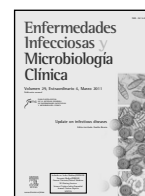




# Enfermedades Infecciosas y Microbiología Clínica

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## Update on bacteraemia in oncology and hematology

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### ABSTRACT

#### Keywords:

Bacteraemia  
Hematology  
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Review

The present article is an update of the literature on bacteraemia in onco-hematologic patients. A multidisciplinary group of Spanish physicians with an interest in this field selected the most important papers published recently. Papers from the fields of basic science, epidemiology, causative microorganisms and clinical syndromes are discussed. Important aspects of these studies include the assessment of different strategies in the management of fever in neutropenic patients and the validation of specific scores. Moreover, early identification of patients at risk of bacterial and of multi-drug resistant infections is a topic of increasing interest.

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### Actualización en bacteriemia en oncohematología

#### RESUMEN

#### Palabras clave:

Bacteriemia  
Hematología  
Oncología  
Actualización  
Revisión

El trabajo que se presenta es una revisión de la bibliografía reciente más relevante publicada en relación con la bacteriemia en pacientes oncohematológicos. Un grupo multidisciplinar compuesto por diferentes especialistas españoles con interés en este campo revisa los artículos más notables. Los trabajos pertenecen a áreas de investigación básica, epidemiología, agentes causales y síndromes clínicos. Se analizan diferentes aspectos, incluyendo estrategias del manejo de la fiebre en el paciente neutropénico y la validación de scores específicos. La identificación precoz de factores de riesgo de infección bacteriana y de infección por microorganismos multirresistentes es objetivo de especial interés.

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### State of the art

A neutropenic cancer patient presenting with fever or with infection signs in the absence of fever or even hypothermia is considered a medical emergency that warrants prompt empirical antibacterial treatment. In this type of patient, the rate of infectious complications is strongly related to the intensity of chemotherapy. Further risk factors are tumour stage, severity of mucosal barrier damage, the presence of a central venous catheter, the type of surgery conducted and genetic factors (e.g., reduced mannose-binding protein concentrations). The most common microorganisms responsible for bloodstream infections are Gram-positive bacteria,

mostly coagulase-negative staphylococci. There are several pros and cons for pursuing antibacterial prophylaxis (mainly with fluoroquinolones) in neutropenic patients with fever. Prophylaxis is not usually indicated in low-risk patients, such as those receiving chemotherapy for solid tumors or lymphomas. In high-risk patients, the benefits of fluoroquinolones should be weighed against the risk of resistance, and an anti-*Pseudomonas* drug should always be part of the empirical regimen when there is fever and infection is suspected under prophylaxis. The survival benefit of empirical therapy in bacteraemic cancer patients is clearly revealed by data on infection-related mortality recorded in the 1960s when empirical therapy was not routinely used compared to present data<sup>1</sup>.

Haematopoietic stem cell transplantation (HSCT) is complicated by severe bacterial infections that most often develop during the pre-engraftment period, both in autologous and in allogeneic HSCT, when patients are granulocytopenic. In this stage, Gram-positive

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cocci are the most frequently isolated pathogens. In the posttransplant course, bacteremias are also common in the absence of neutropenia, especially after allogeneic HSCT. The use of prophylactic fluoroquinolones during pre-engraftment neutropenia is an option both in autologous and allogeneic HSCT. However, as in granulocytopenic patients, the risk of infections by resistant pathogens should be carefully assessed. This decision should be based on local epidemiology, and empirical antibiotherapy should be given to all febrile HCST recipients, regardless of neutropenia. This approach is justified by the high incidence of bacteraemia in any post-transplant period and the high mortality observed when appropriate treatment is delayed<sup>2</sup>.

