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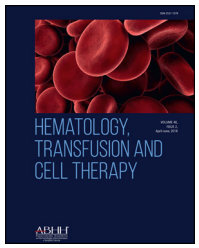

Scientific Comment

Comment on: Bacteremia in pediatric patients with hematopoietic stem transplantation☆

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Bacteraemia is a common complication of haematopoietic stem cell transplantation (HSCT), with an incidence ranging from 20% to 44% and a mortality rate of up to 50% in the post-transplant period, wherein resistant bacterial strains most often come into play.[1–4] Perez et al.[5] recently published a retrospective cohort study on the incidence, microbiological profile, and risk factors possibly associated with bacteraemia in paediatric patients who had undergone HSCT for any indication from 2012 to 2017 at a reference centre in Colombia. Allogeneic HSCT comprised 83% of the 111 studied cases. All patients received antimicrobial prophylaxis with ciprofloxacin. Bacteraemia was defined as the isolation of bacteria from at least one blood culture (for bacteria colonizing the skin, two positive cultures were required), and the antimicrobial susceptibility of the isolates was analysed according to the current Clinical Laboratory Standard Institute criteria.[6] For those who had more than one episode of bacteraemia, only the first one was accounted for in the analysis. The authors found an overall incidence of bacteraemia of 41.4% (n = 46) within the first 100 days post-transplant. An important finding was that most bloodstream isolates (60% of 62 events) comprised Gram-negative bacilli, most of which from resistant strains of *Klebsiella pneumoniae* (51%), *Escherichia coli* (16%), and *Pseudomonas* spp. (14%). Gram-positive isolates were all vancomycin-sensitive and comprised mainly coagulase-negative staphylococci (76%). Rectal swabs were only performed in 39% of the patients and were found to be positive in 25% of such cases, most of which due to carbapenem-resistant Enterobacteriaceae. Half of these patients presented bacteraemia due to the same colonizing pathogen. Moreover, 32% of such episodes were catheter-related infections. The overall mortality rate by day +100 was 18% and rose to 30% (n = 14) in patients with bacteraemia, among whom 10 deaths (71%) were attributed to infection.

It is noteworthy that 75% of the allogeneic transplants reported by Perez et al.[5] were T cell-replete unmanipulated haploidentical bone marrow transplants with high-dose post-HSCT cyclophosphamide, a strategy found to be an independent risk factor for bacteraemia compared to Human Leukocyte Antigen (HLA)-identical transplants in some studies.[7,8] In this case, however, haploidentical HSCT was not found to be a statistically significant factor. Likewise, none of the other analysed risk factors for the development of bacteraemia - graft source, underlying disease, allogeneic *vs.* autologous HSCT, conditioning regimen, prior antibiotic use, prior colonization, mucositis, and acute graft-versus-host disease (aGVHD) - were found to be statistically significant by either univariate or multivariate analysis. These results contrast with findings from other authors who observed that allogeneic HSCT, presence of comorbidities, myeloablative conditioning, mucositis, aGVHD, central venous catheters, severe and prolonged neutropenia, and use of antimicrobial

DOI of original article: https://doi.org/10.1016/j.htct.2019.05.006.
☆ See paper by Perez et al. on pages 5-11.
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https://doi.org/10.1016/j.htct.2020.01.001

prophylaxis were risk factors for bacteraemia.[9–11] Of note, in the study by Perez et al.,[5] there was, in fact, a greater proportion of bacteremic episodes among the allogeneic (*vs.* autologous) HSCT patients, but any comparison is hampered by the small study sample (17.1%) of the autologous arm of their study. Moreover, as recognized by these investigators, changes in antimicrobial susceptibility testing across time may also somewhat limit the analysis of the impact of resistant bacteria in these populations.

In another retrospective cohort study of paediatric patients who had undergone an allogeneic (88.4%) or autologous HSCT for a malignant or non-malignant haematological disorder, Caldas Teixeira et al.[12] reported on the profile of healthcare-associated infections (HAIs) between 2008 and 2016 at Hospital das Clínicas (HC), Federal University of Minas Gerais (UFMG), a reference centre in Brazil. The criteria for HAI were based on those established by the National Healthcare Safety Network.[13] Of the 86 transplants performed on the 81 patients enrolled, a total of 140 HAIs were diagnosed, most of which (46 HAIs) were laboratory-confirmed bloodstream infections (LC-BSIs). Almost all these cases were reported to be central venous catheter-associated LC-BSIs. As in the study by Perez et al.,[5] Gram-negative bacteria accounted for most (58.5%) of the cases. Similarly, almost all the infections occurred within the first 30 days after HSCT, during the period of neutropenia, and, by the end of this period, 40% of the patients had presented an LC-BSI. The antimicrobial profile of the isolated bacteria, however, was not assessed in this study. By 180 days of follow-up, 17 (21%) deaths had been observed, 7 (41%) of which in those with one or more episodes of LC-BSI. The authors concluded that active surveillance of such HAIs in children undergoing HSCT is essential for the health care of these patients.

