Antibacterial antibiotic exposures and cytomegalovirus reactivation after allogeneic hematopoietic stem cell transplantation

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BACKGROUND

- Commensal bacteria modulate susceptibility to viral infections.
- Associations between microbiota changes before and early after hematopoietic cell transplantation (HCT) and HCT outcomes: graft-versus-host disease (GVHD), mortality, relapse.
- Cytomegalovirus (CMV) reactivation: ~25% of allo-HCT recipients; significant morbidity and mortality.
- Antibiotics are the main drivers of microbiota changes in HCT recipients.
- **Hypothesis:** Antibacterial antibiotic exposures in the pre- and early post-transplant period influence CMV reactivation risk.

METHODS

- Retrospective study, adult CMV-seropositive recipients of umbilical cord blood (UCB) or CMV-seronegative matched sibling donors (MSD), 2011-2019.
- Exposure data for antibacterial antibiotic classes between day -7 and +100 or CMV reactivation: fluoroquinolones (FQN), third or higher generation cephalosporins (Ceph3+), vancomycin (Vanc), piperacillin-tazobactam (Pip-Tazo), metronidazole (Metro), clindamycin (Clinda), and carbapenems.
- Exposure to each class from day -7 to +14 (binary variables) or until CMV reactivation (or day +100, whichever occurred first; time-varying variables) were included in multivariable Fine-Gray regression models with competing risk for non-CMV death to estimate the risk of CMV reactivation by day +100.
- Other pre-specified covariates: donor type, ATG in conditioning, grade 2-4 aGVHD, exposure to ganciclovir/valganciclovir (to treat HHV-6 reactivation after UCB transplants) before CMV reactivation.

RESULTS

Table 1. Baseline characteristics

	N = 213
Age (years)	
Mean (SD)	50 (15)
Range	18-73
Donor type	
UCB	146
MSD	67
Underlying disease, n (%)	
Acute leukemia	141 (66)
Myelodysplastic syndrome	28 (13)
Non-Hodgkin lymphoma	16 (8)
Others	28 (13)
Conditioning intensity, n (%)	
Myeloablative	106 (50)
Reduced intensity	107 (50)
Conditioning regimen, n (%)	
Flu/Cy/TBI (13.2 Gy)	69 (32)
Cy/TBI (13.2 Gy)	27 (13)
Flu/Cy/TBI (2 Gy)	97 (46)
Others	20 (9)
GVHD prophylaxis, n (%)	
Calcineurin inhibitor + MMF	155 (73)
Sirolimus + MMF	28 (13)
Calcineurin inhibitor + MTX	22 (10)
Others	8 (4)

Cy, Cyclophosphamide; Flu, Fludarabine; MMF, mycophenolate mofetil; MTX, Methotrexate; TBI, Total body irradiation

Table 2. Antibiotic exposures and CMV reactivation

Antibiotics	HR (95% CI)	P
Model using antibiotic exposures by day +14		
FQN (yes vs. no)	1.53 (0.69-3.43)	0.30
Ceph3+ (yes vs. no)	0.72 (0.39-1.32)	0.28
Vanc (yes vs. no)	1.97 (1.11-3.51)	0.02
Pip-Tazo (yes vs. no)	0.90 (0.51-1.58)	0.71
Carbapenems (yes vs. no)	1.33 (0.78-2.26)	0.29
Metro (yes vs. no)	0.92 (0.51-1.68)	0.79
Clinda (yes vs. no)	0.53 (0.24-1.19)	0.12
ATG (yes vs. no)	0.62 (0.32-1.20)	0.16
Acute GVHD	1.69 (1.05-2.73)	0.03
Ganciclovir/valganciclovir	0.45 (0.22-0.93)	0.03
Donor: UCB vs. MSD	0.19 (0.04-0.97)	0.05
UCB x time (days)	1.05 (1.01-1.09)	0.01
Model using antibiotic exposures by day +100		
FQN (yes vs. no)	1.56 (0.62-3.93)	0.34
Ceph3+ (yes vs. no)	1.21 (0.62-2.39)	0.58
Vanc (yes vs. no)	1.87 (0.99-3.54)	0.05
Pip-tazo (yes vs. no)	0.78 (0.46-1.31)	0.34
Carbapenems (yes vs. no)	1.33 (0.82-2.14)	0.25
Metro (yes vs. no)	0.64 (0.37-1.10)	0.11
Clinda (yes vs. no)	0.56 (0.26-1.18)	0.13
ATG (yes vs. no)	0.62 (0.32-1.19)	0.15
Acute GVHD	1.69 (1.04-2.73)	0.03
Ganciclovir/valganciclovir	0.43 (0.21-0.89)	0.02
Donor: UCB vs. MSD	0.18 (0.04-0.90)	0.04
UCB x time (days)	1.05 (1.02-1.09)	0.01

