. the anti-logarithm of the regression coefficient, was computed [11,12]. The 95% confidence interval was calculated for each OR [13].

All variables included in the univariate analysis were initially included in the multivariate model. For continuous variables, transformed into ordinal ones, the coded values were used and for each a single coefficient was estimated. This represents the average change in the logarithm of the odds of a diagnosis of bacteraemia associated with moving from one level of the variable to the adjacent one. The coefficients (and the OR) reported in the tables were computed using this average estimate multiplied by the coded value of the transformed variable.

The influence of the participating institution was evaluated according to the number of patients included in the study (institutions including less than 30 patients, from 30 to 90 and more than 90). All other variables were nominal variables, including antibacterial prophylaxis (three levels), antifungal prophylaxis (yes/no), presence and type of intravenous line (three levels), underlying disease (five levels), and presence and location of signs of infections at presentation (six levels). For each nominal variable, $n-1$ coefficients were estimated (where n represents the number of levels for that variable), and the association with the outcome was assessed by means of a χ^2 test with $n-1$ degrees of freedom.

Table 1. *Characteristics of episodes in derivation and validation sets (numbers are percentages)*

	Derivation set (n = 558) %	Validation set (n = 276) %
Institution (number of patients enrolled)		
<30	31	31
30–90	34	35
≥91	35	34
Sex		
Males	63	60
Females	37	40
Age (years)		
≤14	19	18
15–30	23	20
≥31	58	62
Underlying disease		
Acute non-lymphoblastic leukaemia	57	47
Acute lymphoblastic leukaemia	18	24
Lymphoma	5	9
Solid tumour	5	6
Bone marrow transplantation (autologous or allogeneic)	20	14
Presence of an intravenous line at enrollment		
No line	27	28
Peripheral line	18	18
Central line	55	54
Antibacterial prophylaxis		
No prophylaxis	46	49
Intestinal decontamination	36	30
Quinolones	18	21
Antifungal prophylaxis		
No prophylaxis	43	44
Non-absorbable antifungals	57	56
Duration of granulocytopenia before enrollment (days)		
0	11	8
1–5	46	51
6–15	33	33
≥16	10	8
Granulocyte count (cells × 10⁹/l) at enrollment		
<0.1	66	71
0.1–0.499	21	19
≥0.5	13	10
Platelet count (cells × 10⁹/l) at enrollment		
<10	18	16
10–49	55	53
≥50	27	31
Highest temperature (°C) before enrollment		
38–38.9	60	61
39–39.9	35	33
≥40	5	6
Shock at enrollment		
No	98	99
Yes	2	1
Site of infection at enrollment		
No site detectable	59	60
Upper respiratory tract	16	18
Lung	10	11
Gut	3	2
Intravenous line	4	4
Other sites	8	5
Final diagnosis of episodes		
Bacteraemia	28	32
Other bacterial factors	5	4
Clinically documented infections	21	20
Possible infections	41	37
Fungal infections	3	1
Viral infections	2	1
Mixed infections	0.4	1

Model fitting. The results of the multivariate analysis in the derivation set were used to develop a clinical prediction model [14]. The probability of bacteraemia was estimated by computing the actual value of the logistic function for each case (bacteraemia) and control (other diagnoses) as $P=1/[1+\exp(b'x')]$ where $b'x'=(b_0+b_1x_1+b_2x_2+\ldots+b_mx_m)$, $x'=(x_1, x_2 \ldots x_m)$ is the vector of the observed covariates for each individual and $b'=(b_1, b_2 \ldots b_m)$ is the vector of the regression coefficients estimated from the data set. The accuracy of the logistic model in discriminating patients with and without a diagnosis of bacteraemia was evaluated both in the derivation and in the validation sets using a receiver-operating characteristic (ROC) curve. Sensitivity and specificity were computed using different levels of predicted risk as cut-off [15].

Aetiology of bacteraemia

In order to understand if variables predicting diagnosis of bacteraemia were distributed differently in the subgroups of patients with gram-positive and gram-negative bacteraemias, two additional multivariate analyses were performed in the derivation set, using the same variables as before. Patients with either gram-negative or gram-positive bacteraemias (excluding polymicrobial infections) were compared with all other patients. Since the purpose of this second analysis was not to build a predictive model, but simply to suggest associations and correlations, no validation was performed.

