Update on bacterial infections in immunosuppressed patients

José Mensa[a], Javier Garau[b], Isidro Jarque[c], Pilar Luque[d], Albert Pahissa[e], Joaquín Portilla[f], Miguel Salavert[c], Miguel Ángel Sanz[c], Amparo Solé[c] and Rafael de la Cámara[g]

[a]Hospital Clínico. Barcelona. Spain. [b]Hospital Mutua de Terrassa. Terrassa. Barcelona. Spain. [c]Hospital La Fe. Valencia. Spain. [d]Hospital Clínico. Zaragoza. Spain. [e]Hospital Vall d'Hebron. Barcelona. Spain. [f]Hospital General. Alicante. Spain. [g]Hospital de la Princesa. Madrid. Spain.

A multidisciplinary group of physicians with expertise in infections in neutropenic and hemato-oncology patients met to discuss the state of the art and the most relevant publications in the field of bacterial infection in neutropenic patients during the last two years.
The group agreed that most studies are favorably inclined toward the use of prophylaxis in this setting, although several areas have yet to be clarified, such as identification of the patients at greatest risk and the period of increased risk, and the emergence of resistant organisms.
Several papers on vancomycin as empirical therapy in febrile patients with neutropenia were discussed. Currently available evidence does not support the need for empirical glycopeptides initially, nor for persistent fever. Withholding specific treatment against Gram-positive infections pending growth of a resistant Gram-positive organism was considered as safe.
As for the management of bacterial infection in low-risk patients with neutropenia, current data indicate that, even in this group, empiric coverage with broad-spectrum antibiotics is necessary, at least until culture results become available.
Finally, the role of *Streptococcus pneumoniae* as a bacterial agent of infection in hematology-oncology patients revealed the low incidence of the problem, the community origin of most episodes, the frequent association with pneumonia, and related mortality not superior to that of the non-neutropenic population.

***Key words*: Febrile neutropenia. Prophylaxis. Pre-emptive therapy. Gram-positive infections. Gram-negative infections. Low-risk neutropenic patients. *Streptococcus pneumoniae*.**

Actualización de las infecciones bacterianas en los pacientes con inmunosupresión

Un grupo multidisciplinario de clínicos con experiencia en las infecciones que sufren los pacientes con neutropenia y hematooncológicos se ha reunido para discutir la situación actual y las publicaciones más relevantes que se han realizado durante los 2 últimos años en el campo de las infecciones bacterianas en los pacientes con neutropenia.
Los participantes señalaron que en la mayor parte de los estudios se propone la aplicación de medidas de profilaxis en este contexto, aunque hay varias áreas que todavía no han sido clarificadas, tal como la identificación de los pacientes con un riesgo mayor y la definición del período de riesgo aumentado, así como la aparición de microorganismos resistentes.
Se comentaron varios artículos relativos al uso de vancomicina como tratamiento empírico en los pacientes febriles con neutropenia. La evidencia actual no apoya el uso de glucopéptidos administrados de manera empírica en las fases iniciales ni tampoco en los cuadros de fiebre persistente. Se consideró seguro el mantenimiento del tratamiento específico frente a las infecciones por microorganismos grampositivos mientras no se demuestre la presencia de microorganismos grampositivos resistentes. En lo relativo al tratamiento de las infecciones bacterianas en los pacientes de riesgo bajo con neutropenia, los datos actuales indican que, incluso en este grupo, es necesaria la cobertura empírica con antibióticos de amplio espectro, al menos hasta que se obtengan los resultados de los cultivos.
Finalmente, la función desempeñada por *Streptococcus pneumoniae* como bacteria causal de las infecciones en los pacientes hematooncológicos reveló la baja incidencia del problema, el origen extrahospitalario de la mayor parte de los episodios, su asociación frecuente con neumonía y el hecho de que la mortalidad asociada dicho microorganismo no es superior a la que se observa en los pacientes que no presentan neutropenia.

***Palabras clave:* Neutropenia febril. Profilaxis. Tratamiento profiláctico. Infecciones por grampositivos. Infecciones por gramnegativos, Pacientes neutropénicos de riesgo bajo. *Streptococcus pneumoniae*.**

Correspondence: Dr. J. Mensa.
Hospital Clinic. Infectious Diseases Service.
Villarroel, 170. 08036 Barcelona. Spain.
E-mail: jmensa clinic.ub.es

State of the art (Dr. Mensa, Dr. de la Cámara)

Of the many different causes of immunosuppression, neutropenia is associated with a higher number and greater severity of bacterial infections. In this review, we describe the main articles published over the two last years on prophylaxis and treatment of bacterial infections in neutropenic patients.

We have selected three topics where there have been important improvements in the management of neutropenic patients: prophylaxis with quinolones, the use of vancomycin at the beginning of empirical treatment of neutropenic fever, and the stratification of neutropenic patients by risk level to optimize treatment, including oral antibiotic treatments. The results of a study on *Streptococcus pneumoniae* bacteremia in cancer patients are also examined.