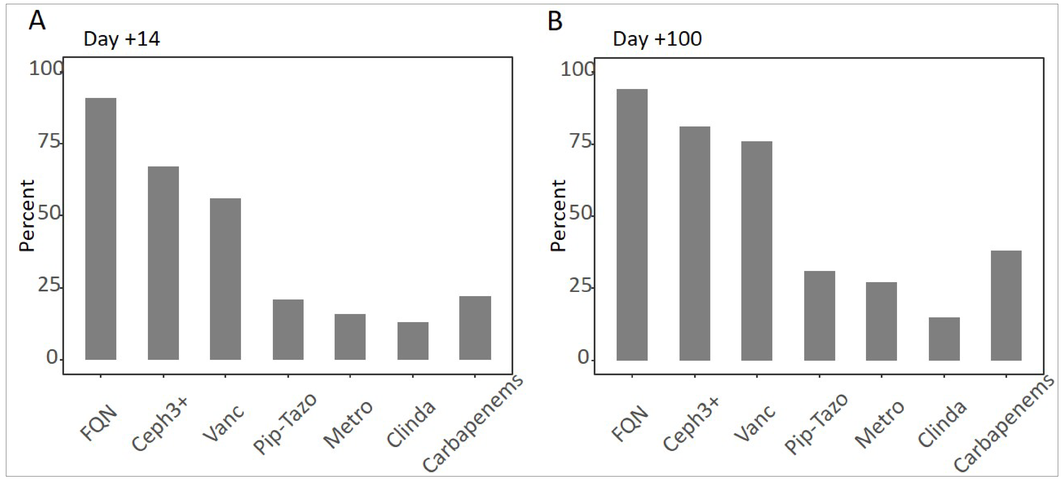

Fig 1. Antibiotic exposures. Antibiotic exposures by day +14 (A) and +100 (B).

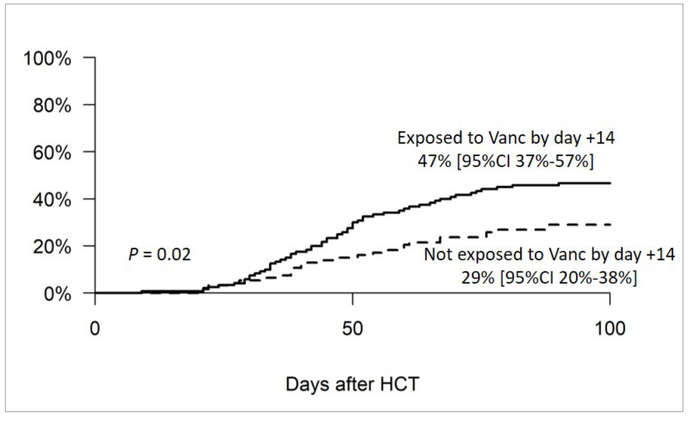

Fig 2. Vancomycin exposure and CMV reactivation. Patients exposed to vancomycin experienced a higher rate of CMV reactivation.

CONCLUSIONS

- Vancomycin ~ Higher risk of CMV reactivation after allo-HCT.
- The specific bacteria and their location unknown.
- Microbiota considerations and antibiotic exposure patterns can help personalize CMV prophylaxis.