Risk factors for Gram-negative bacterial infections in febrile neutropenia

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Background and Objectives. The objective of this study was to evaluate the risk of Gram-negative bacterial infections in febrile neutropenic patients and to develop a specific risk score.

Design and Methods. This prospective study included 513 consecutive febrile neutropenic, evaluable patients. Forty-five per cent of the patients were receiving prophylactic gut decontamination, and 6% were receiving prophylactic quinolones at the onset of febrile neutropenia. Data were collected from the onset of febrile neutropenia until 30 days later. Risk factors for Gram-negative bacterial infection were identified by comparing baseline characteristics of patients with and without Gram-negative bacterial infection. Independent risk factors in multivariate analysis were used to build a predictive score for Gram-negative bacterial infection.

Results. The prevalence of Gram-negative bacterial infection was 55/513 (10.7%). Gram-negative bacterial infections were due to *E. coli* in 30 patients, other enterobacteriae in 11, *Pseudomonas spp.* in 13, and *Salmonella spp*. in one. In multivariate analysis, the occurrence of Gram-negative bacterial infection was significantly associated with age > 45 years (p=0.009), recent administration of betalactams (p=0.04), chills (p=0.0001), urinary symptoms (p=0.01), and absence of gut decontamination with both colimycin and aminoglycosides (p=0.001). The relative risk for Gram-negative bacterial infection was 4.4, 12.6, 25.4 and 100 in the presence of 1, 2, 3 , or at least 4 parameters, respectively. The performances of our scoring system and the post-test probabilities according to different prevalence rates of Gram-negative bacterial infection (0.05, 0.10, 0.20) lead us to propose a Gram-negative risk score of ≥3 as indicating a high probability of Gram-negative bacterial infection.

Interpretation and Conclusions. Our scoring system identifies patients with a high probability of Gram-negative bacterial infection as those with a score ≥3. If confirmed in a validation set, this score could be considered in the choice of the first-line antibiotics in febrile neutropenic patients.

Key words: febrile neutropenia, Gram-negative infections, prevalence rate, risk factors.

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Gram-negative bacterial infections represent one third of the microbiologically documented infections in most febrile series of neutropenic patients.[1-5] The overall mortality of these infected patients varies between 10%[2,3] and up to 50% in high-risk populations,[6] or when the etiological agent is *P. aeruginosa*.[7,8] Because the prognosis of Gram-negative bacterial infections in neutropenic patients has been shown to be influenced by the adequacy of antibiotic therapy and the strain's susceptibility to the antibiotics, it is recommended that Gram-negative bacteria are treated with first-line antibiotic therapy.[2,6,9-12] On the other hand, large consumption of antibiotics is the main source of bacterial resistance in hospitals.[13,14] As the number of new antibiotics available in the next decade will be limited, we need to develop strategies which benefit the individual while concomitantly preserving the ecology of the community. In neutropenic patients, as in other high-risk populations, we need to find key parameters to improve our antibiotic choices at the bedside, in order to achieve the best balance between optimal individual treatment and lowest risk of an increase in resistant organisms.[15] Beta-lactams do not all have equal activities against bacteria isolated from neutropenic patients.[2,15] They also have different costs, and probably different selection pressures.[14] If we had clinical or biological parameters that could anticipate the results of blood cultures with a good probability, we could improve the choice of first-line antibiotic empirical therapy in febrile neutropenia. We recently proposed a score, based on clinical parameters available at the onset of febrile neutropenia in hematology patients, to

predict the risk of staphylococcal and streptococcal infection.[16] The objective of the present study was to evaluate the risk of Gram-negative bacterial infection, in the same cohort of patients, and to develop a specific risk index for Gram-negative infections.

Design and Methods

Patients

All consecutive patients with a first episode of fever during neutropenia were prospectively enrolled at 36 French hematology centers over a two-month period. Fever was defined as a temperature ≥38°C once, or ≥38°C twice within 8 hours. Neutropenia was defined as a granulocyte count <500/mL, or expected to fall below 500 within the 48 hours following inclusion. Patients could be included only once. All patients had at least two aerobic and anaerobic blood cultures before receiving antibiotics.