Neutropenia and induced chemotherapy mucositis facilitate the translocation and subsequent tissue invasion of microorganisms which usually colonize mucosal barriers[1]. The strategies to prevent bacterial infections include oral antibiotics without anti-anaerobic activity in order to selectively reduce Gram-negative aerobic pathogens. Fluoroquinolones have been widely used for this purpose. Their potential benefits may also be due to the high therapeutic plasma concentration achieved following administration. However, despite the number of studies published, controversy still surrounds the use of fluoroquinolones in neutropenic patients[2]. In the mid-90s, several meta-analyses examined quinolone prophylaxis in this setting. The results showed that there was a significant reduction in the incidence of Gram-negative bacteremia and in the number of febrile episodes among these patients when quinolones were administered[3,4]. On the other hand, no benefit was shown in the incidence of Gram-positive and fungal infections and in overall survival. The fact that quinolones do not improve overall survival, together with the development of resistance to quinolones and beta-lactam antibiotics by *Escherichia coli* and other enterobacteriaceae (cross-resistance due to efflux pumps or selection of ESBL-producing strains) explains why the IDSA guidelines do not recommend the routine administration of quinolones for gut decontamination in neutropenic patients[5]. It is worth noting that many studies included in these meta-analyses were performed with norfloxacin, enoxacin and ofloxacin, quinolones with less intrinsic activity than ciprofloxacin or levofloxacin. Furthermore, in some studies included in the meta-analyses, fluoroquinolones were compared with trimethoprim-sulfamethoxazole (TMP-SMZ) and not with placebo. If these analyses were to be performed today, they would have to take into account not only the increasing resistance of *E. coli* to quinolones in several countries, but also the better bioavailability and high intrinsic activity of the new quinolones against Gram-positive aerobic flora.

Coagulase-negative *Staphylococci* are the more frequent microorganisms isolated from neutropenic patients during febrile episodes. Almost 70% of the strains are resistant to methicillin and to the beta-lactam antibiotics used as first-line empirical treatment[6,7]. In some hospitals, there has been an incresase in the incidence of sepsis and shock syndrome due to alfa-hemolytic *Streptococci* (notably *S. mitis*, *S. oralis* and *S. sanguis* II)[8], which can have a high degree of resistance to penicillin[9]. Over the last 20 years, several prospective studies have been performed comparing beta-lactam monotherapy with the combination of a beta-lactam and a glycopeptide. In some studies, the results support the combination with glycopeptides as first-line empirical treatment[10-12], whereas in others, nephrotoxicity, higher cost, and the risk of vancomycin resistance among *Enterococci* mean that a delay of 48-72 hours is recommended in the addition of the glycopeptide until the blood-cultures are positive, due to the low mortality rate attributable to coagulase-negative *Staphylococci* bacteremia[13-15]. Two recently published meta-analyses further clarify this controversial topic.

Neutropenic patients with fever are a very heterogeneous population in terms of severity of infection and risk of complications. If a severe infection is not present, the most likely pathogenic microorganisms involved do not have a special resistance pattern, and there is no severe co-morbidity (diabetes, cirrhosis) or any other immunosuppression (splenectomy, steroids), then an outpatient oral or a once-daily intravenous antibiotic could be considered. Since the study performed by Talcott et al in 1988, several criteria have been developed to identify which patients have a lower risk of complications and therefore are eligible for oral therapy[16-20]. Two years later, Klastersky et al developed the Multinational Association of Supportive Care in Cancer (MASCC) Risk-Index[21], recently validated in another study[22].

Finally, the results of a study on *S. pneumoniae* bacteremia in cancer patients will be discussed.

The papers selected as the most relevant in the field during the study period were reviewed by one or more of the authors and discussed with the whole group.

Antibiotic prophylaxis in the neutropenic patient

The following papers on this topic were selected for discussion:

Bucaneve G, Micozzi A, Menichetti F, Martino P, Dionisi MS, Martinelli G et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Eng J Med. 2005;353:977-87.

Cullen M, Steven N, Billingham L, Gaunt C, Hastings M, Simmonds P et al. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. N Eng J Med. 2005;353:988-98.

Reuter S, Kern WV, Sigge A, Döhner H, Marre R, Kern P et al. Impact of fluoroquinolone prophylaxis on reduced infection-related mortality among patients with neutropenia and hematologic malignancies. Clin Infect Dis. 2005;40:1097-3.

Wetering MD, Witte MA, Kremer LCM, Offringa M, Scholten RJPM, Caron HN. Efficacy of oral prophylactic antibiotics in neutropenic afebrile oncology patients: A systematic review of randomised controlled trials. Europ J Cancer. 2005;41:1372-82.

Gafter-Gvili A, Fraser A, Paul M, Leibovici L. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. Ann Intern Med. 2005;142: 979-95.

