Supplementary materials

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Supplementary table 1. Characteristics of study subjects	
Characteristic	**Number of patients (%)**
Age, median (IQR), years	52 (43-61)
Male sex	80 (54)
Follow-up, median (IQR), posttransplant days	441 (225-833)
Initial CMV viremia, median (IQR), IU/mL‖	137 (96-181)
Peak CMV viremia, median (IQR), IU/mL‖	842 (185-3,962)
CMV viremia preceding therapy, median (IQR), IU/mL†	685 (320-1,449)
Duration of CMV viremia, median (IQR), days^	38 (24-48)
CMV‖	
Asymptomatic	91 (85)
CMV syndrome	12 (11)
Tissue-invasive disease	4 (4)
Underlying diagnosis	
Leukemia	90 (60)
Lymphoma	19 (13)
MDS/MPN	34 (23)
Other	6 (4)

Conditioning regimen	
Myeloablative	49 (33)
ATG[∞]	90 (60)
Stem cell source	
Peripheral blood	135 (91)
Bone marrow	11 (7)
Umbilical cord	3 (2)
Type of donor	
Unrelated or HLA-mismatched	100 (67)
Time to engraftment, median (IQR), days[*]	11 (10-14)
aGVHD (grade 3-4)	12 (8)
CD34+ cells infused (1×10^6), median (IQR)	7.8 (6.1-12)
Charlson Comorbidity Score, median (IQR)	3 (2-4)
Lymphoid malignancy	46 (31)

Data are presented as absolute number (percentage), unless specified otherwise.

aGVHD, acute graft-versus-host disease; ATG, anti-thymocyte globulin; CMV, cytomegalovirus; IQR, interquartile range; MDS/MPN, myelodysplastic syndrome/ myeloproliferative neoplasm.

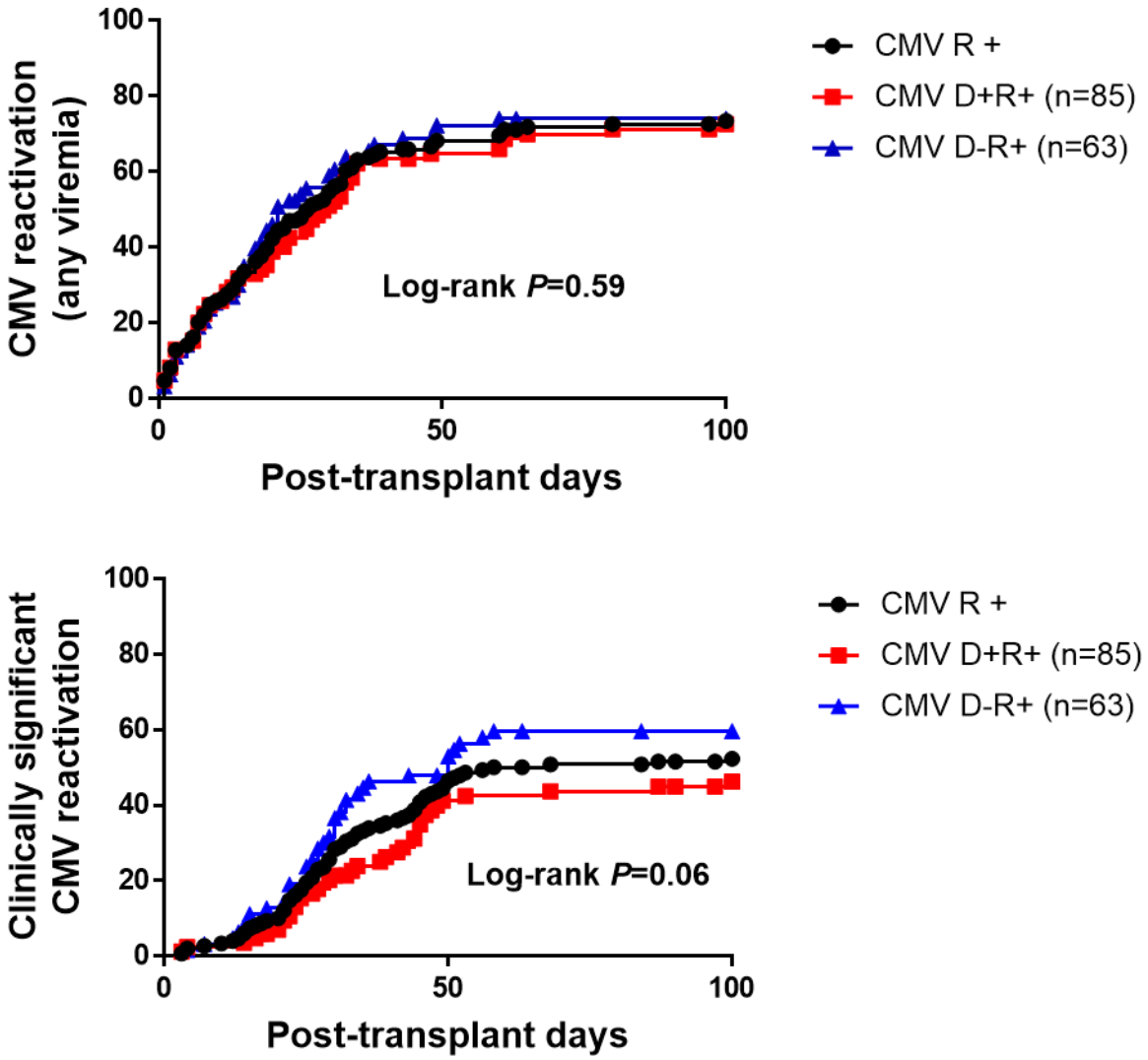
[∞] Typical dose of ATG at our center is 4 mg/kg total