### Basic science

**Vekemans M, Robinson J, Georgala A, Heymans C, Muanza F, Paesmans M, et al. Low mannose-binding lectin concentration is associated with severe infection in patients with hematological cancer who are undergoing chemotherapy. *Clin Infect Dis.* 2007;44:1593-601.<sup>3</sup>**

Mannose-binding lectin, a human plasma protein, plays an important role in the innate immune defense system. MBL levels are genetically determined and approximately 30% of individuals are MBL-deficient. A series of 255 patients was analyzed to test the hypothesis that patients with hematological malignancies who are MBL-deficient have a higher risk of serious infections in the setting of chemotherapy-induced neutropenia. Adult patients with hematological malignancies scheduled to receive at least 1 course of chemotherapy were included. A total of 569 cycles of chemotherapy given to 255 eligible patients were analyzed. A MBL deficiency was documented in 24% of patients. The incidence of serious infection in MBL-deficient patients was 1.96 vs. 1.34 cases per 100 days in non MBL-deficient cases ( $P = .008$ ). After excluding acute leukemia patients the incidence was 1.85 vs. 0.94 ( $P < .001$ ).

*Comments.* A higher risk of early severe infections was associated to lower MBL levels but this association was stronger in non-acute leukemia patients, in patients with short duration neutropenia. In acute leukemia patients, the MBL deficiency did not increase the infectious risk related to prolonged neutropenia itself. In spite of these results, the authors conclude that their study gives support to prospective trials evaluating MBL replacement therapy in this setting. Cost-benefit studies are clearly needed.

### Prognostic factors

**Ramzi J, Mohamed, Z, Zors B, Karima K, Raihane B, Lamia A, et al. Predictive factors of septic shock and mortality in neutropenic patients. *Hematology.* 2007;12:543-8.<sup>4</sup>**

Prediction of septic shock and mortality in patients with febrile neutropenia (FN) is a major objective and crucial to design risk-adapted strategies in the management of neutropenic patients with leukaemia and bacteremia. Ramzi et al have recently reported the results of a study to identify risk factors for septic shock and mortality in a series of 110 episodes of febrile neutropenia focusing on 20 patients with acute myeloblastic leukaemia who developed bacteremia during a period of 1 year. Fourteen of the 110 FN episodes developed septic shock, causing mortality in 7 (35% of episodes with bacteremia). Univariate analysis revealed pulmonary infection and serum bicarbonate  $< 17$  mmol/L as the only variables associated with mortality. In addition, serum lactate  $> 3$  mmol/L was also predictive of septic shock. However, in a multivariate analysis no independent prognostic factor was found to predict death, while pulmonary infection and serum lactate  $> 3$  mmol/L were predictive of septic shock.

*Comments.* Due to some methodological problems of the study and mainly due to the small sample size, these results should be cautiously interpreted until further research establish the usefulness of some biomarkers in predicting septic shock and mortality in neutropenic patients.

**Tumbarello M, Spanu T, Caira M, Trecarichi EM, Laurenti L, Montuori E, et al. Factors associated with mortality in bacteremic patients with hematologic malignancies. *Diagn Microbiol Infect Dis.* 2009;64:320-6.<sup>5</sup>**

This is a retrospective cohort study to identify risk factors for mortality in a large cohort of hematologic patients with bacteremia. From 2000 through 2005, bacteremia was diagnosed in 217 patients with hematologic malignancies. The infections were caused only by Gram-positive organisms in 57.1% (124/217) cases and only by Gram-negative bacteria in 37.8% (82/217); the remaining 5.1% (11/217) were polymicrobial. The overall 30-day mortality rate was 20.3% (44/217). In multivariate analysis, significant predictors of mortality were prolonged neutropenia ( $P < .001$ ), acute renal failure ( $P = .002$ ), nosocomial bacteremia ( $P = .009$ ), age  $> 55$  years ( $P = .007$ ), and monomicrobial bacteremia due to antibiotic-resistant Gram-negative bacteria ( $P = .009$ ).

*Comments.* Reducing fatal outcomes associated with bacteremia in patients with hematologic malignancies is a challenge, and the emergence of resistance to the antimicrobials widely used in this setting is of great concern. Future infection trends must be carefully monitored and treatment guidelines adjusted accordingly.

