

## Review Article

# Association of gut decontamination and graft versus host disease in allogeneic hematopoietic stem cell transplantation: a meta-analysis

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**Abstract:** Objectives: Controversy remains regarding the impact of gut decontamination on acute graft versus host disease (aGVHD), chronic graft versus host disease (cGVHD), and overall survival (OS) during allogeneic stem cell transplantation. The present meta-analysis was conducted to address this controversial topic, including randomized controlled trials and non-randomized controlled trials. Methods: A systemic search of indexed medical literature in four databases (Pubmed, Embase, Web of Science, and Cochrane library) was performed. Primary end points were aGVHD, cGVHD, and OS. Relative risk or risk ratios and 95% confidence intervals were calculated for each outcome for this meta-analysis. Results: Nine clinical trials were included. Of these, three trials were RCTs involving 365 patients while the others were non-RCTs involving 1,154 patients. Incidence of II-IV acute GVHD was higher in allo-HSCT patients with gut decontamination (RR 1.25, [95% CI 1.03-1.52]) and incidence of intestinal acute GVHD was higher in allo-HSCT patients with gut decontamination (RR 1.39, [95% CI 1.02-1.90]). Incidence of skin and liver aGVHD, cGVHD, and OS was not significantly different between allo-HSCT patients with gut decontamination and patients without gut decontamination. Conclusion: Gut decontamination during allogeneic stem cell transplantation may destroy the diversity of microbiota and increase rates of aGVHD, while having no effects on cGVHD and OS of patients undergoing allogeneic stem cell transplantations.

**Keywords:** Gut decontamination, allogeneic stem cell transplantation, graft versus host disease, overall survival, event free survival

## Introduction

Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is an effective method of curing malignant hematological disease. The most common complications of allo-HSCT are infections and graft versus host disease (GVHD). To decrease incidence of infections and transplantation-related mortality, gut decontamination by oral or intravenous antibiotics has been used for prophylaxis infections or treatment of neutropenic fevers during HSCT. Antibiotics, however, may damage commensal gut microflora to various degrees. Emerging evidence has indicated that preserved diversity of gut microbiota is correlated with better clinical outcomes after allo-HSCT [1-6]. Concerns have been raised whether gut decontamination should be performed for prophylaxis before HSCT or use of broad-spectrum antibiotics for neutropenic fevers that target anaerobic bacte-

ria of the gut. The aim of this study was to critically appraise all available evidence and to conduct a meta-analysis of the relationship between gut decontamination and clinical outcomes of allo-HSCT.

## Materials and methods

### *Inclusion and exclusion criteria*

All reports concerning gut decontamination and GVHD were considered eligible for inclusion. Non-randomized comparisons from retrospective studies were also included. Trials comparing the degree of gut microbiota diversity were not considered for inclusion.

### *Literature search strategy*

Four databases (Pubmed, Embase, Web of Science, and Cochrane library) were searched, with keyword combinations involving "gut

**Table 1.** Quality assessment of included randomized controlled trials

Author, year	Randomization generation	Allocation Concealment	Blinding	Incomplete outcome data	Are patients characteristics compared	Selective outcome reporting	Other bios reports
Buckner 1978 [11]	Low risk	Unclear	Not blinded	Unclear	Yes	Low risk	Unclear
Storb R 1983 [3]	Low risk	Unclear	Not blinded	Unclear	Yes	Low risk	Unclear
Beelen DW 1999 [10]	Low risk	Unclear	Not blinded	Unclear	Yes	Low risk	Unclear

According to the Cochrane Handbook for systemic Reviews of interventions (Version 5.3, updated March 2011).