[⁋] Among 107 patients with CMV reactivation

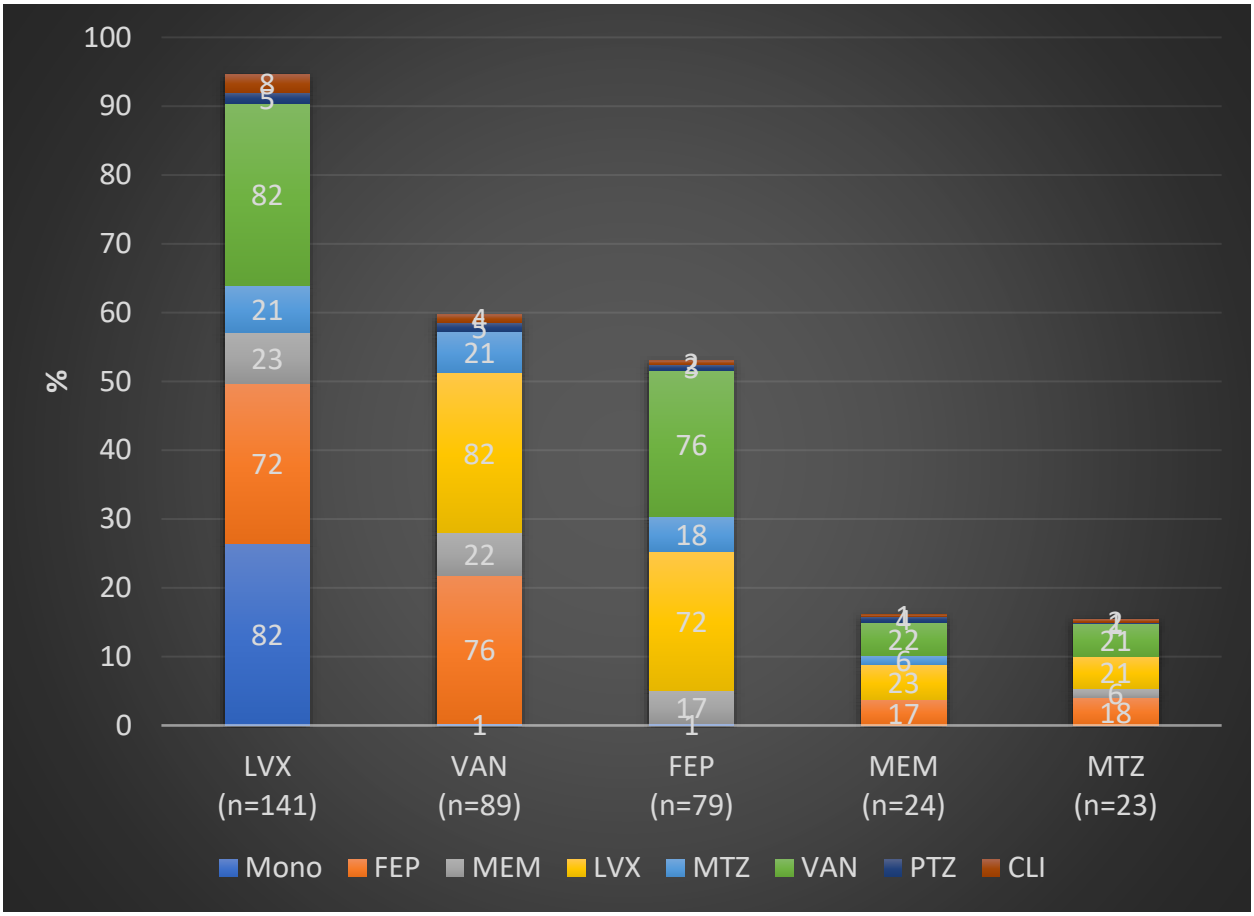
[†] Among 77 treated patients

[^] Among 94 patients who achieved resolution of viremia

[*] Among 142 patients who engrafted

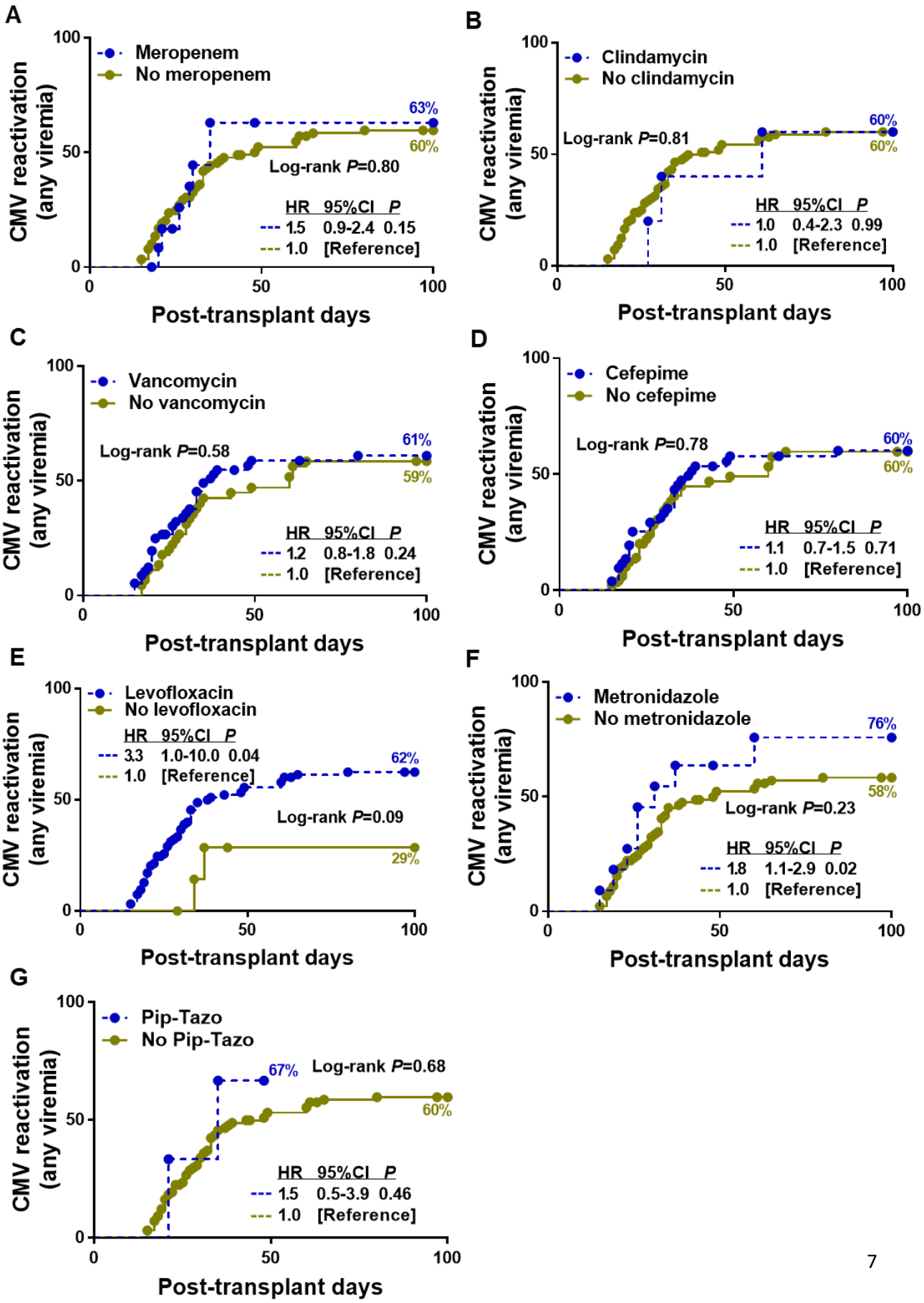


Supplementary figure 1. Incidence of CMV among CMV-seropositive recipients. 100-day CMV reactivation any viremia (top) and clinically significant CMV infection (bottom) are shown. The 100-day incidence of CMV reactivation was dependent on the donor/recipient (D/R) CMV serostatus as follows: 74, 73, 20 and 5% for any CMV viremia (P<0.0001); and 60, 46, 20 and 5% for cs-CMVi (P=0.003), in D-/R+, D+/R+, D+/R- and D-/R- groups respectively. Only data for seropositive donors (n=149) are shown in the figure. There was one donor in whom the CMV serology was equivocal, therefore the sum of D+/R+ and D-/R+ only adds to 148. D, donor. R, recipient.