Since the 1960's, prompt administration of antibiotics has been standard practice in febrile neutropenic patients. As an alternative to this approach, several groups have attempted to minimize the risk of infection with antibiotic prophylaxis in order to protect patients during the period when they are most vulnerable. The results of this strategy have not provided conclusive data; therefore, most guidelines do not recommend this type of intervention.

Two recent articles published by Bucaneve et al and Cullen et al described broad, randomized double-blind studies comparing prophylactic administration of levofloxacin (500 mg per day) with placebo in neutropenic patients. An important difference between these studies is the fact that Bucaneve's paper includes patients considered as high-risk, whereas Cullen's work contains low-risk patients. In the first study, prophylaxis was maintained until neutropenia had resolved, and in the second, prophylaxis lasted seven days. Both groups used the same primary endpoint: the occurrence of fever.

Bucaneve et al reported a significant reduction in the rate of febrile episodes, positive cultures, bacteremia, and infection by Gram-negative rods with levofloxacin prophylaxis; nevertheless, there was no survival benefit. The number of patients who needed to be treated to avoid one episode of febrile neutropenia was estimated to be five. In the levofloxacin group, the incidence of *E. coli* bacteremia was lower (1.2% vs 3.0%), but the percentage of resistance was greater (77% vs 17%). Thus, levofloxacin prophylaxis decreased the number of documented bacterial infections, but increased the percentage of infections caused by resistant bacteria.

Cullen et al reported a significant risk of 56% for the first febrile episode, 28% for probable infection and 36% for hospitalization. However, the absolute reduction in the risk of these events was 4.4%, 5.4% and 3.6%, respectively. The number of patients treated per cycle to avoid one febrile episode was approximately 70. Levofloxacin had no protective effect against the risk of severe infections or death, and the incidence of side effects was higher in this group (78 vs 40 patients).

In 2005, one study[3] reported a considerable increase in mortality when levofloxacin prophylaxis was interrupted in neutropenic patients with cancer. Even though this finding had not been confirmed in other studies, it caused a fast return to the use of antibiotic prophylaxis. Another article[4] that reviewed the controlled studies performed between 1966 and 2002 compared prophylaxis with quinolones or TMP/SMZ with no prophylaxis. A total of 22 trials met the inclusion criteria. The main endpoints were the number of patients with documented bacteremia and infection-related mortality. The incidence of Gram-negative bacteremia decreased significantly without an increase in Gram-positive bacteremia. Quinolone-based regimens generally produced a reduction in Gram-negative bacteremia, while TMP/SMZ-based regimens were more effective against Gram-positive bacteremia. Data on infection-related mortality were retrieved from 13 trials and disclosed a significant reduction with the use of prophylaxis (odds ratio [OR] = 0.56, confidence interval [CI] 0.34-0.96). Lastly, a meta-analysis published in June 2005 attempted to analyze whether antibiotic prophylaxis reduces mortality and the incidence of infection in neutropenic patients. Ninety-five trials performed between 1973 and 2004 met the inclusion criteria. Fifty-two trials addressed quinolone prophylaxis. It was found that prophylaxis with this antibiotic lowered the risk for all-cause mortality (OR, 0.52, CI, 0.35-0.77), as well as infection-related mortality, fever, and clinically and microbiologically documented infections. Fluoroquinolone prophylaxis increased the risk for harboring resistant bacilli, but these results were not statistically significant (OR, 1.69, CI, 0.73-3.92). All the prophylactic antibiotics were associated with an increased risk of adverse events (OR, 1.69, CI, 1.14-2.50). In conclusion, antibiotic prophylaxis, preferably with a fluoroquinolone, should be considered for neutropenic patients.

Even though most studies are favorably inclined toward the use of prophylaxis, the following areas still need to be defined: the patients at greatest risk, the period of increased risk, and the likelihood that resistant organisms will emerge. Efforts to improve risk stratification will be critical to minimize the unnecessary use of antimicrobial agents while simultaneously preserving the benefits.

Vancomycin in the empirical treatment of the febrile neutropenic patient

The following papers on this topic were selected for discussion:

Paul M, Borok S, Fraser A, Vidal L, Leibovici L. Empirical antibiotics against Gram-positive infections for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2005;55:436-44.

Vardakas K, Samonis G, Chrysanthopoulou S, Bliziotis I, Falagas M. Role of glycopeptides as part of initial empirical treatment of febrile neutropenic patients: a meta-analysis of randomised controlled trials. Lancet Infect Dis. 2005;5:431-9.

Infection is a leading cause of death among cancer patients. Early antibiotic therapy reduces mortality and is standard practice for cancer patients with fever and neutropenia. In the last few decades, the etiology of infection among this population has shifted from a predominance of Gram-negative bacteria to that of Gram-positive bacteria. The use of indwelling central venous catheters, the increasing intensity of anticancer chemotherapy, and the use of specific prophylaxis against Gram-negative bacteria in neutropenic patients are the basic reasons leading to this change. Currently used beta-lactams do not provide adequate coverage for the majority of these Gram-positive infections. Empirical beta-lactam therapy, with or without an aminoglycoside, is currently considered safe, despite the rising prevalence of resistant Gram-positive infections. Therefore, it is is important to determine whether a glycopeptide, or other antimicrobials with anti-

Gram-positive activity, should be included in the empirical antimicrobial regimen of febrile neutropenic patients.

