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Impact of the gut microbiome on immune checkpoint inhibitor efficacy—a systematic review

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ABSTRACT

Background Immune checkpoint inhibitors (ICIs) are increasingly being used in clinical practice, improving outcomes for cancer patients. Preclinical models showed significant interaction between the gut microbiome (GM) and response to ICIs. However, that interaction remains unclear in clinical practice.

Methods We performed a systematic review in MEDLINE to determine

- whether antibiotics affect ICI efficacy,
- whether baseline GM composition and ICI efficacy show any correlations,
- whether baseline GM composition and emergence of immune-related adverse events (irAEs) show any correlations, and
- whether GM manipulation can alleviate the irAEs.

Included publications had to be written in English or French and had to describe a quantifiable link between GM composition or its modification and the response to ICIs or the occurrence of irAEs, or both.

Results Of 1451 articles published before December 2018, 13 publications met the inclusion criteria. Five full-text articles and two abstracts highlighted a negative effect of antibiotics on ICI efficacy. The composition of the GM was associated with ICI efficacy in five full-text articles and one abstract, and with irAEs in two full-text articles. In 2 cases, fecal microbiota transplantation was reported to reduce immune colitis.

Conclusions If possible, antibiotics should be avoided before ICI treatment because of their negative effect on ICI anticancer efficacy. No specific commensal bacterium was associated with ICI efficacy, but an intact GM with high bacterial diversity and a good ratio of "responder-associated" bacteria to "non-responder-associated" bacteria seem to be correlated with better patient outcomes. Fecal microbiota transplantation is a promising technique for reducing ICI-associated colitis.

Key Words Antibiotics, cancer immunotherapy, fecal microbiota transplantation, immune checkpoint inhibitors, microbiome

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INTRODUCTION

The human gut microbiome (GM) is composed of more than 100 trillion bacteria[1]. The GM is highly individual, but can be affected by several external factors such as diet[2], antibiotics[3,4], and treatment with proton-pump inhibitors[5].

The composition of the GM is known to play a key role in the development of multiple diseases[6,7] including inflammatory bowel disease[8,9], diabetes mellitus[10], and obesity[2]. More recently, the GM composition has also been implicated in the development of cancers such as colorectal cancer[11]: the presence of certain bacteria, such as *Fusobacterium nucleatum* appears to be a predictive factor in colorectal cancer development[12,13]. Furthermore, the GM could be associated with response to chemotherapy. The GM has been shown to promote an anticancer immune

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response to cyclophosphamide[14], and an intact GM was associated with the efficacy of CpG–oligonucleotide immunotherapy and platinum chemotherapy in some cancer models[15]. The effect of the GM on the immune system is increasingly being explored, particularly in this era of new immune-modulating agents.

Immune checkpoint inhibitors (ICIS) improve outcomes for patients with cancer. Antibodies targeting CTLA-4, PD-1, and PD-L1 are routinely used in multiple cancers, including advanced non-small-cell lung carcinoma (NSCLC)[16], renal cell carcinoma (RCC)[17,18], urothelial carcinoma[19,20], melanoma[21], and squamous cell carcinoma of the head and neck[22]. However, objective response rates (ORRS) are modest, not exceeding 20%–30%[16,17,19,23], and to date, no efficient biomarker to predict the efficacy of ICIS has been discovered.

Preclinical models show that the composition of the GM and its modification in mouse models can influence the efficacy of ICIS[24,25] or the emergence of immune-related adverse events (IRAES)[26]. Moreover, experimental interventions such fecal microbiota transplantation (FMT) might, in animals, restore the response to ICIS[27,28] and reduce IRAES, particularly colitis[24]. Whether such effects would be observed in humans currently remains unknown. In the present review, we evaluated how GM modification by antibiotics might affect ICI efficacy in humans and explored the associations between the composition of the GM and the efficacy and toxicity of ICIS.

METHODS

This systematic review was performed based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[29].

The first objective of the review was to evaluate the effect of GM modification by antibiotics on the efficacy of ICIS, based on ORR, progression-free survival (PFS), and overall survival (OS) in patients treated for a malignancy with ICIS (without other cytotoxic agents). The second objective was to analyze the association between the composition of the GM and ICI efficacy (based on ORR) and toxicity (based on the occurrence of IRAES).

