We report on 232 patients undergoing autologous haematopoietic stem cell transplantation (ASCT) entered into a multicentre, randomised trial comparing the efficacy and tolerability of meropenem (MPM) with that of piperacillin/tazobactam (P/T) as empirical antimicrobial first-line therapy for febrile neutropenia. In 27.6% of patients in the MPM group and 22.4% in the P/T group, therapy was initially supplemented with a glycopeptide for venous catheter infection or bacteraemia because of coagulase-negative staphylococci. Complete response rate after 72 h was 63.8% in the MPM group and 49.6% in the P/T group (P = 0.034). Overall complete response rate after treatment modification was 94.0% in the MPM group and 93.1% in the P/T group. Median time to defervescence was 2 d in the MPM group and 3 d in the P/T group. The most frequently isolated pathogens were Gram-positive cocci. Treatment was well tolerated in both groups. One patient (0.4%) died from infection. Empirical first-line therapy with MPM as well as with P/T is safe and effective in febrile episodes emerging after ASCT. Higher response rates to primary treatment can be achieved with MPM.