**Richardson MW, Grewal SS, Visintainer PF. Emesis predicts bacteremia in immunocompromised children with central venous catheters and fever. *Cancer.* 2009;115:3335-40.<sup>6</sup>**

Fever is one of the most common complications and reasons for hospitalization among children who have cancer or aplastic anemia and a CVC. Most of these episodes are not associated with bacteremia and therefore may result in an overuse of broad-spectrum intravenous antibiotic therapy and inpatient admission. The objective of this study was to determine whether vomiting at presentation of a febrile illness in immunocompromised children with central venous catheters (CVCs) predicts bacteremia. A chart review was conducted of children who were admitted to the hospital with a diagnosis of cancer or aplastic anemia, fever, and a CVC. Data were collected on the presence or absence of vomiting, catheter type, presence or absence of severe neutropenia, C-reactive protein (Crp) value, and culture results. There were 143 admissions for fever among 48 children. Among 35 admissions with emesis, 19 included bacteremia; whereas, among 107 admissions without emesis, 19 included bacteremia ( $P < .001$ ). There was a 5-fold greater risk of bacteremia in children with emesis compared to children without vomiting (odds ratio [OR]: 5.50; 95% confidence interval [CI], 2.20-13.67). Gram-negative organisms were more likely to be associated with vomiting than Gram-positive organisms ( $P = .008$ ). Children with severe neutropenia did not have a significantly higher rate of bacteremia than children who had neutrophil counts  $> 500$  cells/mm<sup>3</sup>. Other factors that were associated with higher rates of bacteremia were underlying diagnosis (acute myelogenous leukemia and bone marrow transplantation) and catheter type.

*Comments.* Immunocompromised children with a CVC and a fever who presented with vomiting were more likely to have bacteremia than similar children who presented without vomiting. Gram-negative organisms were more likely to be associated with emesis than Gram-positive organisms. The absence of severe neutropenia was not associated with a decreased likelihood of bacteremia. These findings may be useful in identifying children who are at high risk for bacteremia and in determining initial, empiric therapy.

**Paganini HR, Aguirre C, Puppa G, Garbini C, Javier RG, Ensínck G, et al. A prospective, multicentric scoring system to predict mortality in febrile neutropenic children with cancer. *Cancer.* 2007;**109**:2572-9.<sup>7</sup>**

Prognostic heterogeneity of patients with cancer who develop febrile neutropenia (FN) is very well-known. However, most studies addressing this issue have been carried out in adult patients, who usually present a higher rate of associated comorbidity than children. A recent paper by Paganini et al, carried out in a very large series of 1,520 episodes of FN in 981 children with cancer, has again addressed a prospective, multicentric study to develop a scoring system to predict mortality in FN in children with cancer. The predictive model obtained from a derivation set of 714 episodes in a single institution was lately validated in a series of 806 episodes (validation set) from seven additional institutions from Argentina. Multivariate analysis revealed the following variables as independent prognostic factors: advanced disease, associated comorbidity, and bacteremia, which were assigned 3, 2, and 1 point respectively in the scoring system. There was no death among patients scoring less or equal to 3 in the derivation set, and only 3 patients died with this score in the validation set. However, mortality rate was 5.8%, 15.4%, and 40% in those scoring 4, 5, and 6, respectively in the derivation set. For children with scores greater than 3, the sensitivity and specificity of the model were, 100% and 84.2%, respectively, with a positive and negative predictive value of 100% and 84.2%, respectively. The high predictive value of the scoring system was clearly validated in a different group of children (validation set), with a sensitivity, specificity, positive and negative predictive value of 84.2%, 83.2%, 89.2% and 99.5%, respectively.

**Comments.** It is a well designed study in which a simple and reliable scoring system is proposed to use in children with cancer and FN. Although the study does not provide any novel information with regard to the variables identified as prognostic factor in this setting, the proposed scoring system can provide a solid and reliable support for designing risk-adapted strategies in the management of FN in children with cancer.