We included studies that evaluated ICIS (anti–CTLA-4, anti–PD-1 and anti–PD-L1) in adult patients with solid cancers and that described a quantifiable link between the composition or modification (by antibiotics, probiotics, FMT, etc.) of the GM and the response to the ICI or the occurrence of IRAES.

To that end, we searched MEDLINE using combinations of the terms "cancer immunotherapy" or "immune checkpoint inhibitors" and "microbiome" or "probiotic" or "antibiotic" or "dysbiosis." Subsequently, the reference lists of included papers were screened to find other studies that met the inclusion criteria. We included only publications written in French or English. All articles published before 9 December 2018 were reviewed. Articles were selected based on a review of the abstract; the full text was subsequently analyzed. The analysis included only full-text articles or abstracts that, through clinical trials or reports, evaluated a link between the GM and ICIS. Reviews, comments, and expert opinions were excluded, but as already mentioned, reference lists in such items were screened to find other publications.

Only the data published in the article and its supplementary contents were gathered; no verification was sought from the authors of the various studies.

The variables analyzed were found in all the included studies: number of patients, type of ICIS, cancer type, GM composition, methods used to assess the GM composition, the intervention to the GM (if applicable), and any quantifiable effect of the GM (or its modification) on the efficacy of the ICI in terms of ORR, PFS, and OS, or on the toxicity of the ICI in terms of the occurrence of IRAES.

The aim of this systematic review was to identify all studies meeting the inclusion criteria, not to perform a quantitative synthesis of the results.

RESULTS

Included Articles

Figure 1 illustrates the selection of the papers as a flow diagram.

We found ten full-text papers and three abstracts that met the inclusion criteria. Five full-text articles[27,30–33] and two abstracts[34,35] analyzed the influence of antibiotics on ICI efficacy; five full-text articles and one abstract evaluated the influence of the GM composition on ICI efficacy; and three full-text articles explored the influence of the GM on IRAES.

Impact of Antibiotics on ICI Efficacy

Table I summarizes the articles and abstracts that considered the effect of antibiotics on ICI efficacy. One study was prospective[32]; the remaining studies were retrospective. All publications presented results for two groups, an antibiotic-naïve (ABn) group and an antibiotic-treated [ABt (before or during receipt of ICIS)] group. Patients generally received oral antibiotics for common indications (dental, urinary, and pulmonary infections). Of the 997 patients included in the publications, 784 were in the ABn group, and 213 were in the ABt group. Most of the patients had NSCLC ($n = 561$) or RCC ($n = 338$). All had received at least one of anti–PD-1 or anti–PD-L1 or anti–CTLA-4 therapy.

Overall, use of antibiotics was associated with lower ICI efficacy. In all publications, use of antibiotics in patients with RCC negatively affected PFS (1.9–4.3 months in ABt patients vs. 7.4–8.1 months in ABn patients) and OS (17.3–23.4 months in ABt patients vs. 27.9–30.6 months in ABn patients). The ORR was also higher in ABn than in ABt patients (35%–78% vs. 13%–25% respectively)[27,30,35]. In all publications (except for two that lacked OS data), use of antibiotics in patients with NSCLC negatively affected OS (4–7.9 months in ABt patients vs. 12.6–24.6 months in ABn patients); no differences in PFS (1.9–3.5 months vs. 2.8–3.8 months) or ORR (25%–60% vs. 23%–63%) were observed[27,30,34]. Data for patients with urothelial carcinoma were limited to a single article that showed poorer outcomes in ABt patients than in ABn patients in terms of PFS (1.8 months vs. 4.3 months) and OS (11.5 months vs. not reached); ORR data were not available[27]. Data for patients with melanoma were similarly limited to one prospective trial in which the response rate to ICIS was similar in the