**Table 2.** Quality assessment of included non-randomized controlled trials

Author, year	Representativeness of the exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Comparability of cohorts	Assessment of outcome	Duration of follow up	Adequacy of follow up	Adequacy score
Vossen JM 2014 [12]	a	a	a	b	d	a	a	6
Billinski J 2016 [16]	b	a	a	b	d	a	a	5
Routy B 2016 [14]	b	b	a	b	d	a	a	4
F Farowski 2017 [13]	a	a	a	b	d	a	a	6
Simms Waldrip TR 2017 [15]	b	a	a	b	d	a	d	4
Weber D 2017 [17]	b	b	a	b	d	a	a	4

Adapted from [http://www.endoedu.com/mobile/guideline/NOS\\_cohort.pdf](http://www.endoedu.com/mobile/guideline/NOS_cohort.pdf) Newcastle-Ottawa Quality Assessment of Cohort Studies. Representativeness of the cohort: (a) truly representative, (b) somewhat representative, (c) selected group, (d) no description (ND). Selection of non-exposed cohort: (a) same community, (b) different source, (c) ND. Ascertainment of exposure: (a) secure record, (b) structured interview, (c) written self-report, (d) ND. Comparability of cohorts: (a) study controls for % of disease risk (b) study controls for age, sex, stem cell source and donor type, (c) study is not controlled. Outcome assessment: (a) independent blind, (b) record linkage, (c) self-report, (d) ND. Duration of follow up: (a) adequate-at least 5 years (if outcomes other than 5 years OS were reported) or at least 3 months (if only acute GVHD was reported), (b) not adequate-does not fit (a). Adequacy of follow up: (a) complete, (b) <10% lost, (c) >20% lost, (d) ND.

decontamination OR Antibiotics” AND (graft versus host disease OR GVHD) OR (allogeneic stem cell transplantation OR allo-HSCT). Two reviewers, independently, selected studies according to inclusion and exclusion criteria and extracted data. Disagreements were resolved by discussion.

*Definition of end points*

Primary outcomes of interest were acute graft versus host disease (aGVHD) and Chronic graft versus host disease (cGVHD). Secondary outcome was OS. aGVHD generally occurs within the first 100 days of transplantation, while cGVHD occurs beyond 100 days. Incidence of grades II-IV or III-IV aGVHD was defined according to the Glucksberg scale [7]. cGVHD included limited and extensive conditions and was defined according to the Seattle criteria [8].

*Quality assessment*

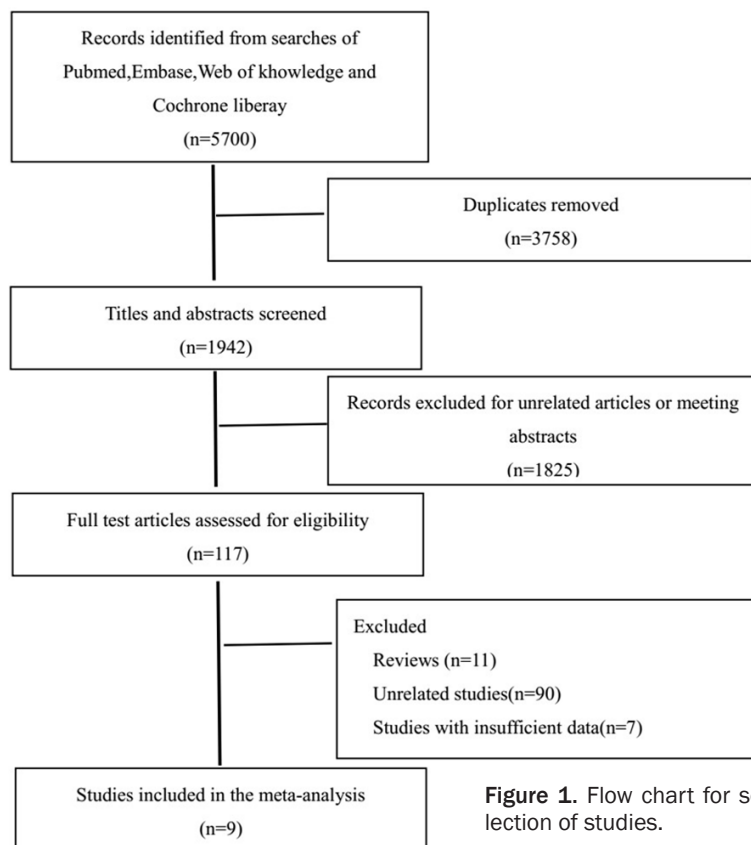
Cochrane’s Collaboration tool was used for assessing risk of bias for randomized controlled trials. It provided a description of what was reported in the study and gave a subjective judgment regarding protection from bias: low risk, high risk of bias, or unclear risk (according

to Cochrane Review’s handbook 5.3) (Table 1). Newcastle-Ottawa scale [9], for non-randomized studies, was used to assess whether the study adjusted for confounders (Table 2).