Of the 532 enrolled patients, 14 did not meet the inclusion criteria, and data were missing for five. Of the remaining 513 patients (291 males and 222 females; mean age 40.8 years ± 21.7 SD), 92 (18%) were children (< 15 years). The number of patients included per center varied between 1 and 48 (median: 11). In accordance with international guidelines for first line treatment,[14] 91% of the patients received betalactam regimens, 66% received aminoglycosides – always in combination with betalactams - and 31% received glycopeptides, usually vancomycin.

Data collection

Data collected at enrollment included diagnosis and status, cause of neutropenia (spontaneous or chemotherapy-induced, with or without stem cell transplantation), chemotherapy received in the month prior to enrollment, anti-infective drugs, antiulcer and antacid drugs, taken within the last 7 days, location during the previous week (laminar air flow room, single room, ≥ 2-bed room, or outpatient), and site of the intravenous line (none, central or peripheral).[16] Clinical data included presence of an infective focus and organ failure. On day 30, the patient's clinical status was recorded or the cause of death was determined by the local investigator and reviewed by two of the three principal investigators (CC, AB or GL).

Classification of patients and definitions

Patients were classified as having fever of unknown origin (FUO), clinically documented infection (CDI), or microbiologically documented infection (MDI), according to the definitions of the Immunocompromised Host Society.[10]

Statistical methods

The prevalence rate of Gram-negative bacterial infection was computed using the total number of included patients as the denominator; 95% confidence intervals (95%CI) were also calculated. In order to identify risk factors for the Gram-negative bacterial infections, the baseline characteristics of patients with such infections, including those with concomitant Gram-positive infections, were compared to those without Gram-negative bacterial infections. Odds ratios with 95% CI were calculated separately for each parameter using unconditional logistic regression models. Age was included in all of the models. Variables with a p value ≤0.15 in univariate analysis were then entered into multivariate logistic models.[17] Multiple two-by-two analyses were used to assess interaction and confusion. When an interaction was found, a composite variable was built. Independent risk factors in multivariate analysis (p≤0.05) were used to create a Gram-negative risk index (GNRI) by summing the number of factors for each patient. The GNRI was then compared between patients with and without Gram-negative bacterial infection. To determine the risk of a Gram-negative bacterial infection, the relative risk (odds ratio) for such an infection was calculated according to the number of factors present at inclusion. A formal goodness-of-fit test was used to evaluate the calibration of the model[18] and the area under the receiver operating characteristic (ROC) curve was calculated to evaluate the discriminatory power of the index.[19] To assess the predictive value of the GNRI, we compared the scores of patients with and without Gram-positive infection, those with both Gram-positive and Gram-negative infections being excluded. To assess whether this scoring system is valuable for clinical practice, we estimated sensitivity and specificity for several cut-offs and calculated likelihood ratios in order to appraise post-test probabilities according to various prevalence rates (pre-test prevalence of 0.05, 0.10, and 0.20) of Gram-negative bacterial infection. The following definitions were applied for the calculation of these operative indices. The *sensitivity* was defined as the proportion of patients with Gram-negative bacterial infection in whom the test was positive, whereas the *specificity* was the proportion of patients without Gram-negative bacterial infection in whom the test was negative. The *positive likelihood ratio* was the ratio of true positive to false positive results, and the *negative likelihood ratio* was the ratio of false negative to true negative results. Data are presented as means ± SD or proportions as appropriate. All significance tests were two-tailed. A p value ≤0.05 was considered statistically significant. Data were analyzed using BMDP software (University of California, Berkeley, USA).