RESULTS

Characteristics of patients

The derivation and validation sets included 558 and 276 episodes of fever and neutropenia, respectively. Table 1 shows the distribution of patients for each variable included in the derivation and validation sets. The two groups were comparable for all the variables evaluated. The median age of the patients was 38 and 37 years, respectively, ranging from 1 to 88 years in the derivation set and from 1 to 74 years in the validation set. Of the 558 episodes included in the derivation set, 157 (28%) had bacteraemia (87 due to gram-positive cocci, 50 to gram-negative rods and 20 polymicrobial in origin), 27 (5%) had microbiologically documented bacterial infections without bacteraemia, 14

(3%) had fungal infections, 10 (2%) had viral infections, two had mixed infections, 119 (21%) had clinically documented infections and 229 (41%) had possible infections. Of the 276 episodes in the validation set, 88 (32%) had bacteraemia (49 gram-positive, 30 gram-negative and nine polymicrobial), 12 (4%) had microbiologically documented bacterial infections without bacteraemia, 14 (5%) had fungal infections, four (1%) had viral infections, three (1%) had mixed infections, 54 (20%) had clinically documented infections and 101 (37%) had possible infections.

Table 2. Incidence of bacteraemia in study episodes according to each level of the evaluated variables with univariate P *values (numbers in parentheses are percentages)*

Variable	No. of episodes (n = 558)	No. with bacteraemia (n = 157)	
Institution (number of patients enrolled)			
<30	172	47 (27)	
30–90	190	42 (22)	$P = 0.09$*
≥91	196	68 (35)	
Patient's age (years)			
≤14	103	24 (23)	
15–30	130	41 (32)	$P = 0.50$*
≥31	325	92 (28)	
Sex			
Male	352	97 (28)	$P = 0.69$†
Female	206	60 (29)	
Underlying disease			
Acute non-lymphoblastic leukaemia	321	89 (28)	
Acute lymphoblastic leukaemia	99	31 (31)	
Lymphoma	27	5 (18)	$P = 0.99$†
Solid tumour	28	9 (32)	
Bone marrow transplantation (autologous or allogeneic)	83	23 (28)	
Antibacterial prophylaxis			
No prophylaxis	257	69 (27)	
Intestinal decontamination	201	56 (28)	$P = 0.37$†
Quinolones	100	32 (32)	
Antifungal prophylaxis			
No prophylaxis	238	50 (21)	$P = 0.001$†
Non-absorbable antifungals	320	107 (33)	
Presence of an intravenous line at enrollment			
No line	150	36 (24)	
Peripheral line	99	28 (28)	$P = 0.18$†
Central line	309	93 (30)	
Granulocyte count at enrollment (cells × 10⁹/l)			
<0.1	369	118 (32)	
0.1–0.499	119	27 (23)	$P = 0.003$*
0.5–1	70	12 (17)	
Duration of granulocytopenia before enrollment (days)			
0	59	11 (19)	
1–5	258	67 (26)	$P = 0.01$*
6–15	187	59 (32)	
≥16	54	20 (37)	
Platelet count at enrollment (elements × 10⁹/l)			
<10	101	44 (44)	
10–49	309	89 (29)	$P < 0.001$*
≥50	148	24 (16)	
Highest temperature before enrollment			
38–38.9 °C	334	75 (22)	
39–39.9 °C	194	69 (36)	$P<0.001$*
>40°C	30	13 (43)	
Presence of shock at enrollment			
No	548	149 (27)	$P < 0.001$†
Yes	10	8 (80)	
Site of infection at enrollment			
No site detectable	330	91 (28)	
Upper respiratory tract	92	24 (26)	
Lung	53	10 (19)	$P = 0.21$†
Gut	17	8 (47)	
Intravenous line	20	10 (50)	
Other sites	46	14 (30)	

*χ^2 test for trend. †χ^2 test for heterogeneity.