### Prophylaxis

**Craig M, Cumpston AD, Hobbs GR, Devetten MP, Sarwari AR, Ericson SG. The clinical impact of antibacterial prophylaxis and cycling antibiotics for febrile neutropenia in a hematological malignancy and transplantation unit. *Bone Marrow Transplant.* 2007;**39**:477-82.<sup>8</sup>**

In this study, the authors analysed, in a prospective cohort of 326 patients, the use of prophylactic levofloxacin during prolonged neutropenia combined with cycling of the antibiotic regimen for empiric treatment of neutropenic fever. The results were compared with the 217 patients treated just before the initiation of the study, in which no prophylaxis and no cycling of the antibiotic regimen for empiric treatment were employed. The rate of gram-negative bacteremia significantly decreased during the period of prophylaxis and cycling compared to the period before. No significant increases in gram-negative resistance were found. The global rate of gram-positive bacteremia was similar between the two treatment periods. However, bacteremia due to *Enterococcus faecium* increased and there was an emergence of resistant organisms, including methicillin-resistant *Staphylococcus aureus* and vancomycin resistant *E. faecium*, during the period with prophylaxis and cycling. Finally, there was no difference in infectious mortality or death during neutropenia between the two periods.

**Comments.** In this paper, the authors explore a combined strategy: levofloxacin prophylaxis for patients with expected prolonged neutropenia and antibiotic cycling of agents for neutropenic fever. As the authors recognize, the analysis had some limitations, including

the retrospective data collection, the use of an historical control group, and the different baseline characteristics of the patient population in the two groups. However, the study shows that the use of levofloxacin prophylaxis and antibiotic cycling are effective in preventing gram-negative infection morbidity in patients with cancer and profound and protracted neutropenia. At the same time, the finding of increased gram-positive antimicrobial resistances reinforces the need of continued monitoring of the rate of bacteremia and resistance patterns in the immunocompromised host.

**Rangaraj G, Granwehr BP, Jiang Y, Hachem R, Raad I. Perils of quinolone exposure in cancer patients: breakthrough bacteremia with multidrug-resistant organisms. *Cancer.* 2010;**116**:967-73.<sup>9</sup>**

The objective of this study was to determine the effect of antibiotic use (including prophylaxis) on the emergence of multidrug-resistant (MDR) breakthrough bacteremia in cancer patients. In this retrospective study, the authors identified all bacteremic episodes from July 2005 to December 2006 at their tertiary cancer center and compared the types of bacteria and antimicrobial resistance in isolates from patients who had received antimicrobial agents as therapy or prophylaxis (breakthrough infections) with those from patients who had not received antimicrobial agents (nonbreakthrough bacteremia). Breakthrough bacteremia was more likely to be associated with MDR *Escherichia coli* ( $P = .002$ ), MDR *Pseudomonas aeruginosa* ( $P = .02$ ), and vancomycin-resistant enterococci ( $P = .01$ ). Multivariate analysis revealed that breakthrough bacteremia was associated with hematologic malignancies and neutropenia (OR: 9.9 and 3.0, respectively). Fluoroquinolone use was associated significantly with the emergence of methicillin-resistant *Staphylococcus aureus* ( $P = .04$ ), MDR *E. coli* ( $P < .001$ ), and MDR *P. aeruginosa* ( $P = .05$ ). A strong association was observed between fluoroquinolone use and breakthrough bacteremia in multivariate analysis (OR: 22;  $P < .001$ ). Patients who had received vancomycin were more likely to have vancomycin-resistant enterococci bloodstream isolates than patients who had not received antibacterial agents ( $P < .001$ ).

**Comments.** Breakthrough infections were more common in neutropenic patients and in patients who had hematologic malignancies. The isolation of MDR organisms was associated strongly with the use of fluoroquinolones. The current findings demonstrated the importance of using a comprehensive approach to the prevention of MDR bacterial infections, including the initiation of antibiotic stewardship programs.

### Vancomycin-resistant *Enterococcus* bacteraemia

**Ghanem G, Hachem MD, Jiang Y, Chemaly RF, Raad I. Outcomes for and risk factors associated with vancomycin-resistant *Enterococcus faecalis* and vancomycin-resistant *Enterococcus faecium* bacteremia in cancer patients. *Infect Control Hosp Epidemiol.* 2007;**28**:1054-9.<sup>10</sup>**