*Data analysis*

Meta-analysis for any outcome of interest was attempted only if relevant data could be extracted from three or more trials. Review Manager (RevMan version 5.3, Copenhagen, The Nordic Cochrane Centre, the Cochrane Collaboration 2011) was used to perform the meta-analysis. Relative risk or risk ratios (RR) and 95% confidence intervals (CI) were calculated for each outcome, presented as forest plots after pooling. Pooled RR, symbolized by a solid diamond at the bottom of the forest plot (the width of which represents the 95% CI), is the best estimate of pooled outcomes. Sensitivity or influence analysis was carried out to assess the influence of each study on overall summary effects. Heterogeneity analysis was performed by Chi-squared test, according to Higgins’ study, with  $P < 0.1$  indicating that heterogeneity exists [10]. The magnitude of between-studies heterogeneity was assessed using the  $I^2$  statistic, with  $I^2 > 50\%$  indicating greater heterogeneity.

## Gut decontamination and GVHD in allo-HSCT



**Figure 1.** Flow chart for selection of studies.

nation and without gut decontamination (RR 0.78, [95% CI 0.47-1.30]). There were no differences in incidence of skin acute GVHD between gut decontamination and without gut decontamination (RR 1.06, [95% CI 0.87-1.29]). Among five non-RCTs, sensitivity analysis showed significant differences between gut decontamination and without gut decontamination (RR 1.46, [95% CI 1.19-1.80]) (Figure 2).

### Chronic GVHD

Data regarding incidence of chronic GVHD could be extracted from 3 trials that were pooled for meta-analysis. There were no differences in incidence of chronic GVHD between gut decontamination and without gut decontamination (RR 0.96, [95% CI 0.75-1.23]) (Figure 3).

## Results

### Studies and patient characteristics

A flow diagram of study search and selection is illustrated in Figure 1. A total of nine studies were included. Of these, three trials were RCTs involving 365 patients while the others were non-RCTs involving 1,154 patients [11-18]. Data regarding host characteristics, transplantation type, donor source, GVHD prophylaxis, and antibiotics used are summarized in Table 3.

### Acute GVHD

Data concerning incidence of acute GVHD could be extracted from seven trials that were pooled for meta-analysis. There was a statistical difference in incidence of II-IV acute GVHD between gut decontamination and without gut decontamination (RR 1.25, [95% CI 1.03-1.52]). There was also a statistical difference in incidence of intestinal acute GVHD between gut decontamination and without gut decontamination (RR 1.39, [95% CI 1.02-1.90]). There were no differences in incidence of liver acute GVHD between gut decontami-

### Overall survival

Four studies provided data regarding overall survival. There were no differences in 5-year overall survival between gut decontamination and without gut decontamination (RR 1.08, [95% CI 0.77-1.5]) (Figure 4).

## Discussion

The prognosis of patients undergoing allogeneic hematopoietic stem cell transplantations (allo-HSCT) can be adversely affected by subsequent infections and GVHD. Bacterial infections are the most common infections. Patient immunocompromised states may require the use of antibiotic treatments as prophylactic regimens or to treat manifest infections and neutropenic fevers. In the early 1970s, several scientists found that disruption of the GI barrier caused by total body irradiation or conditioning regimens resulted in the leakage of bacterial lipopolysaccharides and other microbe/pathogen-associated molecular patterns into the systemic circulation. This may trigger the secretion of inflammatory cytokines, with donor T-cells recruited into host organs by these cytokines,