Results

Among the 513 patients of the study cohort, 51% had acute leukemia, 5% had chronic myeloid leukemia, and 31% had lymphoproliferative disorders. The mean age was 41 years (ranges: 1-86), 92 patients being under 15 years old. The male:female ratio was 1.3. Neutropenia was mostly chemotherapy-induced (58%), or due to the conditioning regimen for autologous (19%) or allogeneic stem cell transplantation (10%). Sixty-nine percent of the patients had a granulocyte count lower than 100/mL at inclusion, 81% had a central venous line, and 77% were already hospitalized at onset of fever. The febrile episode was classified as FUO in 59%, CDI in 8%, and MDI in 33% of the evaluable patients. Among the 168 MDI, 147 (87.5%) were documented by blood cultures. The overall prevalence of Gram-negative bacterial infection was 10.7% [95%CI, 8.0-13.4]. Six patients had both Gram-negative and Gram-positive infections: the Gram-positive organism being a streptococcus in one patient and staphylococcus in five. Among the 55 Gram-negative bacterial infections, there were 30 cases of *E. coli*, 5 *Klebsiella pneumoniae*, 6 *Enterobacter spp.*, 13 *P. aeruginosa*, and 1 *Salmonella spp*. infection.Twenty-eight patients (5%) died within the first 30 days: 3% of the patients with FUO (9/305), 15% of those with CDI (6/40), and 8% of those with MDI (13/168). Death was directly related to the initial episode in six (4%) patients with a microbiologically documented infection, including three with Gram-negative bacterial infections due to *P. aeruginosa* (1), *E. coli* (1), and *K. pneumoniae* (1).

Factors associated with Gram-negative bacterial infections

In univariate analysis, age, steroids at day 1, administration of systemic antifungals within the 7 days preceding the episode, absence of gut decontamination, previous administration of beta-lactams within the last 7 days, chills and urinary symptoms at inclusion were significantly associated with Gram-negative bacterial infection. A non-significant trend for an association was also observed between Gram-negative bacterial infection and absence of buccal disinfectant, a history of bacteremia within the previous 6 months, or a broncho-pulmonary focus. Stem cell transplantation and isolation in a laminar air-flow room were significant factors protecting against the occurrence of Gram-negative bacterial infections. The use of quinolones also appeared to be a protective factor, but due to the small number of exposed patients, quinolones were not considered in the multivariate analysis. Severe neutropenia, underlying disease, high-dose cytarabine, mucositis and diarrhea did not influence the occurrence of Gram-negative bacterial infection (Table 1).

In multivariate analysis, only age (> median value of 45 years), absence of gut decontamination with both colimycin and aminoglycosides, recent administration of beta-lactams, chills, and urinary symptoms were independent risk factors for Gram-negative bacterial infection. The protective effects of stem cell transplantation and isolation in a laminar air flow room found in the univariate analysis were no longer significant in the multivariate analysis either.

Gram-negative risk index

Each of the five independent risk factors for Gram-negative bacterial infection was attributed a value of 1 so that the number of parameters entering the GNRI ranged from 0 (no factor present) to ≥4 (4 or 5 factors present). Table 2 shows the prevalence rates and the relative risks for Gram-negative infections. Additionally, to assess the absence of pertinence of the GNRI for Gram-positive bacterial infections, Table 2 also shows the prevalence rates and relative risks of Gram-positive coccal infections according to the GNRI. The risk for Gram-negative bacterial infection increased 3.8, 8.9, and 105 times when the GNRI was 2, 3, and ≥4, respectively. For each additional point on the GNRI, the odds ratio was 3.12 (95%CI, 2.16-4.51) ($p<10^{-4}$) for Gram-negative bacterial infection, and 1.20 (95%CI, 0.89-1.50) (p=0.15) for Gram-positive infection (Table 2).

The observed (n=53) and expected (n=49) number of Gram-negative bacterial infections were similar, the high p value of the goodness-of-fit test indicated good agreement (calibration) (H^*g = 2.75, df = 4; p>0.60). The area under the ROC curve was 0.76 (± 0.16 SD).

The performances of the scoring system and the post-test probabilities according to several prevalence rates (0.5, 0.10, 0.20), including the one observed (0.10), are presented in Table 3.

Discussion

In this prospective study of 513 hematology patients, we established a risk index to predict Gram-negative bacterial infection at the onset of febrile neutropenia. The use of this index, combined with that of the Gram-positive risk index previously published[16] should optimize first-line therapy for febrile neutropenic patients. The strengths of this study include the prospective data collection, unbiased patient recruitment, classification of patients according to outcome measures, accurate measurement of risk factors, a high proportion of evaluable patients (96%), and representativeness of the participating centers in

Table 1. Comparisons of patients with and without Gram-negative bacterial (GNB) infections.