Factors predicting bacteremia

Table 2 reports the results of the univariate analysis. Variables significantly associated with bacteraemia included antifungal prophylaxis (P=0.001), granulocyte and platelet counts at inclusion (P=0.003 and P<0.001, respectively), duration of granulocytopenia before enrolment (P=0.01), highest temperature before inclusion (P<0.001) and presence of shock (P<0.001). In the multivariate analysis (Table 3), diagnosis of bacteraemia was significantly associated with antifungal prophylaxis (P<0.001), duration of granulocytopenia before fever (P=0.001), platelet count (P<0.001), highest fever before inclusion (P<0.001), shock (P<0.001) and presence and location of signs of infection at presentation (P=0.04). Three other variables (institution, antibacterial prophylaxis and underlying disease) were not removed from the logistic model because of associations with borderline significance. Age, sex, intravenous line and granulocyte count at inclusion in the study were removed from the model as of no relevance for bacteraemia. In comparison with patients without any detectable site of infection at presentation, patients with signs of catheter site and gut infection had a higher risk of being bacteraemic (OR = 3.32 and 3.25, respectively). Similarly, presence of shock was associated with an OR of 13.7. Antibacterial prophylaxis by itself was a relatively weak predictor of bacteraemia (P=0.08). However, the probability of bacteraemia was reduced in patients receiving a quinolone (OR=0.47) or treated with non-absorbable antibiotics (OR=0.72) in comparison with those not receiving any antibacterial prophylaxis.

Discriminating value of the logistic model

The overall performance of the algorithm was calculated both in the derivation and in the validation sets. In the two ROC curves shown in Figure 1, the cumulative proportion of episodes with bacteraemia who were correctly classified by the model in the two sets of data is plotted against the cumulative proportion of episodes without bacteraemia mistakenly classified by the model, for decreasing values of predicted probability. By plot-

Table 3. Multivariate predictors of bacteraemia, logistic coefficients, odds ratios, 95% CI, P values and degrees of freedom

Variable	Coefficient	Odds ratio	95% CI	*P* value	Degrees of freedom
Institution (number of patients enrolled)				0.12	2
<30	0	1 (ref)			
30–90	−0.31	0.73	0.42–1.27		
≥91	0.29	1.34	0.74–2.42		
Underlying disease				0.14	4
Acute non-lymphoblastic leukaemia	0	1 (ref)			
Acute lymphoblastic leukaemia	0.34	1.40	0.81–2.42		
Lymphoma	−0.29	0.74	0.25–2.25		
Solid tumour	0.96	2.62	1.03–6.70		
Bone marrow transplantation (autologous or allogenic)	0.50	1.65	0.89–3.08		
Antibacterial prophylaxis				0.08	2
No prophylaxis	0	1 (ref)			
Intestinal decontamination	−0.32	0.72	0.44–1.20		
Quinolones	−0.74	0.47	0.25–0.92		
Antifungal prophylaxis				<0.001	1
No prophylaxis	0	1 (ref)			
Non-absorbable antifungals	0.91	2.48	1.49–4.13		
Duration of granulocytopenia before enrollment (days)				0.001	1
0	0	1 (ref)			
1–5	0.42	1.53	1.17–1.99		
6–15	1.26	3.53	3.06–4.06		
≥16	1.68	5.37	4.66–6.17		
Platelet count at enrollment (elements × 10⁹/l)				<0.001	1
<10	0	1 (ref)			
10–49	−0.65	0.51	0.38–0.72		
≥50	−1.95	0.14	0.12–0.17		
Highest temperature before enrollment				<0.001	1
38–38.9°C	0	1 (ref)			
39–39.9°C	0.71	2.04	1.45–2.88		
≥40°C	2.13	8.41	7.03–10.07		
Presence of shock at enrollment				<0.001	1
No	0	1 (ref)			
Yes	2.61	13.66	2.49–75.28		
Site of infection				0.036	5
No site detectable	0	1 (ref)			
Upper respiratory tract	0.05	1.05	0.96–3.13		
Lung	−0.45	0.63	0.28–1.44		
Gut	1.18	3.25	1.10–9.65		
Intravenous line	1.20	3.32	1.21–9.08		
Other sites	0.24	1.26	0.61–2.65		
Likelihood of the model					
	Log likelihood = −287.438				
	Goodness of fit = χ^2 6.15, DF 8, P = 0.63 (Hosmer-Lemeshow)				
	Goodness of fit = χ^2 0.14, DF 2, P = 0.93 (C.C. Brown)				