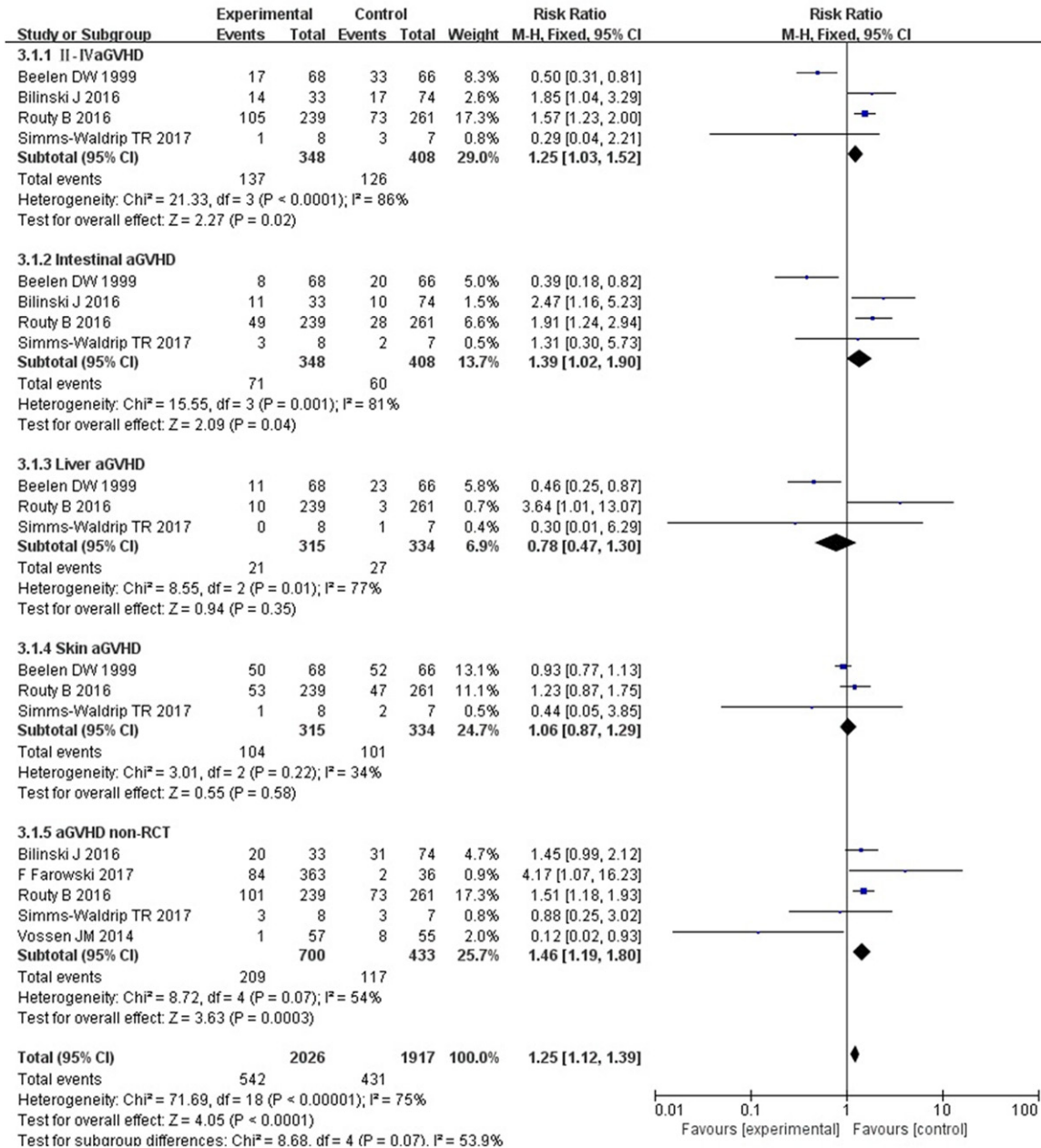
## Gut decontamination and GVHD in allo-HSCT