Two recent meta-analyses of randomized, controlled trials address this issue, and review the available evidence regarding the advantages and disadvantages of the addition of a glycopeptide as part of the empirical therapy of febrile neutropenic patients.

The first meta-analysis, by Paul et al, analyzed randomized trials comparing antibiotics with an anti-Gram-positive spectrum with a control or placebo. No restrictions on inclusion were imposed. Relative risks with 95% confidence intervals were pooled using the fixed effect model. The primary outcome assessed was all-cause mortality. Thirteen studies including 2392 participants met the inclusion criteria. Glycopeptides were assessed in 9 trials. No significant difference in all-cause mortality was observed [RR 0.86 (0.58-1.26), 7 studies, 852 participants]. Overall failures at the end of therapy occurred equally [RR 1.00 (0.79-1.27), 6 studies, 943 participants]. Failure associated with therapy modifications was more frequent in the control arm when empirical initial glycopeptides were assessed [RR 0.70 (0.61-0.80), 5 studies, 1178 participants]. Adverse events were significantly more common with the additional antibiotic and nephrotoxicity was significantly more common with additional glycopeptides [RR 1.88 (1.10-3.22), 6 studies, 1282 participants].

In the second meta-analysis, by Vardakas et al, a study was considered eligible if it was a randomized, controlled clinical trial, or if it studied the role of glycopeptides as part of empirical treatment, with the beta-lactam with or without an aminoglycoside, for the treatment of febrile neutropenic patients. Overall treatment success (survival and disappearance of all symptoms and signs) without the need for a modification of the initial regimen, all-cause mortality, and adverse effects due to study regimens were considered as primary outcome measures. Of the 32 published randomized controlled trials identified, 18 were excluded for a variety of reasons. Thus, 14 randomized controlled trials were included in the meta-analysis. Prophylaxis during neutropenia until the development of fever and enrolment in the study was used in patients from 7 trials. The addition of a glycopeptide to the empirical regimen was associated with better treatment success without modification of the initial regimen (1812 episodes, random effects model (OR, 1.63, 95% CI, 1.27-2.28). There was no significant difference in mortality between the two comparison groups—those who received a glycopeptide as part of the empirical regimen and those who did not (1073 patients, fixed effects model, OR, 0.67, 95% CI, 0.42-1.05). On the other hand, the inclusion of glycopeptide in the empirical antimicrobial regimen did not reduce the time to defervescence; in fact, the addition of a glycopeptide as part of the empirical regimen was associated with more adverse effects (883 patients, OR, 4.98, 95% CI, 2.91-8.55), specifically with more nephrotoxicity (1508 patients, fixed effects model OR, 2.1, 95% CI, 1.12-3.95).

There may be subsets of febrile neutropenic patients with specific risk factors who may benefit from the inclusion of a glycopeptide in the empirical regimen. Thus, the presence of septic shock at onset has been associated with a significantly higher mortality to infection ratio. Septic shock complicated only 1% of cases of bacteremia due to Gram-positive organisms, but mortality of patients with septic shock was close to 60%, with only 2 of 22 patients for whom initial therapy failed surviving long enough to permit modifications of therapy[23]. Empirical glycopeptides are recommended for these patients. Furthermore, some studies suggest that centers in which *S. viridans* bacteremia is a common cause of serious infections, or is commonly associated with penicillin resistance, should consider empirical use of glycopeptides[24]. Other risk factors for viridans streptococcal bacteremia identified in different trials include profound neutropenia, oral mucositis, high dose cytosine arabinoside therapy, prophylaxis with TMP-SMZ or fluoroquinolones, and the use of antacids or histamine type 2 blockers. The presence of one or more of these factors should prompt a careful assessment of the need for empirical glycopeptide therapy.

In summary, currently available evidence from randomized controlled trials does not support the need for empirical glycopeptides initially or for persistent fever. Withholding specific treatment against Gram-positive infections pending growth of a resistant Gram-positive organism is safe. Both meta-analyses provide further evidence in support of guidelines from the IDSA and The Infectious Diseases Working Party of the German Society of Hematology and Oncology. The Japanese guidelines, which were based on the findings of the trial by the EORTC and The National Cancer Institute of Canada, do not suggest the inclusion of a glycopeptide in the routine, initial empirical regimen of febrile neutropenic patients. Future trials assessing empirical glycopeptide therapy are warranted if the spectrum of infections in cancer patients progresses towards Gram-positive infections.