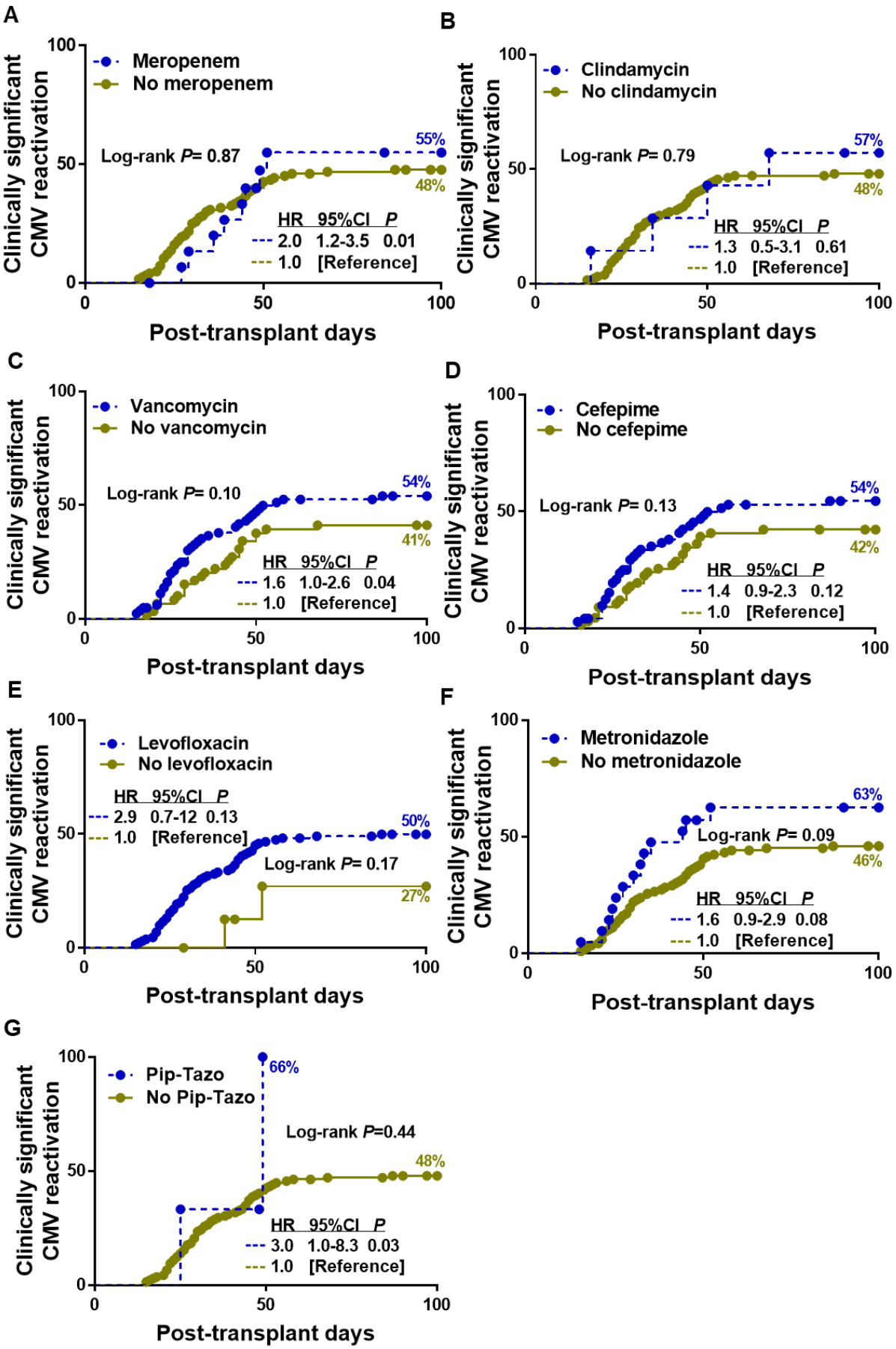


Supplementary figure 2. Antibiotic exposure by day +14 following allogeneic HCT. Exposures for the five most common antibiotics are shown. For vancomycin, only intravenous vancomycin exposure was considered in the present study. Each column corresponds to a single antibiotic. Monotherapy or concurrent exposures by day +14 are shown in color code within each column and numbers in the insert correspond to a given specific antibiotic combination. For example, 141 (94%) of the patients were exposed to levofloxacin during the first 14 days post-transplant; 82 of them received it as monotherapy, while 72 of them were subsequently exposed to cefepime and 23 to meropenem within the same period. Fifty-six (38%) patients received antibiotics as prophylaxis only; others underwent antibiotic escalation for culture-negative neutropenic fever in 67 (45%), bacteremia in 18 (12%) and other reason in 8 (5%) cases. Causes