**Table 3.** Characteristics of included studies

Study, Year	No. of patients		Sex		Median age (years)		Antibiotics used		Conditioning regimen	Induced disease	Graft source	Donor's characteristic	GVHD prophylaxis
	GD	No GD	GD	No GD	GD	No GD	GD	No GD					
Buckner CD 1978 [11]	56	45	28 M, 18 F	26 M, 18 F	22 (8-37)	20 (9-49)	Gentamicin vancomycin paromomycin polymyxin	No	Myeloablative (101)	AL (n=56) nAL (n=45)	BMT (n=101)	RD (n=101)	Unclear
Storb R 1983 [3]	39	91	Unclear	Unclear	Unclear	Unclear	Oral nonabsorbable antibiotics	No	Myeloablative (130)	AA (n=130)	BMT (n=130)	RD (n=130)	MTX
Beelen DW 1999 [10]	68	66	33 M, 35 F	29 M, 37 F	36 (17-56)	37 (17-57)	Metronidazole Ciprofloxacin	Ciprofloxacin	Myeloablative (134)	AL (n=44) nAL (n=90)	Unclear	RD (n=99) NRD (n=35)	CsA MTX
Vossen JM 2014 [12]	55	57	Unclear	Unclear	Unclear	Unclear	Cefaloridine Gentamycin Amphotericin B Vancomycin Piperacillin/tazobactam	No	Myeloablative (112)	AL (n=85) nAL (n=27)	BMT (n=112)	RD (n=112)	CsA MTX
Routy B 2016 [14]	239	261	145 M, 94 F	156 M, 105 F	51.6 (18-69)	49.9 (16-70)	Ciprofloxacin Trimethoprim sulfamethoxazole Levofloxacin Moxifloxacin Carbapenems Vancomycin	No	Myeloablative (n=262) Non-myeloablative (n=238)	Unclear	BMT/ PBSCT/ Cord blood (67/417/16)	RD (n=335) NRD (n=165)	CsA Tacrolimus MTX
Billinski J 2016 [16]	33	74	16 M, 48 F	39 M, 53 F	48 (20-78)	47 (18-65)	Carbapenems Vancomycin Piperacillin-tazobactam Linezolid Colistin	No	Myeloablative/ric (61/39)	AL (n=53) nAL (n=54)	PBSCT/BMT (94/2)	RD (n=38) NRD (n=69)	ATG CsA MTX MMF
Farowski F 2017 [13]	363	36	Unclear	Unclear	Unclear	Unclear	Penicillin derivatives Carbapenems	No	Myeloablative/ric (67/322)	AL (n=239) nAL (n=160)	Unclear	RD (n=120) NRD (n=279)	ATG/calcineurin inhibitors/MMF/sirolimus/steroids
Simms-Waldrup TR 2017 [15]	8	7	6 M, 2 F	1 M, 6 F	5.1-7.2 (1.6-14.5)	10.79 (5.06-14.46)	Levofloxacin	No	Myeloablative/ric (9/6)	AL (n=5) nAL (n=10)	BMT/PBSCT (14/1)	RD (n=7) NRD (n=8)	Tacrolimus/CsA/ MTX/MMF/ prednisone
Weber D 2017 [17]	533	88	Unclear	Unclear	Unclear	Unclear	Ciprofloxacin Metronidazole Rifaximin Vancomycin	No	Unclear	AL (n=296) nAL (n=325)	non-T cell-depleted grafts	RD (n=168) NRD (n=453)	Unclear

GD: gut decontamination; NRD: unrelated donors; RD: related donors; AL: acute leukemia; nAL: non-acute leukemia; AA: aplastic anemia; M: male; F: female; ATG: antithymocyte globulin; CsA: cyclosporine A; MTX: methotrexate; MMF: mycophenolate mofetil; RIC: reduced intensity myeloablative.