Management of low-risk febrile neutropenic patients

The following papers on this topic were selected for discussion:

Kamana M, Escalante C, Mullen CA, Frisbee-Hume S, Rolston KVI. Bacterial Infections in Low-Risk, Febrile Neutropenic Patients Over a Decade of Experience at a Comprehensive Cancer Center. Cancer. 2005;104:422-6.

Patients with febrile neutropenia are a highly heterogeneous population. Accurate identification of low-risk febrile neutropenia patients has become possible only in recent years. Two predictive models developed and validated during the past decade (Talcott 1992, Klastersky 2000) are useful tools to define a low-risk group among patients with febrile neutropenia. As a consequence, trials evaluating oral and/or parenteral outpatient antibiotic therapy (most commonly with amoxicillin/clavulanate plus a fluoroquinolone) have been conducted in such patients. However epidemiologic and clinical data as well as data on susceptibility/resistance patterns in the spectrum of infections specific to low-risk patients are scarce.

The study by Kamana et al published in Cancer was carried out at The University of Texas M. D. Anderson Cancer Center. Pooled clinical and microbiological data from 757 episodes in patients recruited for several trials of

outpatient antibiotic therapy were analyzed in order to describe the nature and spectrum of infections in low-risk patients. Talcott's eligibility criteria were used for all trials. This is probably the largest single-institution experience in the world in this setting.

A solid tumor was the underlying disease in most patients (> 95%), with sarcoma and breast carcinoma accounting for > 85% of patients. Less than 5% of patients had an underlying hematologic malignancy, and there were no HSCT recipients.

As could be expected in low-risk patients, most episodes (58%) were of unexplained fever.

Clinically documented infections (CDIs) and microbiologically documented infections (MDIs) were distributed evenly (21% each). The frequency of CDIs was similar to that reported in series not limited to low-risk patients, but very few respiratory tract infections (most involved the upper respiratory tract) were observed since pneumonia was considered an exclusion criterion for low-risk.

Among MDIs, bloodstream infections occurred most often (92 episodes, 58%), although their overall frequency was 12%, followed by urinary tract infections (40 episodes, 25%). Monomicrobial Gram-positive infections were predominant (49%), followed by monomicrobial Gram-negative infections (36%), and polymicrobial infections (15%). The most common Gram-positive pathogens isolated were coagulase-negative staphylococci, followed by *S. aureus*, *Enterococcus* species, and β-hemolytic streptococci, i.e., similar to those isolated from high-risk subgroups, with the notable exception of viridans group streptococci. Of note, vancomycin-resistant enterococci were not isolated in these patients.

Monomicrobial Gram-negative infections were caused primarily by *Enterobacteriaceae*, with *Escherichia coli* the most frequent isolate (26%), although non-fermentative, Gram-negative rods (*Pseudomonas aeruginosa*, other *Pseudomonas* spp, *Acinetobacter* spp, and *Stenotrophomonas maltophilia*) were also isolated (most often from the urinary tract). Although *P. aeruginosa* was isolated from 7 patients, only 1 patient was bacteremic, whereas the remaining patients had urinary tract infections. The overall frequency of *P. aeruginosa* infection was < 1% (7 out of 757 episodes). Monomicrobial anaerobic infections were not documented.

It is important to note that all polymicrobial infections had a Gram-negative component, with *E. coli* the most common organism isolated. Seven of 23 polymicrobial infections (30%) were caused by Gram-negative organisms only. Finally, fungi (*Candida albicans*) were isolated from only one patient who had an *E. coli* urinary tract infection and oral candidiasis.

Current data indicate that even low-risk febrile neutropenia patients require initial empiric coverage with broad-spectrum antibiotics. Potent Gram-negative coverage is essential (including coverage against *P. aeruginosa*) at least until culture results become available. On the other hand, although Gram-positive organisms are isolated most often, the exclusion of patients with significant mucositis and the lack of infections caused by viridans group streptococci obviate the need for agents such as vancomycin in the initial regimen. Anaerobic coverage does not appear to be necessary. However, the choice of specific agents for empiric therapy will depend on epidemiology and susceptibility/resistance patterns at individual institutions.

Nijhuis CO, Kamps WA, Daenen SM, Gietema JA, Van der Graaf WT, Groen HJ et al. Feasibility of Withholding Antibiotics in Selected Febrile Neutropenic Cancer Patients. J Clin Oncol. 2005;23: 7437-44.

After the landmark report by Gerald P. Bodey et al in 1966, in which the authors clearly demonstrated a close relationship between the incidence of serious infection and both nadir of absolute neutrophil count (ANC) and duration of neutropenia, another seminal study by Schimpff et al in 1971 dramatically changed the management and prognosis of febrile neutropenic patients with the introduction of the concept of "empirical therapy". They demonstrated that the time to initiation of intravenous broad-spectrum antibiotic therapy for febrile neutropenic patients, even before clinical or microbiological documentation, had a favorable impact on infection-related morbidity and mortality. Since then, and until recently, the standard of care for febrile neutropenia has consisted of early, in-hospital administration of intravenous antibiotics, with broad-spectrum coverage of the most prevalent microorganisms.