In the past decade, vancomycin-resistant enterococci (VRE) have emerged as major nosocomial pathogens. VR *E. faecium* accounts for most cases of VRE infection. Nevertheless, in some hospitals VR *E. faecalis* constitutes 2-20% of VRE isolates. The aim of this study was to compare VR *E. faecalis* bacteremia and VR *E. faecium* bacteremia in cancer patients with respect to risk factors, clinical presentation, microbiological characteristics, antimicrobial therapy and outcomes. The authors demonstrate that recent receipt of carbapenem therapy appears to be associated with VR *E. faecalis*. This result can indicate that the use of broad-spectrum antibiotics results in the elimination of normal commensal flora, subsequent colonization with VRE strains endemic in the environment, overgrowth of VRE and, ultimately, clinical infection when host defenses are overwhelmed. Despite a higher incidence of concomitant bacteraemia in patients with VR *E. faecalis* bacteraemia, the study demonstrated a higher mortality rate

associated with VR *E. faecium* bacteraemia. These findings parallel findings that mortality rates are higher for vancomycin-susceptible *E. faecium* infection than with *E. faecalis* infection.

**Comments.** This study suggests that *E. faecium* is possibly more virulent than *E. faecalis* regardless of the vancomycin susceptibility profile in cancer patients.

**Worth LJ, Thursky KA, Seymour JF, Slavin MA. Vancomycin-resistant *Enterococcus faecium* infection in patients with hematologic malignancy: patients with acute myeloid leukemia are at high-risk. Eur J Haematol. 2007;79:226-33.<sup>11</sup>**

Patients with hematologic malignancy represent a population at high-risk for colonization and infection. Knowledge of risk factors for systemic infection would allow high-risk patients to be identified and targeted for more intensive surveillance or preventive strategies. An outbreak of 14 cases of vancomycin-resistant *Enterococcus faecium* van B infection (VRE) is studied. Control patients were randomly selected from a complete listing of inpatients matched according to ward, unit and time (within 2 wk of admission date for cases). A multivariable logistic regression modelling was used to determine risk factors. An underlying diagnosis of AML (OR: 15; 95%CI, 1.6-139;  $P = .017$ ) and vancomycin therapy during the previous 30 d (OR: 18; 95%CI, 1.2-265.3;  $P = .036$ ) were identified as independent risk factors.

**Comments.** The authors conclude that patients with AML represent a high-risk population, and targeted prevention strategies must include judicious use of vancomycin.

**Poutsiaika DD, Skiffington S, Miller KB, Hadley S, Snyderman DR. Daptomycin in the treatment of vancomycin-resistant *Enterococcus faecium* bacteremia in neutropenic patients. J Infect. 2007;54:567-71.<sup>12</sup>**

Authors sought to assess the outcome of neutropenic patients with VRE bacteraemia treated with daptomycin. Nine patients with VRE bacteraemia were assessed in this study. The source of bacteraemia was unknown for all patients, except for one who had subclavian vein septic thrombophlebitis. Four patients (44%) experienced microbiological and clinical cures. Two patients (22%) died within 3 days after the initiation of daptomycin, and were considered as microbiological and clinical failures. The remaining three patients (33%) survived more than 3 days after the initiation of daptomycin, but experienced treatment failure; two of those patients had received the drug at doses adjusted for renal failure. Daptomycin was well tolerated, and no patient experienced elevation in CPK.

**Comments.** Daptomycin is a bactericidal agent that might have a role in treating VRE BSI in immunocompromised hosts. The current is an observational study with a number of limitations. First of all, it includes very few patients. Another limitation is that the dosing of daptomycin was not uniform, including patients with no renal failure treated at 4 mg/kg/day, which is now considered inadequate for the treatment of gram positive bacteremia. On the other hand, it is unclear if the deaths of 3 patients with renal failure were due or not to the insufficient dosing of daptomycin. Despite those limitations, the paper shows that it is possible to successfully treat neutropenic patients with VRE bacteraemia with daptomycin.