	Percentage with factor		*Univariate analysis*[a]		*Multivariate analysis*[a,b]
	GNB infection (n=55)	*No GNB infection (n=458)*	*p value*	*Odds ratio [95 % CI]*	*p value*
Age < 15 years	13	19	0.38		
Mean age (±SD)	48.0±21.3	39.9±21.6	0.008		
Age > median value (45 years)				2.28 [1.22-4.28]	0.009
Hematologic disease					
Acute leukemia	58	50			
Lymphoproliferative diseases	27	31			
Chronic myeloid leukemia	4	5			
Others (aplastic anemia ...)	11	18	0.71		
Status (missing=8)					
Initial phase, complete remission, chronic phase or partial response	56	68			
Relapse, acute transformation, or terminal phase	44	32	0.07	1.21 (0.59-3.85)	0.60
Stem cell transplantation	13	31	0.005	0.59 [0.24-1.47]	0.24
Total body irradiation[c]	7.3	16.2	0.09		
Living conditions before day 1[d]					
Home	20	23	–	1	
Conventional hospital room	56	39	–	1.60 [0.70-3.40]	
Laminar air-flow room (missing=4)	24	38	0.06	0.75 [0.40-1.89]	0.27
Past bacteremia (within 6 months)	22	14	0.14	2.09 [0.96-4.57]	0.07
Drugs at day 1					
Steroids (missing=1)	35	23	0.02	1.71 [0.89-3.28]	0.11
Anti-ulcer drugs	31	33	0.76		–
Antacids (missing=9)	11.1	8.7	0.70		
Non-absorbable antifungals	73	75	0.73		
Systemic antifungals	22	12	0.03	1.81 [0.82-4.01]	0.15
No buccal disinfectant	40	27	0.07		–
No chlorhexidine	38	71	0.11	0.68 [0.34-1.34]	0.26
Gut decontamination	31	47	0.04	–	
No colimycin	82	62	0.003	–	
No aminoglycosides	86	69	0.007	–	
Neither colimycin nor aminoglycosides	94	75	<.0001	4.69 [1.39-15.30]	0.003
Any systemic antibiotics	33	31	0.74		
Beta-lactams	11	4	0.04	3.85 [1.31-11.30]	0.02
Fluoroquinolones	0	7	0.06*		
At day 1					
Granulocyte count < 100 µL 3 (missing=6)	74	69	0.20		
Chills (missing=8)	53	23	0.0001	3.34 [1.81-6.15]	<0.0001
Mucositis (WHO score ≥1) (missing=4)	27	37	0.17		-
Bronchopulmonary focus	16	8	0.08	1.41 [0.57-3.51]	0.40
Urinary symptoms (missing=3)	9	2	0.03	5.5 [1.64-18.50]	0.01
Diarrhea	18	15	0.49		

[a]All analyses were adjusted for median age; [b]Only factors emerging from univariate analysis with a p value < 0.15 were used for multivariate analysis; [c]Due to the strong association between total body irradiation and stem cell transplantation, only this later parameter was entered into the multivariate analyses; [d]The reference class was "home".

France. We chose Gram-negative bacteremia as the end-point of this study rather than any other complication of febrile neutropenia, because of the demonstrated benefit for the patient of receiving appropriate antibacterial therapy as soon as possible in the case of bacteremia.[6] In our study, the prevalence of Gram-negative bacterial infections (10.7%), and the overall mortality rate of 5% were in the ranges of those

Table 2. Prevalence rates and relative risks of Gram-negative bacterial and Gram-positive coccal infections according to the Gram-negative risk index.

Gram-Negative Risk Index		Gram-negative bacterial infection		Gram-positive cocci infection	
	No. of patients	Infection rate Percent	Odds ratios [95% CI]	Infection rate Percent	Odds ratios [95% CI]
0	41	0	–	17.1	1
1	205[a]	4.4	1	17.6	1.0 [0.4-2.5]
2	191[b]	12.6	3.8 [1.7-8.4]	23.6	1.4 [0.6-3.3]
3	71[a]	25.4	8.9 [3.8-21.0]	28.2	1.6 [0.6-4.3]
≥4	5	80.0	105.0 [10.6-1050.0]	0	