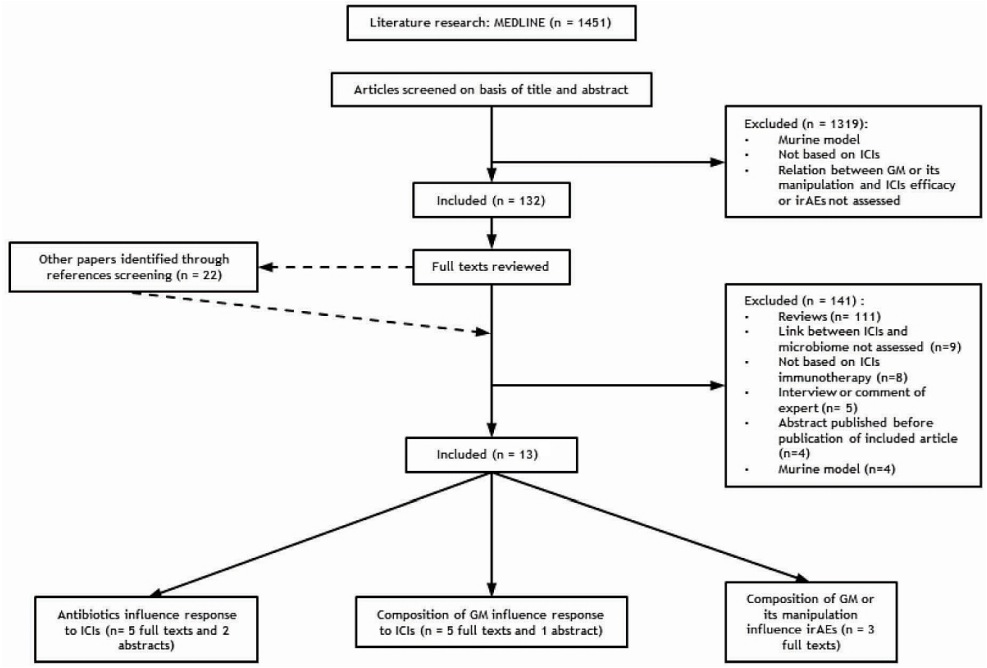

FIGURE 1 Flow diagram of the literature search. ICI = immune checkpoint inhibitor; GM = gut microbiome; irAEs = immune-related adverse events.

ABt and ABn groups (67% vs. 63%), and PFS and OS data were not available. However, the comparison groups were unbalanced, with just 3 patients in the ABt group and 35 in the ABn group[27].

Composition of the GM and Response to ICIs

Table II summarizes the articles and abstracts that considered the relationships between the GM composition and ICI efficacy.

The studies analyzed 228 fecal samples and 171 saliva samples from patients who had not yet started ICIs (anti–CTLA-4, anti–PD-1 or anti–PD-L1). Most of the patients providing fecal samples had advanced melanoma (n = 154); the rest had advanced NSCLC and RCC. Of the 171 patients who provided saliva samples, 85 had squamous cell carcinoma of the head and neck, and 86 had melanoma. The patients were subsequently classified as responders or non-responders to ICIs, in most cases using RECIST (the Response Evaluation Criteria in Solid Tumors). The GM composition was assessed using any one or more of a variety of assays, including meta-genomic shotgun sequencing, quantitative polymerase chain reaction, and 16S ribosomal RNA sequencing.

In all publications, authors found a significant association between the commensal microbial composition and clinical response[27,28,32,36,38]. The species of bacteria identified were different in the reports. For example, Matson *et al.*[38] found that the species more abundant in responder–patients with melanoma included *Bifidobacterium longum, Collinsella aerofaciens,* and *Enterococcus faecium*. Routy *et al.*[27] noted correlations between the clinical response to ICIs and the relative abundance of *Akkermansia muciniphila* in patients with NSCLC and RCC. Gopalakrishnan *et al.*[28] found a relative abundance of bacteria of the Ruminococcaceae family in responder–patients with melanoma. Chaput *et al.*[36] observed longer PFS and OS durations in patients with melanoma whose GM contained *Faecalibacterium genii* and other Firmicutes. In a prospective study, Frankel *et al.*[32] showed that, depending on the ICI, commensal flora could be different in responders. In responders to nivolumab–ipilimumab, the GM was enriched for *Faecalibacterium prausnitzii, Bacteroides thetaiotaomicron,* and *Holdemania filiformis*. In responders to pembrolizumab, the GM was enriched for *Dorea formicigenerans*. Conversely, no association between the oral microbiome and ICI efficacy was evident[29,30].

Bacteria that have been reported to affect the response to ICIs are shown by phylum in Table III.

The GM and irAEs

Table IV summarizes the articles that considered the association between IRAEs and the GM.

Of three articles, two[27,36] found a correlation between the GM composition and the occurrence of ICI-mediated colitis in patients with melanoma. Patients experiencing immune-mediated colitis showed a high quantity of Firmicutes in stool samples. In contrast, an abundance of Bacteroidetes was correlated with a low incidence of colitis in ICI-treated patients[26,36].

An article by Wang *et al.*[39] reported two cases of using FMT to successfully treat ICI-mediated colitis.