P values for duration of granulocytopenia, platelet count and highest temperature are calculated with 1 degree of freedom (χ^2 for trend). ref. = reference value.

ting the true positive rate against the false positive rate, this curve defines the performance of the model independently of the threshold that is used: the further to the left and upward the curve, the better the model. The discriminating power of the model was unsatisfying, since in the validation set appreciable numbers of episodes were misclassified at various thresholds. The model proved to be reliable only in identifying a small subgroup of patients at low risk of bacteraemia, with a negative predictive value of 90% at a 10% threshold. Unfortunately, this prediction was possible in only 43 out of 276 episodes (16%).

gram-positive versus gram-negative bacteraemia

With the aim of generating hypotheses and of suggesting trends, we analysed which factors were associated with a diagnosis of gram-positive or of gram-negative bacteraemia. The results of this analysis are shown in Table 4. Antifungal prophylaxis, platelet count and high fever were associated with both gram-positive and gram-negative bacteraemias, while age, sex, institution, presence of an intravenous line, underlying disease and granulocyte count at onset were removed from both models. Shock was a strong predictor of gram-negative, but not of

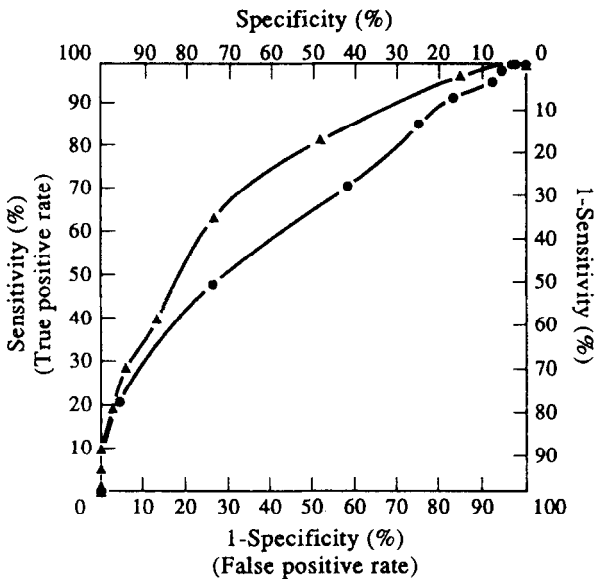

Fig. 1. Receiver operating characteristic (ROC) curve for the algorithm in the derivation (black triangle) and in the validation (black circle) sets. The cumulative proportion of patients with bacteraemia who were correctly classified by the model is plotted against the cumulative proportion of patients without bacteraemia mistakenly classified by the model, for decreasing values of predicted probability.

gram-positive bacteraemia. Duration of granulocytopenia before enrolment and presence of an identifiable site of infection, especially at the intravenous line, were associated only with gram-positive bacteraemias. Antibacterial prophylaxis seemed to be relevant only in patients with gram-negative bacteraemia, in whom the quinolones significantly reduced the predictive risk (OR=0.30).

DISCUSSION

Granulocytopenia is generally recognised to be the major factor predisposing cancer patients to infection, especially bacteraemia. Trials performed by the IATCG of the EORTC have identified additional factors, such as shock, temperature higher than 40°C and thrombocytopenia ($<1 \times 10^9$ platelets/cm^3) as significant univariate variables associated with a diagnosis of gram-negative bacteraemia [2–6]. Given the poor outcome of bacteraemia in cancer patients with fever and granulocytopenia, and the delay between onset of fever and reporting of culture results, it is common practice to start intensive antibacterial treatment in all febrile and granulocytopenic cancer patients, on the assumption that all these patients are potentially bacteraemic or at risk of developing life-threatening infections. However, patients with cancer, granulocytopenia and fever do not represent a homogeneous group, and both the clinical course and the diagnosis of febrile episodes vary considerably. The problem remains of how to identify the subgroups of patients at different risk, on a scientific rather than an empirical basis.