### ***Streptococcus pneumoniae* bacteraemia**

**Youssef S, Rodríguez G, Rolston KV, Champlin RE, Raad II, Safdar A. *Streptococcus pneumoniae* infections in 47 hematopoietic stem cell transplantation recipients: clinical characteristics of infections and vaccine-breakthrough infections, 1989-2005. Medicine. 2007;86:69-77.<sup>13</sup>**

In this paper, Youssef et al review their experience with pneumococcal disease spectrum in a large, single-center, cohort of

7888 Hematopoietic Stem Cell Recipients (HSCT) along 17 years: 54 *S. pneumoniae* episodes were observed in 47 HSCT recipients (51 of the episodes corresponded to severe infections). Overall incidence was higher among allogeneic than autologous HSCT patients (9 and 5 per 1000 patients, respectively;  $P < .012$ ). Late pneumococcal infections were also more common in allogeneic recipients. Most *S. pneumoniae* episodes presented as pneumonia (80%), with associated bacteraemia in 61%. Uncomplicated bacteraemia accounted for 15% of episodes. No extra pulmonary organ infection was observed. Infections were observed at a median of  $433 \pm 669$  days after transplant. There was a trend towards a higher incidence of bacteraemic pneumonia in patients with GVHD but systemic corticosteroid therapy was the only variable associated with an increased risk for bacteraemic pneumonia (88% vs 50%;  $P < .01$ ). Mortality rate was similar to the reported in other studies (13%).

**Comments.** *S. pneumoniae* infections among HSCT recipients have a high morbidity and mortality. Pneumonia, often with bacteremia, was seen in about 80% of patients. Frequently associated with GVHD in the late phase of the transplant, it should be noted that about 10% of episodes are observed in the first 100 days after HSCT and that a high grade of suspicion in the late phase, even in the absence of GVHD, is necessary.

**Meisel R, Toschke AM, Heilingensetzer C, Dillo D, Laws HJ, Von Kries R. Increased risk for invasive pneumococcal diseases in children with acute lymphoblastic leukemia. B J Haematol. 2008;137:457-60.<sup>14</sup>**

There are very limited data about the risk of invasive pneumococcal disease in children with acute lymphoblastic leukemia. This study combined data from a nation-wide surveillance for invasive pneumococcal disease and the German childhood cancer registry. In this study, they showed that the relative invasive pneumococcal disease risk in paediatric ALL patients was significantly increased.

**Comments.** Preventive strategies for invasive pneumococcal disease including chemoprophylaxis and active immunization have proven efficacious in high-risk populations (sickle cell disease). As a significant proportion of invasive pneumococcal disease cases occur during maintenance chemotherapy, the pneumococcal immunization of children with invasive pneumococcal disease ALL might prevent invasive pneumococcal disease and therefore warrant evaluation in prospective trials.

### **Bacterial epidemiology**

**Moreno A, Cervera C, Gavalda J, Rovira M, De la Cámara R, Jarque I, et al. Bloodstream infections among transplant recipients: results of a nationwide surveillance in Spain. Am J Transplant. 2007;7:2579-86.<sup>15</sup>**

The authors present the incidence, microbiology and outcomes of bloodstream infection in 3926 transplant recipients (2935 solid organ and 991 haematopoietic stem cell transplants) in the Spanish RESITRA cohort. BSIs were recorded with an incidence rate ranging from 3 episodes per 10 000 transplant days in kidney recipients to 44 episodes per 10 000 transplant days in allogeneic haematopoietic stem cell transplantation (HSCT). Crude mortality of BSIs was 7.8%, being highest in liver recipients (16%). Multidrug resistant non fermentative gram-negative BSIs had significantly worse prognosis than those caused by their susceptible counterparts

**Comments.** BSIs are still a major concern in transplant recipients. A significant percentage of multidrug resistant bacteria may be related with a poor prognosis. These data may portend changes in the choices of empiric antimicrobial agents when faced with a transplant recipient with a suspected BSI.