DISCUSSION

The data presented here strongly attest that use of antibiotics can reduce the efficacy of ICIs and affect outcomes in patients receiving ICIs for cancer. Use of antibiotics is

TABLE I Human studies that assess the efficacy of immunotherapy in patients receiving or not receiving antibiotics near in time to the administration of immune checkpoint inhibitors (ICIs)

Reference	Cancer site	ICI	Pts (*n*)	Intervention and timing	ORR (%)	*p* Value	PFS (months)	*p* Value	OS (months)	*p* Value	Design
Frankel *et al.*, 2017[32]	Melanoma	Pembrolizumab	11	No antibiotics	63						Prospective
		Ipilimumab–nivolumab	22								
		Ipilimumab–nivolumab	1	Ceftriaxone for 2 weeks before ICI Ciprofloxacin, vancomycin, and metronidazole for 2 weeks after 2 cycles of ICI Nitrofurantoin after 4 cycles of ICI	67	NA	NA		NA		
		Pembrolizumab	2								
		Ipilimumab–nivolumab	1	Daily doses of the probiotic *Lactobacillus rhamnosus*	100						
Kaderbhai *et al.*, 2017[31]	NSCLC	Nivolumab	59	No antibiotics	49	0.75	NA	0.72	NA	NA	Retrospective
			15	Antibiotics from 3 months before to end of ICI	60						
Thompson *et al.*, 2017[34]	NSCLC	Anti–PD-1	56	No antibiotics	23	0.20	3.8	<0.001	12.6	0.005	Abstract, retrospective
		(95% nivolumab)	18	Antibiotics[a] from 6 weeks before to initiation of ICI	25		2		4		
Ahmed *et al.*, 2018[33]	24 NSCLC, 3 RCC, 4 UC, 1 melanoma, 3 SCCHN, 5 HCC, 3 others	Nivolumab	31	No antibiotics	63	0.024	NA	0.048	89 Weeks	0.003	Retrospective
		Pembrolizumab	6								
		Atezolizumab	2								
		ICI and chemotherapy	4								
	10 NSCLC, 1 RCC, 1 UC, 2 melanoma, 3 others	Nivolumab	8	Antibiotics[b] from 2 weeks before to 2 weeks after initiation of ICI	29				23 Weeks		
		Pembrolizumab	4								
		Atezolizumab	1								
		ICI and chemotherapy	1								
Derosa *et al.*, 2018[30]	NSCLC	Anti–PD-(L)1 ± ipilimumab	191	No antibiotics	57	0.26	3.8	0.03	24.6	<0.01	Retrospective
			48	Antibiotics[c] from 30 days before to initiation of ICI	48		1.9		7.9		
	RCC	Anti–PD-(L)1 ± ipilimumab or	105	No antibiotics	78	<0.01	7.4	<0.01	30.6	0.03	
		anti–PD-(L)1 + bevacizumab	16	Antibiotics[c] from 30 days before to initiation of ICI	25		1.9		17.3		
Lalani *et al.*, 2018[35]	RCC	PD(L)1	115	No antibiotics	35	0.026	8.1	0.008	NA		Abstract, retrospective
			31	Antibiotics from 8 weeks before to 4 weeks after initiation of ICI			13		2.6		

TABLE I Continued

Reference	Cancer site	ICI	Pts (*n*)	Intervention and timing	ORR (%)	*p* Value	PFS (months)	*p* Value	OS (months)	*p* Value	Design
Routy *et al.*, 2018[27]	NSCLC	Anti–PD-(L)1	103	No antibiotics	NA		2.8	0.571	15.3	0.001	Retrospective
			37	Antibiotics[d] from 2 months before to 1 month after initiation of ICI			3.5		8.3		
	RCC	Anti–PD-(L)1	47	No antibiotics			7.4	0.012	27.9	0.154	
			20	Antibiotics[d] from 2 months before to 1 month after initiation of ICI			4.3		23.4		
	UC	Anti–PD-(L)1	30	No antibiotics			4.3	0.049	NR	0.098	
			12	Antibiotics[d] from 2 months before to 1 month after initiation of ICI			1.8		11.5		

[a] 50% Quinolones.
[b] Mostly cephalosporins, then vancomycin, then quinolones.
[c] Mostly beta-lactam ± inhibitors, then quinolones or sulfonamides.
[d] Beta-lactams ± inhibitors, fluoroquinolones, or macrolides.