As recently reviewed [16], some authors have already tried to deal with this subject, focusing on attempts to identify patients at low risk of medical complications, likely to deserve short-term or out-patient antibacterial therapy and early discharge from hospital. With this in mind, Talcott and coworkers [17] analysed data available within the first 24 h in patients with fever and granulocytopenia, in order to identify patients at lower risk of unfavourable course and, therefore, most likely to benefit from early discharge and outpatient care. In these analyses, the dependent variable was defined as the development of severe medical complications, including infection. A long list of such complications was provided. Judgements were based on a prospective evaluation partially combined with a blind review performed by an independent physician. Patient's risks of developing complications were classified according to control of cancer, presence of comorbidity factors and type of care (outpatient or inpatient). The results were validated in an independent set of data but sensitivity and specificity of the model (discriminant capacity) were not calculated [18]. Another approach has been to evaluate early signs of haematological recovery as predictors of a favourable outcome in febrile and granulocytopenic children with cancer. The appearance of monocytosis seemed to correlate well with favourable patient outcome and these patients underwent safe, early discharge [19]. Finally, in a pragmatic, randomised study, outpatient treatment was shown to be as safe as the traditional inhospital approach, in a selected group of febrile and neutropenic cancer patients, staying in a range of 30 miles from the cancer centre and free of any type of comorbidity. However, in this study, the choice of the patient to be given outpatient care was not based on any risk assessment or result of clinical prediction rule [20]. In all studies, the cost-effectiveness of the approach appeared evident.

In the present analysis, we have chosen to focus on a simpler, more objective dependent variable, a diagnosis of bacteraemia, making the assumption that bacteraemia carries an increased risk of unfavourable outcome. This assumption may not be completely true, because some studies have found that bacteraemic patients are more likely to respond to antibacterial therapy than are other infections, especially pneumonias [21,22]. However, bacteraemia is known to be associated with some incremental risk of complication and clinical deterioration [2–8,23–25]. In addition, comparative clinical trials of empiric therapy usually base their conclusions on data stemming from the subgroup of bacteraemic patients, since the response to empiric antimicrobial therapy is usually similarly good in the other febrile and neutropenic patients. The aim of the present study was to create a clinical prediction rule for diagnosis of bacteraemia and to identify factors more predictive of a specific diagnosis of gram-positive or gram-negative bacteraemia. Shock, very high fever, presence and location of signs of infection, long-lasting granulocytopenia, thrombocytopenia and administration of antifungal prophylaxis were predictive of bacteraemia in our patient population. Weaker predictive factors included the institution where the patient was treated, the underlying disease and the administration of antibacterial prophylaxis. Age, sex, intravenous line and granulocyte count at onset were not associated with diagnosis of bacteraemia. Presence of shock and lack of antibacterial prophylaxis were associated with gram-negative bacteraemia, while signs of intravenous catheter site infection were suggestive of gram-positive bacteraemia. Interestingly, some variables not associated with bacteraemia in the univariate analysis (institution, underlying disease, antibacterial prophylaxis and presence and location of an initial site of infection), showed a statistically significant correlation with bacteraemia in the multivariate analysis, thus emphasising the relevance of this methodological approach. Likewise, granulocyte count at inclusion in the study, which was significantly associated with bacteraemia in the univariate analysis, was removed from the multivariate model. Interestingly, the duration of granulocytopenia before the development of fever was more important that the granulocyte count at the onset of fever in predicting a diagnosis of bacteraemia. Both factors, however, carry the

Table 4. Comparison of multivariate predictors of single-agent gram-positive and gram-negative bacteraemia (variables not included in the table were removed from both models)

	Gram-positive bacteraemias (n = 87)			Gram-negative bacteraemias (n = 50)		
Variables	P value	OR	95% CI	P value	OR	95% CI
Antibacterial prophylaxis		Removed		0.06		
No prophylaxis					1 (ref.)	
Intestinal decontamination					0.71	0.35–1.43
Quinolones					0.30	0.11–0.86
Antifungal prophylaxis	0.004			0.11		
No prophylaxis		1 (ref.)		1 (ref.)		
Non-absorbable antifungals		2.09	1.24–3.51		1.71	0.86–3.40
Duration of granulocytopenia before enrollment (days)	0.12				Removed	
0		1 (ref.)				
1–5		1.25	0.94–1.69			
6–15		1.93	1.67–2.25			
≥16		2.41	2.08–2.80			
Platelet count at enrollment (elements × 10^9/l)	0.03			<0.001		
<10		1 (ref.)			1 (ref.)	
10–49		0.72	0.50–1.04		0.35	0.22–0.58
≥50		0.37	0.32–0.43		0.05	0.03–0.06
Highest temperature before enrollment	0.14			0.001		
38–38.9°C		1 (ref.)			1 (ref.)	
39–39.9°C		1.33	0.91–1.97		2.21	1.38–3.56
≥40°C		2.39	1.95–2.92		10.7	8.41–13.6
Presence of shock at enrollment		Removed		0.02		
No					1 (ref.)	
Yes					6.05	1.48–24.77
Site of infection	0.14				Removed	
No site detectable		1 (ref.)				
Upper respiratory tract		1.48	0.80–2.75			
Lung		0.87	0.34–2.20			
Gut		2.01	0.61–6.59			
Intravenous line		3.43	1.26–9.41			
Other sites		0.74	0.27–2.00			