**Trecarichi EM, Tumbarello M, Spanu T, Caira M, Fianchi L, Chiusolo P, et al. Incidence and clinical impact of extended-spectrum-beta-lactamase (ESBL) production and fluoroquinolone resistance in bloodstream infections caused by *Escherichia coli* in patients with hematological malignancies. *J Infect.* 2009;58:299-307.<sup>16</sup>**

The objective of this work was to identify risk factors for mortality in patients suffering from hematological malignancies with concurrent bacteremia caused by *Escherichia coli*. Particular attention was focused on defining the impact of extended-spectrum-beta-lactamase (ESBL) production and fluoroquinolone resistance by the bacterial isolates on mortality. A retrospective eight-year cohort study design was employed. The outcome measured was death within 30 days of the first positive blood culture. Survivor and non-survivor subgroups were compared to identify predictors of mortality. A total of 62 episodes of bacteremia caused by *E. coli* were analyzed. The overall incidences of ESBL production and fluoroquinolone resistance were 41.9% and 62.9%, respectively. The overall 30-day mortality rate was 20.9% (13/62). In a multivariate analysis, significant predictors of mortality were inadequate initial antimicrobial therapy (OR: 14.96; 95%CI, 1.95-114.51;  $P = .009$ ), infection caused by ESBL-producing isolates (OR: 8.84; 95%CI, 1.48-52.91;  $P = .01$ ), and prolonged neutropenia (OR: 8.10; 95%CI, 1.29-50.57;  $P = .02$ ).

*Comments.* Sound knowledge of the local distribution of pathogens and their susceptibility patterns and prompt initiation of effective antimicrobial treatment are essential in patients suffering from hematological malignancies with BSIs caused by *E. coli*.

**Castagnola E, Fontana V, Caviglia I, Caruso S, Faraci M, Fioredda F, et al. A prospective study on the epidemiology of febrile episodes during chemotherapy induced neutropenia in children with cancer or after hemopoietic stem cell transplantation. *Clin Infect Dis.* 2007;45:1296-304.<sup>17</sup>**

This is a 3-year prospective, observational, study to evaluate the incidence and clinical characteristics of febrile complications during neutropenic periods in children with cancer and in children who underwent haematopoietic stem cell transplantation (HSCT). Fever of unknown origin (FUO) was the most frequent clinical associated with the primary febrile episodes (79%) followed by microbiologically documented infection (MDI) with bacteraemia (2%). Invasive fungal infection was diagnosed in only 2%. The highest proportions of neutropenic periods with primary febrile episodes were observed after autologous haematopoietic stem cell transplantation (58%) aggressive treatment for acute leukemia (48%) and allogeneic haematopoietic stem cell transplantation (44%).

*Comments.* Authors confirmed that severe infectious complications occur during long-lasting neutropenia, but the majority of primary febrile episodes occurred shortly after onset of neutropenia. The positive effect of antibacterial prophylaxis might disappear in patients with repeated neutropenic periods.

**Puig N, De la Rubia J, Jarque I, Salavert M, Montesinos P, Sanz J, et al. A study of incidence and characteristics of infections in 476 patients from a single center undergoing autologous blood stem cell transplantation. *Int J Hematol.* 2007;86:186-92.<sup>18</sup>**

Autologous stem cell transplantation is usually associated with a low incidence of severe complications and a low transplant-related mortality rate. A series of 476 consecutive patients transplanted in a single institution during a 15-year period (1990-2005) was studied. All bacterial and fungal infectious episodes that developed within two months after transplantation were included in the study. Similarly to other studies, bacterial organisms were responsible for most of the febrile episodes and the pattern of infectious complications did not change significantly throughout the study

period. Fever occurred in 95% of patients (clinically documented infection in 29%, microbiologically documented infection in 17%). There were 65 episodes of bacteremia (33 episodes caused by Gram-positive cocci and 32 episodes by Gram-negative bacilli). A greater incidence of Gram-positive bacteremia was seen in the first 5-year period.

*Comments.* The present report documents the favourable outcome of patients receiving autologous stem cell transplantation with a low rate of infectious complications. Although common (14%), bacteraemia was only rarely considered to be the cause of death in these patients. However, pneumonia was the leading cause (90%) of infection-related deaths. Therapeutic strategies directed at improving the management of respiratory infections are needed.