The Gram-negative risk index represents the number of parameters among the five emerging from the multivariate analysis comparing patients with and without Gram negative bacterial infection with a p value ≤0.05 (age > 45 years, recent administration of beta-lactam, absence of gut decontamination with both colimycin and aminoglycosides, presence of chills, presence of urinary symptoms); a weight of 1 was assigned to each independent parameter. [a]1 and [b]4 patients with both Gram-positive cocci and Gram-negative infections were excluded from the analysis comparing patients with and without Gram-negative infection.

reported in prospective trials on febrile neutropenia.[2-5,20] On the same cohort of patients, we recently showed that Gram-positive infections were significantly associated with high-dose cytarabine, colimycin without glycopeptide, non-absorbable antifungals and the presence of diarrhea.[16] From that analysis, a specific score was established to predict Gram-positive infections. The present study allowed us to build a specific score to predict Gram-negative bacterial infections, based on five independent risk factors for which data are available at the onset of fever: age > 45 years, absence of gut decontamination with both colimycin and aminoglycosides, recent administration of beta-lactams, chills, and urinary symptoms. Most of the authors who have designed predictive scores in neutropenic patients have done so in order to identify the low-risk patients who could be candidates for outpatient management.[21,22] Few authors have tried to identify risk factors for Gram-positive or Gram-negative bacteremia. In a large retrospective study, Viscoli *et al*. showed that shock was associated with Gram-negative bacteremia, while signs of infection at the catheter site were predictive of Gram-positive bacteremia.[23] However, the model was finally poorly predictive on the validation set, except for its negative predictive value. A larger study was conducted by the same group on the patients included in four empirical trials of the EORTC-IATCG.[24] It showed that the following factors were independently associated with a high rate of – not specifically Gram-negative – bacteremia: age > 30 years, diagnosis of acute lymphoblastic leukemia, disease status, longer duration of in-hospital stay, granulocyte count < 0.1×10^9 cells/L, presence of central venous access other than a totally implantable catheter, presence of fever > 39°C, and shock. A similar approach was used in a retrospective analysis in children, but with more negative than positive predictive value.[25]

Other authors have evaluated biological inflammation markers as predictors of subgroups of febrile neutropenic patients, especially C-reactive protein, procalcitonin, interleukin-8 and lipopolysaccharide-

Table 3. Performances of the scoring system.

Gram-Negative Risk Index	Sensitivity (95%CI)	Specificity (95%CI)	Likelihood ratios Positive (95%CI)	Likelihood ratios Negative (95%CI)	Prevalence rate	Post-test probabilities Positive	Post-test probabilities Negative
≥1	1.0 (0.94-1.0)	09 (0.07-.12)	1.10 (1.07-1.10)	0 (–)	0.05 0.10 0.20	0.05 0.11 0.22	1 1 1
≥2	0.84 (0.71-0.92)	0.52 (0.47-0.56)	1.73 (1.49-2.01)	0.32 (0.17-0.58)	0.05 0.10 0.20	0.08 0.16 0.30	0.98 0.97 0.93
≥3	0.40 (0.27-0.54)	0.88 (0.85-0.91)	3.39 (2.25-5.11)	0.68 (0.55-0.85)	0.05 0.10 0.20	0.15 0.27 0.46	0.97 0.93 0.85
≥4	0.07 (0.02-0.18)	1.0 (0.99-1.0)	33.31 (3.79-293)	0.93 (0.86-1.0)	0.05 0.10 0.20	0.64 0.79 0.89	0.95 0.91 0.81

binding protein.[26-30] However, these markers seem to be more pertinent for the prediction of low-risk, not bacteremic, patients, rather than to predict Gram-negative infection.[12]

The main interest of our Gram-negative risk index is its simplicity, since it is limited to five factors available at the onset of the febrile neutropenia. Among the five factors we identified, age had already been reported as a risk factor for bacteremia.[24] The recent administration of beta-lactams may have facilitated the selection of hospital strains and acted through a change in colonization. Chills are common factors for Gram-positive[16] and Gram-negative bacteremia in univariate analysis, but remained significant in the multivariate analysis for Gram-negative, and not for Gram-positive, infections. Urinary symptoms are predictive of urinary infection, likely the portal of entry of bacteremia in these cases.