## Gut decontamination and GVHD in allo-HSCT

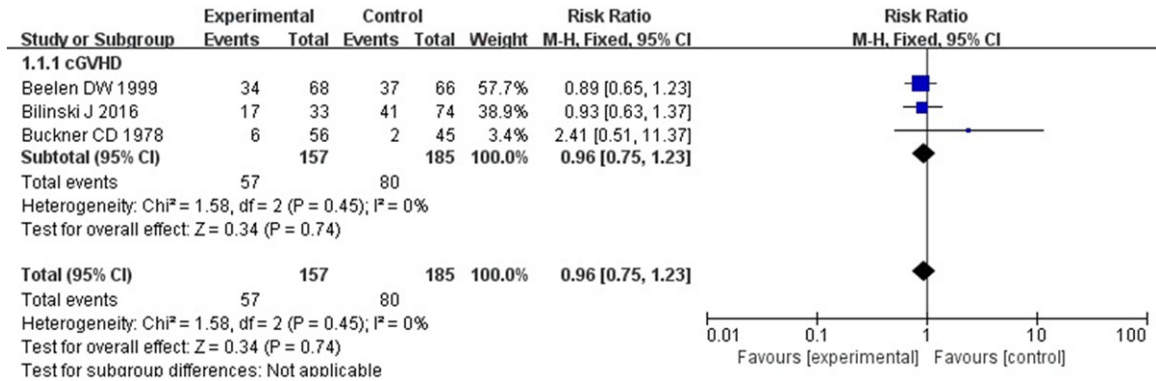


**Figure 2.** Meta-analysis of acute GVHD.

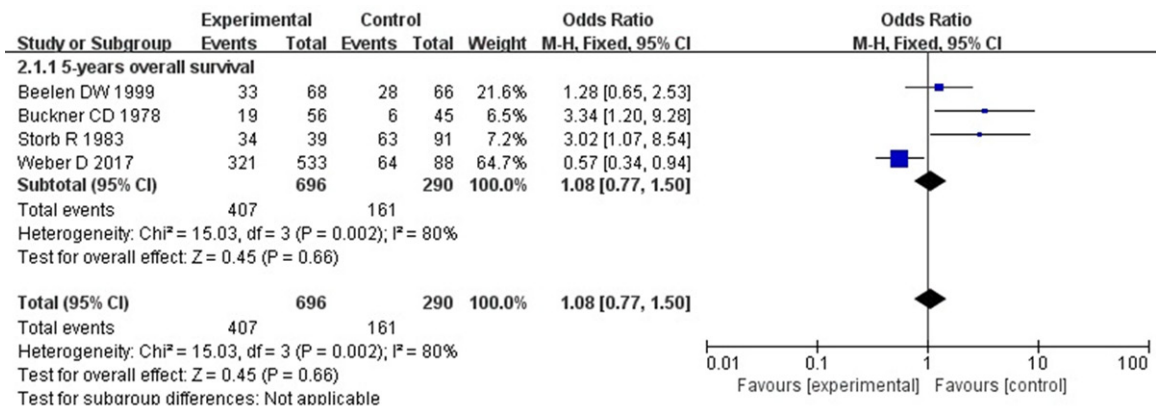
resulting in aGVHD [19-22]. The absence of gut microbiota by using antibiotics has resulted in reduced acute GVHD and prolonged survival. Thus, gut decontamination (GD) by oral broad-spectrum antibiotics as a prophylactic strategy is a common practice in allo-HSCT. In recent years, researchers have found that loss of gut bacterial diversity may increase mortality from GVHD. There is accumulating evidence that preserving intestinal anaerobic bacteria after allo-HSCT may reduce incidence of acute GVHD

and TRM and prolong OS, although studies in randomized prospective methods are lacking. Anaerobic Clostridia, a polyphylactic class of the phylum Firmicutes, plays an important part in anti-inflammatory homeostatic roles, regulating Treg cells. Reduced abundance of Clostridiales has been observed during GVHD [23-28]. This emerging knowledge regarding the role of gut bacterial diversity in allo-HSCT patients raises questions regarding the practice of the gut decontamination as well as the

## Gut decontamination and GVHD in allo-HSCT



**Figure 3.** Meta-analysis of chronic GVHD.



**Figure 4.** Meta-analysis of 5-year overall survival.

ideal choices of antibiotics for neutropenic fevers.

The present study compared and analyzed differences of incidence of aGVHD and cGVHD between allo-HSCT patients with gut decontamination and allo-HSCT patients without gut decontamination. There was a significant difference of incidence of aGVHD. Incidence of aGVHD in allo-HSCT patients with gut decontamination was higher than in allo-HSCT patients without gut decontamination, especially intestinal aGVHD. There were no significant differences of liver and skin aGVHD. Moreover, there were no significant differences of cGVHD and 5-year overall survival between allo-HSCT patients with gut decontamination and allo-HSCT patients without gut decontamination. Results suggest that gut decontamination may destroy gut bacterial diversity. This may result in increased intestinal aGVHD, but with no effects on cGVHD and OS.

However, there were many limitations to this meta-analysis. Included studies were mostly retrospective controlled studies, lacking comparable gut decontamination regimens with varying antibiotic regimens between centers and lacking detailed gut microbiome analyses. Large randomized controlled studies are needed to confirm these results and provide high quality research evidence for a second evaluation.

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### Disclosure of conflict of interest

None.

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