A prompt diagnosis of infection after transplant is often challenging, given the frequent scarcity of specific signs of infection in the neutropenic setting. Therefore, early detection of a febrile episode and timely treatment of bacteraemia are key to minimizing the morbidity and mortality so commonly related to this complication.[3,14] In the study by Perez et al.,[5] fever occurred in 89% of the cases and was the primary sign of infection in most patients, as previously observed.[15] Most patients were neutropenic (80%) and presented an elevated (91%) C-reactive protein (CRP) at the onset of bacteraemia, which is also in accordance with previous reports.[16,17] CRP levels >9 mg/L were noted in 56% of the patients presenting with a first bacteremic episode. Other studies have previously shown a high specificity of CRP >9 mg/L for the detection of BSI.[17,18] This highlights the utility of serum CRP level monitoring as an extra tool for the early detection of bacteraemia in the post-transplant period. In this regard, in a prospective, observational study by Macedo et al.,[19] which included 57 neutropenic patients with haematological malignancies treated at HC-UFMG, Brazil, between 2010 and 2011, the serum levels of an array of biomarkers were analysed. CRP levels were assessed on the day preceding the onset of fever, on the day of the febrile episode, and on the first day after the episode. Overall, among the 81 episodes of neutropenia observed during a 28-day follow-up period, fever occurred in 61 (75.3%), and BSIs were documented in roughly a third (37.7%) of such cases. An increase in CRP levels was noted from the day prior to fever onset to the day after the first febrile episode ($p < 0.001$), whereas no statistically significant increase was noted among the neutropenic patients who did not present with fever during follow-up. Furthermore, an increase of 22.5 mg/L between these time points was shown to have a specificity of 93% and a positive predictive value of 95% for fever prediction. Even though this study did not include paediatric patients and was not restricted to the HSCT setting, this further suggests the potential utility of CRP measurement for the timely initiation of antimicrobial therapy in both children and adults undergoing HSCT.

Lastly, the predominance of resistant Gram-negative bacilli among the bacterial isolates in the study by Perez et al.[5] may most likely be explained by the routine ciprofloxacin prophylaxis used in their study, as nicely depicted by these authors. Similar findings have been reported by others, particularly over the past two decades.[11,20–26] This seems to differ from previous reports, mostly from Europe,[21,27–34] according to which Gram-positive bacteraemia was said to predominate. Of note, in a previous study by Garnica et al.,[35] multidrug resistant Gram-negative bacteraemia was shown to be associated with a seven-fold increase in the risk of death in HSCT recipients. Still in this regard, a previous systematic review and meta-analysis by Gafter-Gvili et al.[36] of 56 randomized controlled trials from 1987 to 2005 comparing quinolone prophylaxis with placebo or no intervention, or with another antibiotic, for the prevention of bacterial infections in afebrile neutropenic patients showed a non-statistically significant increase in colonization by quinolone-resistant bacteria under quinolone prophylaxis when compared with placebo or no intervention. Nonetheless, no difference in the occurrence of infections caused by quinolone-resistant pathogens was found. Similar findings had already been reported in another meta-analysis which included 95 trials performed between 1973 and 2004.[37] Interestingly, in trials comparing quinolone *vs.* trimethoprim/sulfamethoxazole prophylaxis, fewer incidents of colonization by bacteria resistant to the prophylactic agent used were noted in the quinolone arm.[36] Unfortunately, data on baseline resistance of colonizing isolates, resistance development and beta-lactam cross-resistance were not analysable.[36] Gafter-Gvili et al.[36] conclude that the potential risk associated with colonization and infection caused by quinolone-resistant organisms should not outweigh the possible gain in reducing the risk of death in neutropenic patients. This matter, however, remains unresolved.[38]

In short, the high rate of resistant Gram-negative strains described by Perez et al.[5] stresses the need for strict surveillance of the antimicrobial profile harboured by each HSCT centre for deciding upon the use of antibiotic prophylaxis and the most appropriate empirical therapy in neutropenic children and adults undergoing HSCT. In such high-risk settings (not specific to the paediatric population), tailoring therapy to the microbiological profile of each institution and defining subgroups of neutropenic patients who are at higher risk for bacteraemia and may most likely benefit from antibiotic prophylaxis should always be sought.

Conflicts of interest

The author declares no conflicts of interest.

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