Although this paradigm of treatment provided a significant reduction in infection-related morbidity and mortality when it was used following a "one-size-fits-all" strategy, the assumption that the risk of bacterial infection and medical complications is very heterogeneous among neutropenic patients has led, particularly during recent years, to a growing interest in the development of predictive models for risk assessment in order to design risk-adapted strategies for the management of patients with febrile neutropenia. In this regard, appropriate selection of low-risk patients could have important repercussions on cost and quality of life, bearing in mind the feasibility of oral antibiotic therapy and outpatient management.

Since the pioneering study by Talcott et al in 1988, which defined a low-risk group of cancer patients with fever and neutropenia and was the basis for a first proposal of home antibiotic therapy in a pivotal pilot study in low-risk cancer patients six years later, a number of studies have shown that adult patients with a low risk of infection can be treated safely with oral rather than intravenous antibiotics.

The study by Nijhuis et al published last year in the Journal of Clinical Oncology (October 20 issue) is another step toward changing the rules for the management of low-risk patients. This study shows that it is also feasible to withhold antibiotics and early hospital discharge in adult and pediatric cancer patients with febrile neutropenia at low risk of bacterial infection. The results were based on outpatients who were selected by a new risk assessment model using objective clinical parameters and the plasma IL-8 level. Outpatients with febrile neutropenia were allocated to one of three groups by a risk assessment model combining objective clinical parameters and plasma interleukin 8 level (cutoff value 60 ng/L). Patients with signs of a bacterial infection and/or abnormal vital signs indicating sepsis were considered high-risk. Based on their interleukin-8 level, the remaining patients were

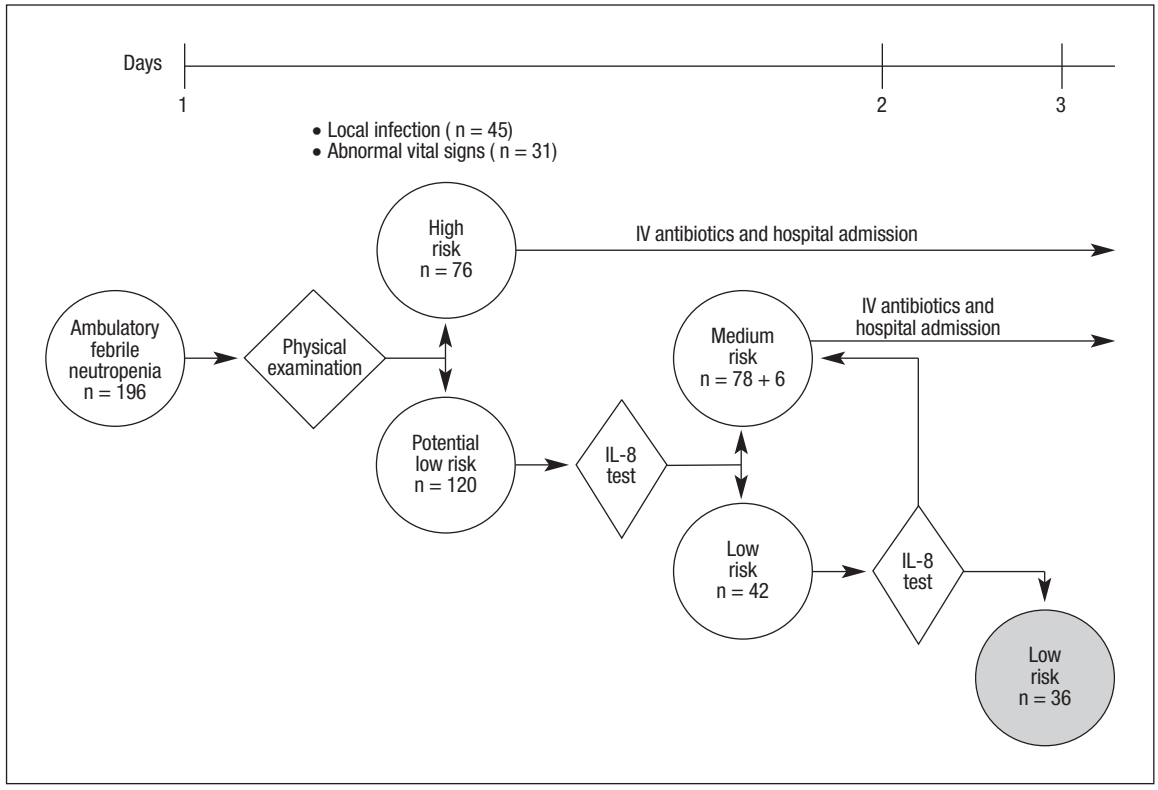

Figure 1. Patients distribution according to clinical parametes and IL-8 value.

allocated to low or medium-risk of bacterial infection (fig. 1).