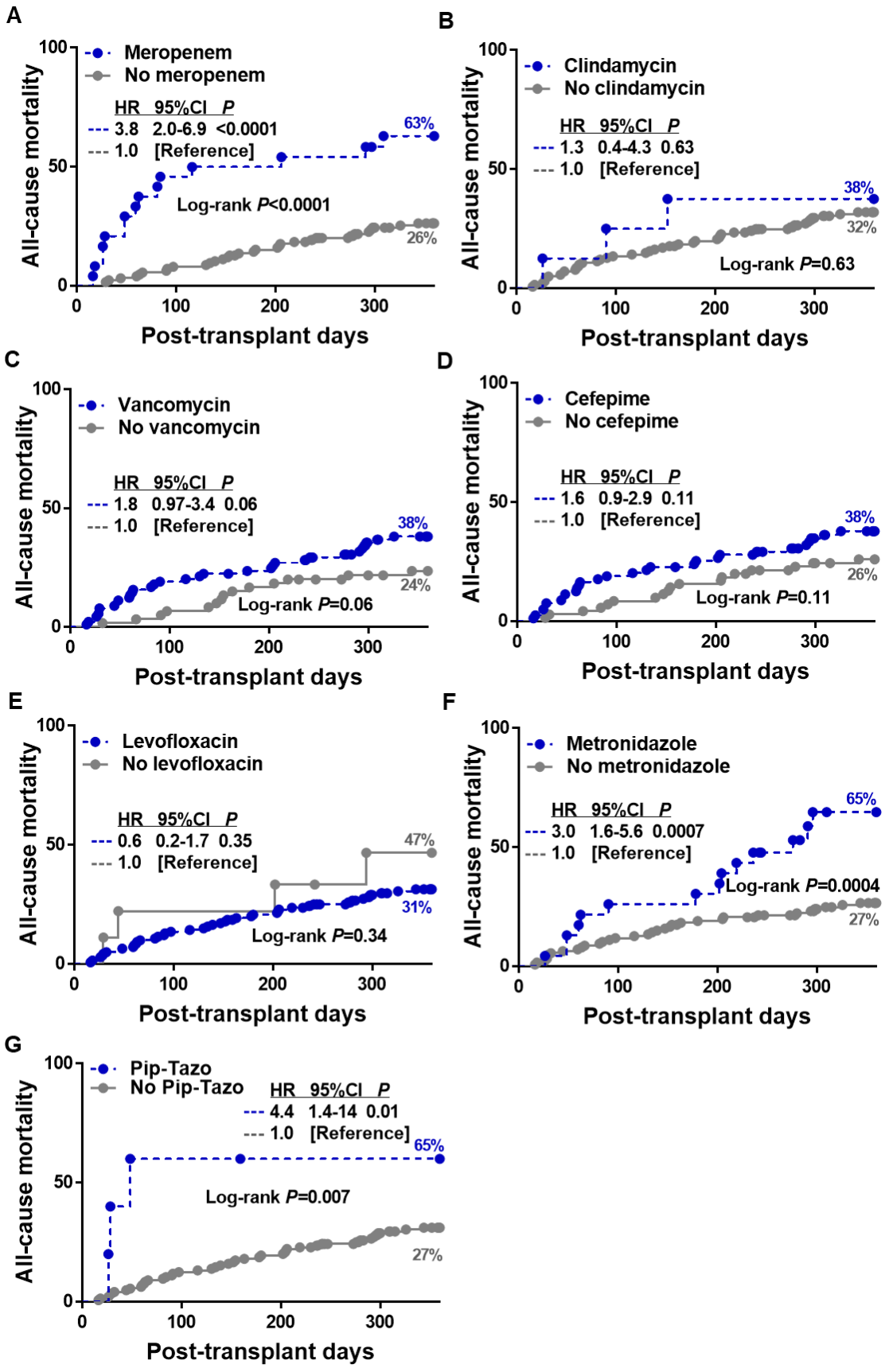
of bacteremia were as follows: *Escherichia coli* (n=10), *Pseudomonas aeruginosa* (n=2), *Streptococcus mitis* (n=2), *Propionibacterium acnes* (n=1), *Klebsiella pneumoniae* (n=1), *Fusobacterium spp.* (n=1), *coagulase-negative Staphylococcus* (n=1). Median duration of antibiotic exposure was as follows: levofloxacin (94%; median 7 days, range 1-14), intravenous vancomycin (60%; median 5 days, range 1-14), cefepime (53%; median: 7 days, range 1-14), meropenem (16%; median: 7 days, range 1-14), metronidazole (15%; median: 9 days, range 1-14), clindamycin (5%; median: 2 days, range 2-5), and piperacillin-tazobactam (3%; median: 3 days, range 1-6). Mono, monotherapy; LVX, levofloxacin; VAN, vancomycin; FEP, cefepime; MEM, meropenem; MTZ, metronidazole; piperacillin-tazobactam; CLI, clindamycin.