Finally, we found that gut decontamination with colimycin and aminoglycoside protected against Gram-negative bacterial infection, while being a risk factor for Gram-positive infections when not associated with glycopeptides.[16] This could be expected.[31] With similar objectives, quinolones were widely used in Europe[32] until an increase in Gram-positive, especially streptococcal, infections[33] and an increase of quinolone resistance in Gram-negative bacteria[15] led to a restriction in their prophylactic use. In France, most patients receiving chemotherapy for acute leukemia or stem cell transplantation are given non-absorbable antibiotics during the neutropenic phase. Previous studies in countries where gut decontamination is not used could not identify its protective effect. On the other hand, the low percentage of patients receiving quinolones in our series may have precluded us from showing their impact on the occurrence of Gram-negative bacteremia.[32] Systemic antifungals were associated, in the univariate analysis, with an increased risk of Gram-negative bacterial infection in our study. Although this factor was no longer significant in the multivariate analysis, several studies have already mentioned the relationship between antifungals and bacteremia.[23,34,35]

The antibiotics usually recommended for high-risk patients are ceftazidime, cefepime, imipenem, and tazocillin, all molecules which are usually part of the antimicrobial control programs in most hospitals. Recent important trials have shown that monotherapy is probably as efficacious as dual therapy with aminoglycosides in febrile neutropenia.[20,36] On the other hand: (i) neutropenic animals infected with Gram-negative bacteria clearly benefit from the combination with aminoglycosides,[37] a result which is consistent with the rapid bactericidal effect of aminoglycosides on bacterial growth; (ii) historical series argue for the relationship between serum bactericidal activity and clinical efficacy, and for the benefit of aminoglycosides in subgroups of patients, e.g. those with *P. aeruginosa* bacteremia;[38,39] (iii) initial regimens containing two drugs were superior to single drug regimens in neutropenic patients,[6] especially in the case of *P. aeruginosa* bacteremia.[7,40]

More accurate identification of specific risk factors for Gram-negative infections should open new possibilities to revisit the combinations with aminoglycosides during febrile neutropenia, in order to target the Gram-negative infections. According to our Gram-negative risk index, the risk of Gram-negative bacterial infection was increased three-fold in patients with two risk factors, and increased 100-fold in patients with ≥4 risk factors. A risk index ≥3 selected 15% of our whole population, and its use should result in a close selection of the expected 10% of patients infected with Gram-negative bacteria. However, although this model fits well, this index needs first to be validated in a new prospective cohort of neutropenic patients since we built this score from a derivation set only. Second, analysis of several cut-offs (Table 3) demonstrated that this score does not perform well as a decision-making tool. It is usually considered for positive test results that a positive likelihood ratio < 2 indicates that the test is useless, whereas a likelihood between 2 and 5 indicates that the test has some value, and higher positive likelihood ratios indicate that the test would be of considerable value.[41] Therefore, one can consider that a score > 3 indicates a high probability of Gram-negative bacterial infection and that clinicians should consider this high probability in their therapeutic choice by giving antibiotics or antibiotic combinations highly active against the most severe Gram-negative bacterial infection.

By contrast for patients with a score <1, considering the very high sensitivity (1.0 95% CI .94-1.0) and negative post-test probability, the probability of Gram-negative bacterial infection is very low. In this case, even though a Gram-negative bacterial infection cannot be ruled out completely (because of the lower band of the confidence interval of sensitivity), less active – and usually less expensive - antibiotics could be considered.

By anticipating the microbiology results, the combined use of our Gram-negative and Gram-positive risk indices should help the daily management of patients, and the design of antibacterial trials to specifically address the question of the optimal strategies in high-risk febrile neutropenic patients. We are prospectively validating the combined use of the two risk indices – Gram-positive and Gram-negative – in a new cohort of neutropenic patients.

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CC: conception and design of the study, writing the article and final approval; RH, AB, GL, GN: conception of the study, revising the manuscript, and final approval; RL: design of the study, revising the manuscript, and final approval; SB-G: analysis and intepretation of data, drafting the manuscript and final approval. All authors also declare they have no potential conflict of interest.

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