Pts = patients; ORR = objective response rate; PFS = progression-free survival; OS = overall survival; NA = not assessed; NSCLC = non-small-cell lung carcinoma; RCC = renal cell carcinoma; UC = urothelial carcinoma; SCCHN = squamous cell carcinoma of the head and neck; HCC = hepatocellular carcinoma; anti–PD-(L)1 = antibodies against PD-1 or PD-L1; NR = not reached.

associated with poorer ORR, PFS, and OS, regardless of cancer type. Those data suggest that modification of the GM can negatively affect the course of immunotherapy. Interestingly, proton-pump inhibitors—medications that can also alter the gut microbiota—were not observed by Routy *et al.*[27] to affect PFS or OS in patients with cancer, reflecting a specific effect of antibiotics.

The influence of antibiotics on ICI efficacy could be explained in various ways. First, as discussed in the present review, modification of the GM by antibiotics could lead to the selection of bacterial species that negatively affect the response to ICIs. In preclinical mouse models, transplantation of certain species of "favourable" bacteria restored the response to ICIs after treatment with broad-spectrum antibiotics[24,25]. Similar research in human patients has not been yet been performed. A second way to elucidate the effect of antibiotics on the response to ICIs is the intrinsic anti-inflammatory effect of certain antibiotics. Indeed, quinolones lower the levels of pro-inflammatory cytokines (such as tumour necrosis factor α or interleukine 1)[40] and macrolides reduce the T cell response, resulting in a potential antagonist effect against ICIs[41]. Moreover, independent of ICI treatment, some antibiotics might also have an intrinsic negative effect on the clinical course of cancer by favouring carcinogenesis and metastases[42].

Currently, determining the type of antibiotics that most strongly affect ICI efficacy is difficult, although it seems logical that broad-spectrum antibiotics are likely to have the most significant effect. Indeed, Ahmed *et al.*[33] reported that the ORR was significantly lower in patients receiving broad-spectrum antibiotics than in those who were naïve to such antibiotics. In contrast, no difference was observed between patients who did and did not receive narrow-spectrum antibiotics. In addition, questions remain about the optimal time interval that has to pass after a course of antibiotic therapy before ICIs to treat cancer are started; however, we observed a similar negative effect of antibiotics in the Derosa *et al.*[30] report (antibiotics administered within the 30 days before ICI start) and in the Routy *et al.*[27] report (antibiotics administered between 60 days before and 30 days after ICI start), suggesting that the effect of antibiotics on the anticancer activity of ICIs could be deleterious for several months[30]. All those observations highlight the importance of balancing the benefits and inconveniences of starting antibiotics when considering immunotherapy in a patient.

Preclinical studies in mice demonstrated that certain bacteria are associated with ICI efficacy[25,26]. In the present review, identifying specific species or phyla that are clearly associated with ICI efficacy in a specific cancer or a variety of cancers is impossible. All the publications included in the review identified different commensal bacteria. That variation could be explained by the different assays used, the different baseline characteristics of patients, and differences in the medical and infectious history of the patients. Notably, the five major phyla of GM bacteria are present in both responder and non-responder patient groups (Table III). Conversely, the oral microbiome seems to have no correlation with ICI efficacy[28,37]. It might be hypothesized that a GM with a high diversity of commensal bacterial[28] and a favourable ratio between high-ORR-associated

TABLE II Human studies that assess a link between the gut microbiome and response to immune checkpoint inhibitors (ICIs)