A
Meropenem
No meropenem
63%
60%
Log-rank P=0.80
HR 95%CI P
1.5 0.9-2.4 0.15
1.0 [Reference]
B
Clindamycin
No clindamycin
Log-rank P=0.81
60%
60%
HR 95%CI P
1.0 0.4-2.3 0.99
1.0 [Reference]
C
Vancomycin
No vancomycin
Log-rank P=0.58
61%
59%
HR 95%CI P
1.2 0.8-1.8 0.24
1.0 [Reference]
D
Cefepime
No cefepime
Log-rank P=0.78
60%
60%
HR 95%CI P
1.1 0.7-1.5 0.71
1.0 [Reference]
E
Levofloxacin
No levofloxacin
HR 95%CI P
3.3 1.0-10.0 0.04
1.0 [Reference]
62%
Log-rank P=0.09
29%
F
Metronidazole
No metronidazole
76%
58%
Log-rank P=0.23
HR 95%CI P
1.8 1.1-2.9 0.02
1.0 [Reference]
G
Pip-Tazo
No Pip-Tazo
67%
Log-rank P=0.68
60%
HR 95%CI P
1.5 0.5-3.9 0.46
1.0 [Reference]
CMV reactivation (any viremia)
Post-transplant days
0
50
100

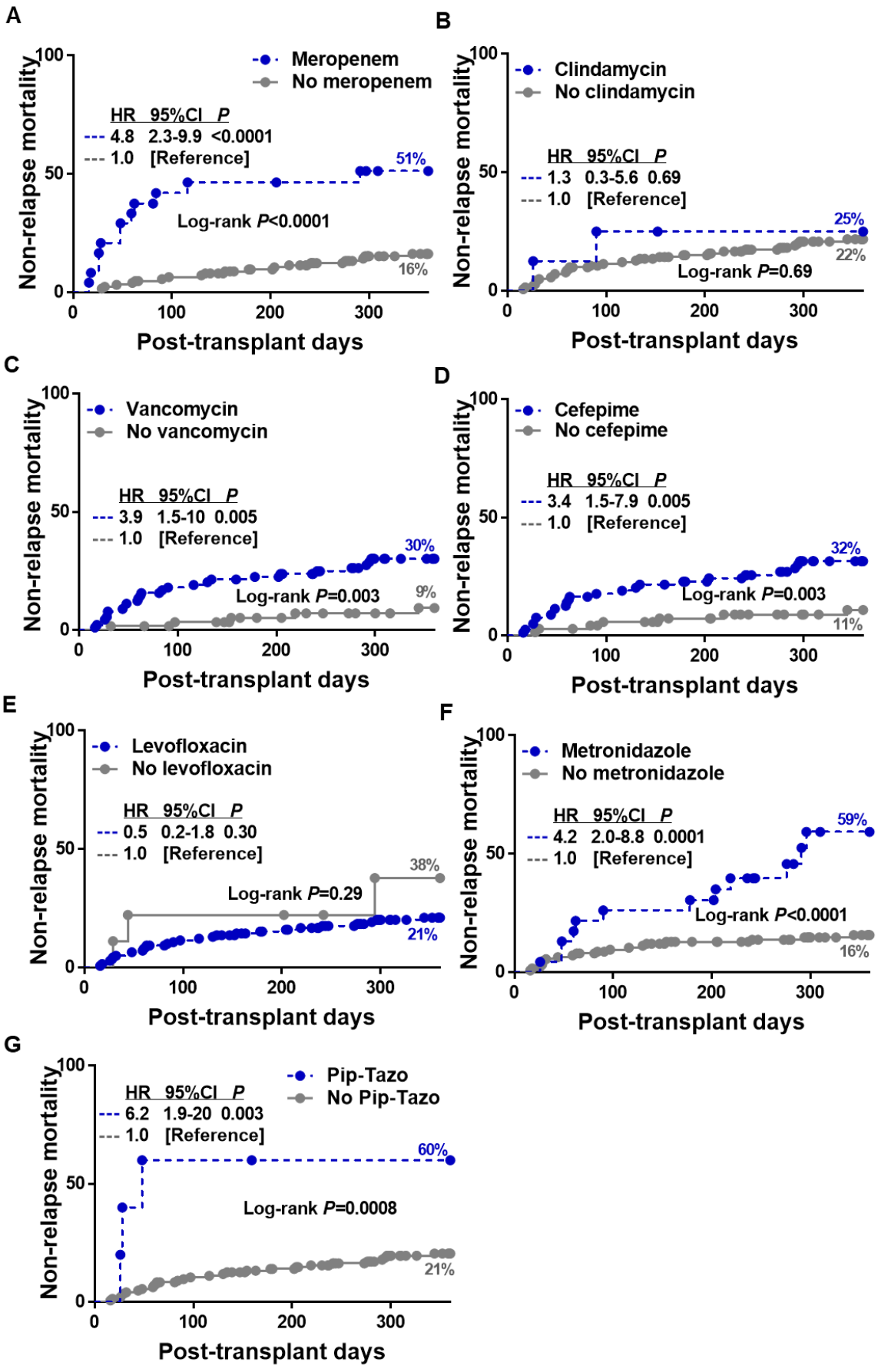
Supplementary figure 3. 100-day cumulative incidence of CMV reactivation (any viremia) by antibiotic use by day +14. Number of subjects in Log-rank analysis was as follows: meropenem (n=13), no meropenem (n=89); clindamycin (n=5), no clindamycin (n=97); vancomycin (n=57), no vancomycin (n=45); cefepime (n=52), no cefepime (n=50); levofloxacin (n=94), no levofloxacin (n=8); metronidazole (n=11), no metronidazole (n=91); piperacillin-tazobactam (n=3), no piperacillin-tazobactam (n=99). Insert corresponds to hazard ratios estimated by using Cox regression. CMV, cytomegalovirus.


