Increased GVHD-related mortality with broad-spectrum antibiotic use after allogeneic hematopoietic stem cell transplantation in human patients and mice.

Intestinal bacteria may modulate the risk of infection and graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Allo-HSCT recipients often develop neutropenic fever, which is treated with antibiotics that may target anaerobic bacteria in the gut. We retrospectively examined 857 allo-HSCT recipients and found that treatment of neutropenic fever with imipenem-cilastatin and piperacillin-tazobactam antibiotics was associated with increased GVHD-related mortality at 5 years (21.5% for imipenem-cilastatin-treated patients versus 13.1% for untreated patients, P = 0.025; 19.8% for piperacillin-tazobactam-treated patients versus 11.9% for untreated patients, P = 0.007). However, two other antibiotics also used to treat neutropenic fever, aztreonam and cefepime, were not associated with
GVHD-related mortality (P = 0.78 and P = 0.98, respectively). Analysis of stool specimens from allo-HSCT recipients showed that piperacillin-tazobactam administration was associated with perturbation of gut microbial composition. Studies in mice demonstrated aggravated GVHD mortality with imipenem-cilastatin or piperacillin-tazobactam compared to aztreonam (P< 0.01 and P< 0.05, respectively). We found pathological evidence for increased GVHD in the colon of imipenem-cilastatin-treated mice (P< 0.05), but no difference in the concentration of short-chain fatty acids or numbers of regulatory T cells. Notably, imipenem-cilastatin treatment of mice with GVHD led to loss of the protective mucus lining of the colon (P< 0.01) and the compromising of intestinal barrier function (P< 0.05). Sequencing of mouse stool specimens showed an increase in Akkermansia muciniphila (P< 0.001), a commensal bacterium with mucus-degrading capabilities, raising the possibility that mucus degradation may contribute to murine GVHD. We demonstrate an underappreciated risk for the treatment of allo-HSCT recipients with antibiotics that may exacerbate GVHD in the colon.