

Correspondence

Prophylactic meropenem during neutropenia in allogeneic stem cell transplant recipients

Bone Marrow Transplantation (2004) **33**, 973–974.
doi:10.1038/sj.bmt.1704459
Published online 8 March 2004

We read with interest the paper by Pérez-Simón *et al*¹ on the use of meropenem as antibacterial prophylaxis after allogeneic stem cell transplantation.¹ The authors evaluated a small number of patients comparing two cohorts in a nonrandomized manner: in the first cohort (17 patients), meropenem was started on the day of the first fever, and in the second cohort (21 patients) the same antibiotic was given to afebrile neutropenic patients. They showed that the proportion of patients who developed fever was significantly lower in the group that received meropenem as prophylaxis (while afebrile). In addition, fewer patients in this group required a second-line antibiotic and the overall duration of antibiotic use was shorter. They also reported that resistance did not emerge with this strategy.

The history of antibacterial prophylaxis in neutropenic patients has been one of illusion and delusion. All strategies tested so far have had periods of great use because most studies have shown a reduction in the overall incidence of fever and Gram-negative infections.^{2,3} However, after a honeymoon period, most of these strategies have been abandoned and strongly discouraged by experts^{4,5} because more significant outcome variables (such as infectious-related death) were not influenced by these measures,^{6–8} and the emergence of resistance.^{9,10}

Gram-negative resistance has been a major problem in hospitalized patients worldwide,^{11,12} and the use of carbapenems has been identified as an independent risk factor for infection caused by multiresistant Gram-negative organisms.^{13–15} Furthermore, among different anti-Gram-negative antibiotics, the carbapenems seem to be more associated with the development of multiresistant *Pseudomonas aeruginosa*.¹⁶ Specifically in stem cell transplant recipients, in one institution where the frequency of use of β -lactam antibiotics in afebrile patients increased from less than 10% in 1991 to 57% in 1997, the frequency of streptococcal resistance to carbapenems increased from zero prior to 1996 to 25% in 1996 and 1997.¹⁷ Considering that β -lactams are the main antibiotic class used in the empirical antibiotic therapy (a strategy that results in a significant reduction in mortality), the emergence of resistance to β -lactam antibiotics is a major concern. In the study by Pérez-Simón *et al*, even though the authors did not identify any resistance, the very small number of patients evaluated hampers any conclusion regarding this issue. Furthermore, the differences observed in the proportion of patients who needed modifications in the antibiotic regimen could have been due to other factors, since this is not a randomized trial. The difference observed could be related to the fact that most methicillin-resistant organisms

were isolated from patients in the empirical therapy group; an imbalance that would be less likely to occur in a randomized study.

We have observed a low incidence of Gram-negative resistance among our stem cell transplant recipients. Among 245 transplants performed between 1995 and 2002, a resistant Gram-negative organism was identified as a cause of bacteremia in 4.5% of transplants (data not published). However, a multivariate analysis showed that having a bloodstream infection caused by resistant Gram-negative organisms was an independent risk factor for death in the early post-transplant period, with an odds ratio of 7.66.

In summary, although this study showed some benefit of prophylaxis like many others before it, clinically relevant outcome variables were not influenced by this strategy. In addition, its impact on the incidence of resistance was not adequately assessed. Therefore, the benefit observed may be achieved at a high price that may be evident months or years later. We think that this strategy is of limited value and should be strongly discouraged.

M Nucci
SA Nouér
M Garnica
ALM de Oliveira
A Maiolino

University Hospital,
Universidade Federal do
Rio de Janeiro,
Rio de Janeiro, Brazil

References

- 1 Pérez-Simón JA, García-Escobar I, Martínez J *et al*. Antibiotic prophylaxis with meropenem after allogeneic stem cell transplantation. *Bone Marrow Transplant* 2004; **33**: 183–187.
- 2 Dekker AW, Rozenberg-Arska M, Sixma JJ, Verhoef J. Prevention of infection by trimethoprim-sulfamethoxazole plus amphotericin B in patients with acute nonlymphocytic leukaemia. *Ann Intern Med* 1981; **95**: 555–559.
- 3 Dekker AW, Rozenberg-Arska M, Verhoef J. Infection prophylaxis in acute leukemia: a comparison of ciprofloxacin with trimethoprim-sulfamethoxazole and colistin. *Ann Intern Med* 1987; **106**: 7–11.
- 4 Centers for Disease Control Prevention. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients: recommendations of the CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow transplantation. *Morb Mortal Wkly Rep* 2000; **49**: 1–125.
- 5 Hughes WT, Armstrong D, Bodey GP *et al*. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002; **34**: 730–751.
- 6 Cruciani M, Rampazzo R, Malena M *et al*. Prophylaxis with fluoroquinolones for bacterial infections in neutropenic patients: a meta-analysis. *Clin Infect Dis* 1996; **23**: 795–805.
- 7 Cruciani M, Malena M, Bosco O *et al*. Reappraisal with meta-analysis of the addition of Gram-positive prophylaxis to fluoroquinolone in neutropenic patients. *J Clin Oncol* 2003; **21**: 4127–4137.
- 8 Engels EA, Lau J, Barza M. Efficacy of quinolone prophylaxis in neutropenic cancer patients: a meta-analysis. *J Clin Oncol* 1998; **16**: 1179–1187.

- 9 Frere P, Hermanne JP, Debouge MH *et al*. Changing pattern of bacterial susceptibility to antibiotics in hematopoietic stem cell transplant recipients. *Bone Marrow Transplant* 2002; **29**: 589–594.
- 10 Yeh SP, Hsueh EJ, Yu MS *et al*. Oral ciprofloxacin as antibacterial prophylaxis after allogeneic bone marrow transplantation: a reappraisal. *Bone Marrow Transplant* 1999; **24**: 1207–1211.
- 11 Pellegrino FL, Teixeira LM, Carvalho Md MG *et al*. Occurrence of a multidrug-resistant *Pseudomonas aeruginosa* clone in different hospitals in Rio de Janeiro, Brazil. *J Clin Microbiol* 2002; **40**: 2420–2424.
- 12 Waterer GW, Wunderink RG. Increasing threat of Gram-negative bacteria. *Crit Care Med* 2001; **29**: N75–N81.
- 13 Harris AD, Smith D, Johnson JA *et al*. Risk factors for imipenem-resistant *Pseudomonas aeruginosa* among hospitalized patients. *Clin Infect Dis* 2002; **34**: 340–345.
- 14 Harris AD, Perencevich E, Roghmann MC *et al*. Risk factors for piperacillin–tazobactam-resistant *Pseudomonas aeruginosa* among hospitalized patients. *Antimicrob Agents Chemother* 2002; **46**: 854–858.
- 15 Troillet N, Samore MH, Carmeli Y. Imipenem-resistant *Pseudomonas aeruginosa*: risk factors and antibiotic susceptibility patterns. *Clin Infect Dis* 1997; **25**: 1094–1098.
- 16 Carmeli Y, Troillet N, Eliopoulos GM, Samore MH. Emergence of antibiotic-resistant *Pseudomonas aeruginosa*: comparison of risks associated with different antipseudomonal agents. *Antimicrob Agents Chemother* 1999; **43**: 1379–1382.
- 17 Collin BA, Leather HL, Wingard JR, Ramphal R. Evolution, incidence, and susceptibility of bacterial bloodstream isolates from 519 bone marrow transplant patients. *Clin Infect Dis* 2001; **33**: 947–953.