A
Meropenem
No meropenem
Log-rank P= 0.87
55%
48%
HR 95%CI P
2.0 1.2-3.5 0.01
1.0 [Reference]
B
Clindamycin
No clindamycin
Log-rank P= 0.79
57%
48%
HR 95%CI P
1.3 0.5-3.1 0.61
1.0 [Reference]
C
Vancomycin
No vancomycin
Log-rank P= 0.10
54%
41%
HR 95%CI P
1.6 1.0-2.6 0.04
1.0 [Reference]
D
Cefepime
No cefepime
Log-rank P= 0.13
54%
42%
HR 95%CI P
1.4 0.9-2.3 0.12
1.0 [Reference]
E
Levofloxacin
No levofloxacin
HR 95%CI P
2.9 0.7-12 0.13
1.0 [Reference]
50%
Log-rank P= 0.17
27%
F
Metronidazole
No metronidazole
63%
Log-rank P= 0.09
46%
HR 95%CI P
1.6 0.9-2.9 0.08
1.0 [Reference]
G
Pip-Tazo
No Pip-Tazo
66%
Log-rank P=0.44
48%
HR 95%CI P
3.0 1.0-8.3 0.03
1.0 [Reference]
Clinically significant CMV reactivation
Post-transplant days
0
50
100

Supplementary figure 4. 100-day cumulative incidence of clinically significant CMV reactivation by antibiotic use by day +14. Number of subjects in Log-rank analysis was as follows: meropenem (n=16), no meropenem (n=124); clindamycin (n=7), no clindamycin (n=133); vancomycin (n=81), no vancomycin (n=59); cefepime (n=73), no cefepime (n=67); levofloxacin (n=131), no levofloxacin (n=9); metronidazole (n=21), no metronidazole (n=119); piperacillin-tazobactam (n=3), no piperacillin-tazobactam (n=137). Insert corresponds to hazard ratios estimated by using Cox regression. CMV, cytomegalovirus.

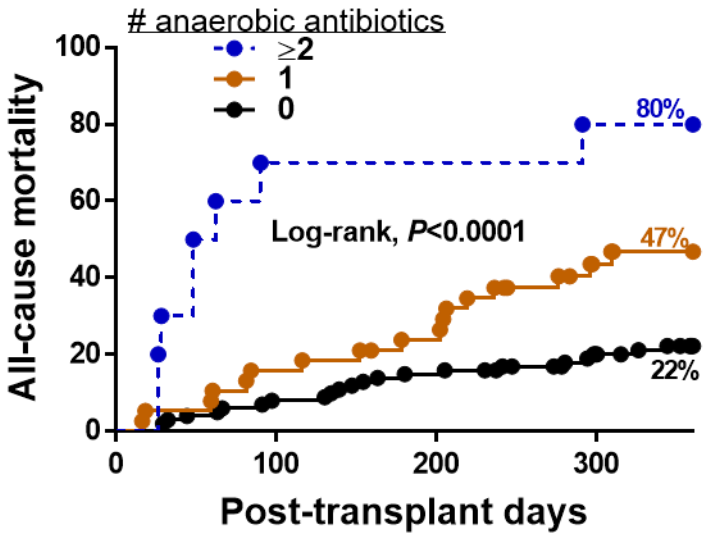

A
Meropenem
No meropenem
HR 95%CI P
3.8 2.0-6.9 <0.0001
1.0 [Reference]
63%
26%
Log-rank P<0.0001
All-cause mortality
Post-transplant days
B
Clindamycin
No clindamycin
HR 95%CI P
1.3 0.4-4.3 0.63
1.0 [Reference]
38%
32%
Log-rank P=0.63
All-cause mortality
Post-transplant days
C
Vancomycin
No vancomycin
HR 95%CI P
1.8 0.97-3.4 0.06
1.0 [Reference]
38%
24%
Log-rank P=0.06
All-cause mortality
Post-transplant days
D
Cefepime
No cefepime
HR 95%CI P
1.6 0.9-2.9 0.11
1.0 [Reference]
38%
26%
Log-rank P=0.11
All-cause mortality
Post-transplant days
E
Levofloxacin
No levofloxacin
HR 95%CI P
0.6 0.2-1.7 0.35
1.0 [Reference]
47%
31%
Log-rank P=0.34
All-cause mortality
Post-transplant days
F
Metronidazole
No metronidazole
HR 95%CI P
3.0 1.6-5.6 0.0007
1.0 [Reference]
65%
27%
Log-rank P=0.0004
All-cause mortality
Post-transplant days
G
Pip-Tazo
No Pip-Tazo
HR 95%CI P
4.4 1.4-14 0.01
1.0 [Reference]
65%
27%
Log-rank P=0.007
All-cause mortality
Post-transplant days