*P values for duration of granulocytopenia, platelet count and highest temperature are calculated with 1 degree of freedom (χ^2 for trend). ref. = reference value.

message of the crucial role of bone marrow failure. Another sign of bone marrow failure is represented by thrombocytopenia. That this factor might play a role in the development of bacteraemia was already suggested in the past, with the possible explanation that an effective platelet function might be important in maintaining the integrity of the mucosal barriers [2].

The clinical prediction rule derived from our data discriminates poorly episodes with bacteraemia from other episodes. At best, it allows a reliable prediction for a small subgroup of patients at lower risk. In order to improve the discriminant ability of the model we explored other possibilities, such as adding interaction terms, fitting a model with continuous variables retaining their original values and introducing quadratic terms and interaction terms. Unfortunately, not one of these approaches produced an improvement in the validation set. This might be because other factors influencing the probability of bacteraemia in neutropenic cancer patients were not recorded in our case report form. For example, the information provided by the variable "underlying disease" might be of little value if not accompanied by information about the stage and status of the disease. Conversely, since our definition of bacteraemia is based on a laboratory parameter, i.e. isolation of bacteria in blood culture, some patients classified as having non-bacteraemic infections, clinically documented or possible infections, might have had occult bacteraemia not detected by standard microbiological methods. Microbiological skills or technical facilities may vary among centres and this might explain the effect of the "institution" variable on the prediction of bacteraemia.

The present study provides some additional insight on the management of infection in neutropenic cancer patients. For example, systemic antibacterial prophylaxis with the new fluoroquinolone antibiotics is currently controversial. Some authors have reported positive results [25–30], but a meeting of the International Immunocompromised Host Society was unable to reach a consensus on the need for, or optimal use of, antimicrobial prophylaxis. The multivariate analysis showed the predictive risk of bacteraemia to be lower in patients receiving oral non-absorbable antibiotics and even lower in those receiving a fluoroquinolone. This reduction was seen only for gram-negative bacteraemia, while the risk of gram-positive bacteraemia appeared not to be affected by prophylaxis. These findings are compatible with reports of prophylactic fluoroquinolones

reducing gram-negative bacteraemias, with an accompanying increase in streptococcal bacteraemias [25–30]. However, no definitive conclusion regarding fluoroquinolone prophylaxis should be drawn from our data, because they are not derived from a randomised prophylactic trial, and because the effect of antibacterial prophylaxis might be due to a reduction in bacteraemia documentation, rather than true prevention. Nevertheless, these results demonstrate the need for a large, multicentre, randomised, placebo-controlled clinical trial of prophylaxis with fluoroquinolones. Antifungal prophylaxis, almost exclusively with non-absorbable polyenes, was also a factor predicting bacteraemia. Other studies have shown some association between antifungal prophylaxis and bacterial infections [7,30], but we are unable to provide a convincing explanation for this association, which might not be necessarily causal.

Although other medical complications can jeopardise the outcome of fever and infection in granulocytopenic cancer patients, the development of a risk profile for occurrence and aetiology of bacteraemia would provide useful information in the management of this patient population. Unfortunately, the present study does not allow a completely reliable prediction, since it detects only a small subgroup of patients at low risk of being bacteraemic. Further studies are needed to refine the effort of scientifically predicting diagnosis of febrile episodes in neutropenic and febrile cancer patients. Additional variables, including types of antineoplastic treatments and status of the underlying disease, should be studied, with twin aims of improving our understanding of infectious complications in cancer patients and of rationalising patient's care.

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