**Tomonari A, Takahashi S, Ooi J, Tsukada N, Konuma T, Kobayashi T, et al. Bacterial bloodstream infection in neutropenic adult patients after myeloablative cord blood transplantation: experience of a single institution in Japan. *Int J Hematol.* 2007;85:238-41.<sup>19</sup>**

The slower haematopoietic reconstitution observed after cord blood transplant (CBT) makes bacterial bloodstream infection (BSI) more common in this setting than with the use of bone marrow or peripheral blood stem cells as progenitor source. In this paper, Tomonari et al. report their experience in a series of 101 adult patients who received a myeloablative unrelated CBT. BSI occurred in 12 patients within 30 days after CBT, what makes a cumulative incidence of 12%. BSI was observed at a median of 6 days after transplant, during the period of deep neutropenia. Gram-positive bacteria accounted for BSI in 67% of cases. Only 2 of the 12 patients with BSI died. One hundred days transplant related mortality was 6%.

*Comments.* These low rates of BSI and mortality contrast sharply with the reported by other groups. It is difficult to explain this low rate of BSI since all patients, most transplants were performed in high-risk patients and conditioning schemes were myeloablative and intensified with cytarabine in most cases. This fact –the improved selection of cord unit–, and the large experience of the group in handling CBT complications, may be the two most important reasons to explain differences among this series and others.

**Raad I, Hachem R, Hanna H, Bahna P, Chatzinikolaou I, Fang X, et al. Sources and outcome of bloodstream infections in cancer patients: the role of central venous catheters. *Eur J Clin Microbiol Infect Dis.* 2007;26:549-56.<sup>20</sup>**

Authors conducted this study to determine the frequency with which central venous catheters were the source of bloodstream infections in neutropenic patients and the outcome of patients with catheter-related bacteraemia (CRB). Among 169 patients with bloodstream infections, 56% were CRB. Gram-positive bacteraemia was found to be catheter related in 55% and 69% of patients with haematological malignancy and solid tumours, respectively, whereas gramnegative bacteraemia was catheter-related in only 19% of patients with underlying haematologic malignancy and in 60% of patients with solid tumour ( $P = .01$ ). By multivariate analysis, poor response was associated with critical illness and persistent neutropenia. In neutropenic patients with catheter-related bloodstream infections, peripheral quantitative blood cultures of  $\geq 100$  CFU/mL was also associated with poor response ( $P = .05$ ).

*Comments.* This study confirms that in onco-haematologic patients, central venous catheters were the major source of bloodstream infection, particularly in patients with solid tumours. In addition to critical illness and persistent neutropenia, quantitative blood cultures might be useful in predicting outcomes for neutropenic patients with catheter-related bloodstream infections.

## Diagnosis

**Hummel M, Warga C, Hof H, Hehlmann R, Buchheidt D. Diagnostic yield of blood cultures from antibiotic-naïve and antibioticly treated patients with haematological malignancies and high-risk neutropenia. Scand J Infect Dis. 2009;41:650-5.<sup>21</sup>**

In patients with prolonged episodes of neutropenia, infections are associated with significant mortality. The exact diagnostic yield of blood cultures in this high-risk population is still unclear. To assess the yield of blood cultures, the spectrum of pathogenic organisms and the influence of blood culture results on the therapeutic management, the authors retrospectively evaluated the results from 2520 blood cultures obtained from 126 consecutive patients with high-risk neutropenia. Bacterial pathogens were detected in 219 blood culture samples (8.7%) of which 172 were Gram-positive and 47 were Gram-negative bacteria. Fungal pathogens were found in 13 blood cultures. A higher rate of Gram-positive pathogens and of fungi was found in patients with central venous catheters. Pathogens were detected in 14.3% of blood cultures obtained before the institution of antibiotic treatment and in 7% of blood cultures obtained under antibiotic treatment. Treatment was modified in 116/232 (50%) of positive blood culture findings.

**Comments.** In patients with high-risk neutropenia, blood cultures are a valid diagnostic tool, both in antibiotic-naïve patients and in patients receiving antibiotic treatment, and provide important information for clinical decision making. The epidemiological data obtained are helpful for selecting empirical antibiotic treatment regimens.

## Conflict of interest

J. Fortún has received consultancy fees, honoraria, presentation fees and travel reimbursement from Pfizer, Astellas, Novartis, Merck & Shering-Plough, Gilead and Roche.

The remaining authors have not declared any conflict of interest.

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