Supplementary figure 5. One-year cumulative incidence of all-cause mortality by antibiotic use by day +14. Number of subjects in Log-rank analysis was as follows: meropenem (n=24), no meropenem (n=125); clindamycin (n=8), no clindamycin (n=141); vancomycin (n=89), no vancomycin (n=60); cefepime (n=79), no cefepime (n=70); levofloxacin (n=140), no levofloxacin (n=9); metronidazole (n=23), no metronidazole (n=126); piperacillin-tazobactam (n=5), no piperacillin-tazobactam (n=144). Insert corresponds to hazard ratios estimated by using Cox regression.

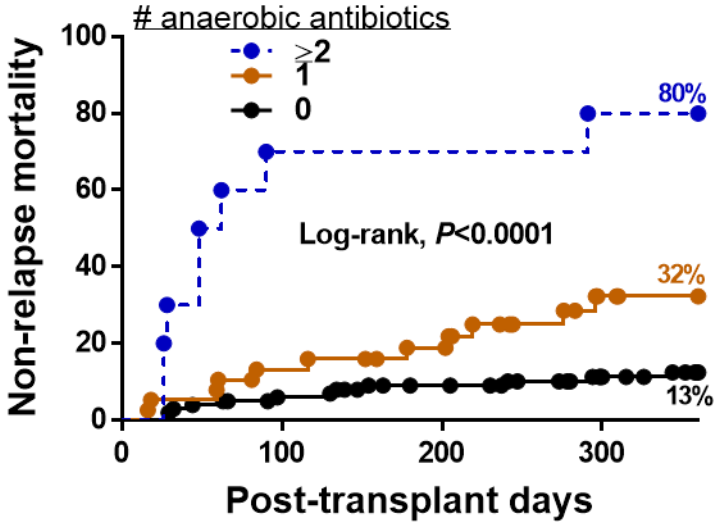

A
Meropenem
No meropenem
HR 95%CI P
4.8 2.3-9.9 <0.0001
1.0 [Reference]
51%
16%
Log-rank P<0.0001
Non-relapse mortality
Post-transplant days
B
Clindamycin
No clindamycin
HR 95%CI P
1.3 0.3-5.6 0.69
1.0 [Reference]
25%
22%
Log-rank P=0.69
C
Vancomycin
No vancomycin
HR 95%CI P
3.9 1.5-10 0.005
1.0 [Reference]
30%
9%
Log-rank P=0.003
D
Cefepime
No cefepime
HR 95%CI P
3.4 1.5-7.9 0.005
1.0 [Reference]
32%
11%
Log-rank P=0.003
E
Levofloxacin
No levofloxacin
HR 95%CI P
0.5 0.2-1.8 0.30
1.0 [Reference]
38%
21%
Log-rank P=0.29
F
Metronidazole
No metronidazole
HR 95%CI P
4.2 2.0-8.8 0.0001
1.0 [Reference]
59%
16%
Log-rank P<0.0001
G
Pip-Tazo
No Pip-Tazo
HR 95%CI P
6.2 1.9-20 0.003
1.0 [Reference]
60%
21%
Log-rank P=0.0008

Supplementary figure 6. One-year cumulative incidence of non-relapse mortality by antibiotic use by day +14. Number of subjects in Log-rank analysis was as follows: meropenem (n=24), no meropenem (n=125); clindamycin (n=8), no clindamycin (n=141); vancomycin (n=89), no vancomycin (n=60); cefepime (n=79), no cefepime (n=70); levofloxacin (n=140), no levofloxacin (n=9); metronidazole (n=23), no metronidazole (n=126); piperacillin-tazobactam (n=5), no piperacillin-tazobactam (n=144). Insert corresponds to hazard ratios estimated by using Cox regression.

A


anaerobic antibiotics
≥2
1
0
All-cause mortality
100
80
60
40
20
0
80%
47%
22%
Log-rank, P<0.0001
0
100
200
300
Post-transplant days

B


anaerobic antibiotics
≥2
1
0
Non-relapse mortality
100
80
60
40
20
0
80%
32%
13%
Log-rank, P<0.0001
0
100
200
300
Post-transplant days

Supplementary figure 7. Increased mortality in patients exposed to anaerobic antibiotics. Panel A corresponds to one-year cumulative incidence of all-cause mortality by anaerobic antibiotic use by day +14. Panel B corresponds to one-year cumulative incidence of non-relapse mortality by anaerobic antibiotic use by day +14. Number of subjects in Log-rank analysis was as follows: >2 (n=10), 1 (n=38) or 0 (n=101) anaerobic antibiotics.