Medium-risk and high-risk patients received standard antibiotic therapy, whereas low-risk patients did not receive antibiotics and were discharged from hospital after 12 hours with fever. Of 196 assessable episodes, 76 (39%) were classified as high-risk, 84 (43%) as medium-risk, and 36 (18%) as low risk. There were no treatment failures in the low-risk group (95% CI, 0% to 10%). Therefore, the sensitivity of the risk assessment model was 100% (95% CI, 90% to 100%), and the specificity, positive, and negative predictive values were 21%, 13%, and 100%, respectively. Median duration of hospitalization was three days in the low-risk group compared with seven days in the medium- and high-risk groups ($p < 0.0001$). The incremental costs of the experimental treatment protocol amounted to a saving of € 471 (US $572) for every potentially low-risk patient.

The study shows that there is a subpopulation of febrile neutropenic patients who do not need antibiotic therapy for a favorable outcome. This subpopulation with a low risk of bacterial infection can be identified in children and adults based on objective clinical parameters and the plasma IL-8 level. The authors discuss the differences between this model, which was designed to select patients at low risk of bacterial infection, and the MASCC risk index, which was designed to select patients at low risk of medical complications who might be treated with oral antibiotics in the hospital

Before recommending implementation of such a risk assessment strategy, as suggested by the authors, further studies to test the reliability of the decision rule proposed are warranted.

Streptococcus pneumoniae bacteremia in patients with cancer

The following paper on this topic was selected for discussion:

Kumashi P, Girgawy E, Tarrand JJ, Rolston KV, Raad II, Safdar A. *Streptococcus pneumoniae* bacteremia in patients with cancer: Diseasecharacteristics and outcomes in the era of escalating drug resistance (1998-2002). Medicine. 2005;84:303-12.

This retrospective study, performed in a cancer center, analyzes consecutive episodes of *S. pneumoniae* bacteremia in patients with cancer over a five-year period. The analysis focuses on characteristics of *Streptococcus pneumoniae* infection and outcome in patients with hematologic malignancies (63/122) and solid tumors.

The authors found a low prevalence of *S. pneumoniae* (8.5/1000 positive blood cultures). Community-acquired infections were more frequent than hospital-acquired episodes (88% vs 12%): 9/16 hospital-acquired *S. pneumoniae* infection episodes occurred in patients with profound neutropenia, whereas 15/119 episodes of community-acquired infection occurred during neutropenia ($p < 0.0002$).

Pneumonia was a prominent infection (86%). Fever was frequent (76%) and close to 25% of cases occurred despite

antimicrobial therapy. They found that more than a third of *S. pneumoniae* bloodstream isolates had penicillin resistance, and this probably reflects the common use of broad-spectrum cephalosporins in cancer patients.

Univariate analysis showed no significant increase in the risk of short-term death in patients with infection due to organisms not susceptible to penicillin, initially discordant treatment, presence of pneumonia, neutropenia, systemic corticosteroid use, type of cancer, hematopoietic transplant or antineoplastic therapy.

The mortality rate and outcome were similar to those of non-immunosuppressed patients: 19 patients (16%) died within two weeks of diagnosis of infection and complete resolution was noted after two weeks of antimicrobial therapy in 98 patients (80%).

In summary, the authors found that most *S. pneumoniae* bloodstream infections in cancer patients were acquired in the community, hospital-acquired infections were much less common, and most of these occurred in neutropenic patients. As was observed in other reports, pneumococcal bacteremia in cancer patients was often accompanied by pneumonia. Of particular interest, infections due to organisms not susceptible to penicillin were not associated with a significantly higher mortality rate than those due to penicillin-susceptible *S. pneumoniae*. Furthermore, the presence of conventional predictors of unfavorable outcome had no significant influence on short-term mortality rates in patients with cancer. In addition, comparable outcomes were seen in patients who were initially treated with antibiotics that *S. pneumoniae* was not susceptible to, and in patients who received concordant therapy from the start. The lack of association between initially discordant therapy and risk of treatment failure, especially in immunosuppressed cancer patients, may in part represent disease modification due to extensive prior exposure to broad-spectrum antibiotics, or a less severe *S. pneumoniae* infection may have occurred in patients who were receiving fluoroquinolone prophylaxis.

These results do not agree with reports that invasive pneumococcal disease due to organisms not susceptible to penicillin is more severe and is associated with more infection-related deaths.

References

1. Schimpff S, Young V, Greene W, Vermeulen G, Moody M, Wiernik P. Origin of infection in acute nonlymphocytic leukaemia. Significance of hospital acquisition of potential pathogens. Ann Intern Med. 1972;77:707-14.
2. Freifeld A, McNabb J, Anderson J, Ullrich FA. Low-risk patients with fever and neutropenia during chemotherapy: Current clinical practice patterns. Proc Am Soc Clin Oncol. 2004;23:747. (Abstract)
3. Cruciani M, Rampazzo R, Malena M, Lazzarini L, Todeschini G, Messori A. Prophylaxis with fluorquinolones for bacterial infections in neutropenic patients: a meta-analysis. Clin Infect Dis. 1996;23:795-805.
4. Engels E, Lau J, Barza M. Efficacy of quinolone prophylaxis in neutropenic cancer patients: a meta-analysis. J Clin Oncol. 1998;16:1179-87.
5. Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, et al. 2002 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer Clin Infect Dis. 2002;34:730-51.
6. Ortega M, Rovira M, Almela M, Marco F, De la Bellacasa JP, Martínez JA, et al. Bacterial and fungal bloodstream isolates from 796 hematopoietic stem cell transplant recipients between 1991 and 2000. Ann Hematol. 2005;84:40-7.
7. Cordonnier C, Buzyn A, Leverger G, Herbrecht R, Hunault M, Leclercq R. Epidemiology and risk factors for Gram-positive infections in neutropenia: toward a more targeted antibiotic strategy. Clin Infect Dis. 2003;36:149-58.
8. Yves P, Cometta A, Francioli P. Virulent infections caused by alpha-haemolytic streptococci in cancer patients and their management. Curr Op Infect Dis. 1997;10:422-30.
9. Doern GV, Ferraro MJ, Brueggemann A, Rufo KL. Emergence of high rates of antimicrobial resistance among viridans group Streptococci in the United States. Antimicrob Agents Chemother. 1996;40:891-4.
10. Karp J, Dick JD, Angelopulos C, Charache P, Green L, Burke PJ, et al. Empiric use vancomycin during prolonged treatment-induced granulocytopenia. Am J Med. 1986;81:237-42.
11. Shenep JL, Hughes WT, Roberson PK, Blankenship KR, Baker DK Jr., Meyer WH, et al. Vancomycin, ticarcillin and amikacin compared with ticarcillin-clavulanate and amikacin in the empirical treatment of febrile, neutropenic children with cancer. N Engl J Med. 1988;319:1053-8.
12. Micozzi A, Nucci M, Venditti M, Gentile G, Girmenia C, Meloni G, et al. Piperacillin / tazobactam / amikacin versus piperacillin / amikacin / teicoplanin in the empirical treatment of neutropenic patients. Eur J Clin Microbiol Infect Dis. 1999;12:1-8.
13. Rubin M, Hathorn JW, Marshall D, Gress J, Steinberg SM, Pizzo PA. Gram-positive infections and use of vancomycin in 550 episodes of fever and neutropenia. Ann Intern Med. 1988;108:30-5.
14. IV prot. EORTC. Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic cancer patients. J infect Dis. 1991; 163:951-8.
15. Ramphal RM, Bolger M, Oblon DJ, Sherertz RJ, Malone JD, Rand KH, et al. Vancomycin is not an essential component of the initial empiric treatment regimen for febrile neutropenic patients receiving ceftazidime: a randomized prospective study. Antimicrob Agents Chemother. 1992;36:1062-7.
16. Talcott JA, Finberg R, Mayer RJ, Goldman L. The medical course of cancer patients with fever and neutropenia. Clinical identification of a low-risk subgroup at presentation. Arch Inten Med. 1988;148:2561-8.
17. Freifeld A, Marchigiani D, Walsh T, Chanock S, Lewis L, Hiemenz J, et al. A Double-Blind Comparison of Empirical Oral and Intravenous Antibiotic Therapy for Low-Risk Febrile Patients with Neutropenia during Cancer Chemotherapy. N Engl J Med. 1999;341:303-11.
18. Kern.WV, Cometta A, De Bock R, Langenaeken J, Paesmans M, Gaya H. Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer. N Engl J Med. 1999;341:312-8.
19. Talcott JA, Siegel RD, Finberg R, Goldman L. Risk assessment in cancer patients with fever and neutropenia: a prospective, two-center validation of a prediction rule. J Clin Oncol. 1992;10:316-22.
20. Talcott JA, Whalen A, Clark J, Rieker PP, Finberg R. Home antibiotic therapy for low-risk cancer patients with fever and neutropenia: a pilot study of 30 patients based on a validated prediction rule. J Clin Oncol. 1994;12:107-14.
21. Klastersky J, Paesmans M, Rubenstein EB, Boyer M, Elting L, Feld R, et al. The Multinational Association for Supportive Care in Cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. J Clin Oncol. 2000;18:3038-51.
22. Uys A, Rapoport BL, Anderson R. Febrile neutropenia: a prospective study to validate the Multinational Association of Supportive Care of Cancer (MASCC) risk-index score. Support Care Cancer. 2004;8:555-60.
23. Elting LS, Rubenstein EB, Rolston KV et al. Outcomes of bacteremia in patients with cancer and neutropenia: observations from two decades of epidemiological and clinical trials. Clin Infect Dis. 1997;25:247-59.
24. Hughes WT, Amstrong D, Bodey GP et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis. 2002;34:730-51.