Reference	Cancer site	ICI	Pts (*n*)	Assessment method	Sample type	Responders		Non-responders	
						(*n*)	Associated bacteria	(*n*)	Associated bacteria
Chaput *et al.*, 2017[36]	Melanoma	Ipilimumab	26	16S ribosomal RNA sequencing	Fecal	9	Firmicutes, *Faecalibacterium prausnitzii* L2-6, butyrate-producing bacterium L2-21, and *Gemmiger formicilis* ATCC 27749	17	Bacteroidetes (genus *Bacteroides*)
Ferris *et al.*, 2017[37]	SCCHN	Nivolumab	85	16S ribosomal RNA sequencing	Salivary	No association			
Frankel *et al.*, 2017[32]	Melanoma	Pembrolizumab	13	Meta-genomic shotgun sequencing	Fecal	24	*Streptococcus parasanguinis, Bacteroides caccae, Dorea formicigenerans* (latter for pembrolizumab only)	15	*Faecalibacterium prausnitzii, Holdemania filiformis, Bacteroides thetaiotaomicron* (phylum Firmicutes)
		Ipilimumab–nivolumab	24						
		Nivolumab	1						
		Ipilimumab	1						
Gopalakrishnan *et al.*, 2018[28]	Melanoma	Anti–PD-1	89	Meta-genomic shotgun sequencing	Fecal	30	Clostridiales, Ruminococcaceae, *Faecalibacterium,* and high alpha diversity	13	*Bacteroides thetaiotaomicron, Escherichia coli,* and *Anaerotruncus colihominis,* low alpha diversity
					Salivary	54	No association	32	Bacteroidales
Matson *et al.*, 2018[38]	Melanoma	Anti–PD-1	38	16S Ribosomal RNA sequencing, meta-genomic shotgun sequencing, quantitative PCR	Fecal	16	High *Enterococcus faecium, Collinsella aerofaciens, Bifidobacterium adolescentis, Klebsiella pneumoniae, Veillonella parvula, Parabacteroides merdae, Lactobacillus species, and Bifidobacterium longum*	26	*Ruminococcus obeum, Roseburia intestinalis*
		Ipilimumab	4						
Routy *et al.*, 2018[27]	NSCLC, RCC	Anti–PD-(L)1	78	Meta-genomic shotgun sequencing	Fecal	42	High *Akkermansia muciniphila, Ruminococcus* species, *Alistipes* species, and *Eubacterium*; low *Bifidobacterium adolescentis, Bifidobacterium longum,* and *Parabacteroides distasonis*	36	NA

Pts = patients; ATCC = American Type Culture Collection; SCCHN = squamous cell carcinoma of the head and neck; anti–PD-(L)1 = antibodies against PD-1 or PD-L1; PCR = polymerase chain reaction; NSCLC = non-small-cell lung carcinoma; RCC = renal cell carcinoma; NA = not assessed.

TABLE III Gut microbiome bacteria in responders and non-responders to immune checkpoint inhibitors, by phylum

Responders	Phylum				
	Firmicutes	Bacteroidetes	Actinobacteria	Proteobacteria	Verrucomicrobia
Yes	Butyrate-producing bacterium L2-21, Clostridiales, *Dorea formicigenerans, Enterococcus faecium, Eubacterium, Faecalibacterium, Faecalibacterium prausnitzii* L2-6, *Gemmiger formicilis, Lactobacillus, Ruminococcus, Streptococcus parasanguinis, Veillonella parvula*	*Alistipes, Bacteroides caccae, Parabacteroides merdae*	*Collinsella aerofaciens, Bifidobacterium adolescentis, Bifidobacterium longum*	*Klebsiella pneumoniae*	*Akkermansia muciniphila*
No	*Anaerotruncus colihominis, Faecalibacterium prausnitzii, Holdemania filiformis, Roseburia intestinalis, Ruminococcus obeum*	*Bacteroides* species, *Bacteroides thetaiotaomicron, Parabacteroides distasonis*		*Escherichia coli*	

Pts = patients; ATCC = American Type Culture Collection.

TABLE IV Human studies that assess associations of the composition of the gut microbiome with immune checkpoint inhibitor (ICI)–induced colitis

Reference	Cancer site	ICI	Pts *(n)*	Sample type	Method	Adverse effect		
						Pts *(n)*	Type	Associated bacteria
Dubin *et al.*, 2016[26]	Melanoma	Ipilimumab	33	Fecal	16S ribosomal RNA sequencing	13	Colitis	Low Bacteroidaceae
		Ipilimumab–nivolumab	1			21	None	High Bacteroidaceae, Rikenellaceae, Barnesiellaceae
Chaput *et al.*, 2017[36]	Melanoma	Ipilimumab	26	Fecal	16S ribosomal RNA sequencing	7	Colitis	High *Faecalibacterium prausnitzii* L2-6, butyrate-producing bacterium L2-21, *Gemmiger formicilis* ATCC 27749
						19	None	High *Bacteroides*

species and low-ORR-associated species[38] should provide the best clinical outcomes, but would have to be confirmed in future clinical trials.

Even if ICI-mediated colitis shares some clinical and histologic features with inflammatory bowel diseases such as Crohn disease, the GM compositions in the two entities are completely different, suggesting that the two diseases cannot be confused[9]. Specific bacterial species might be associated with development of immune-related adverse events, particularly colitis[26,36]. It is interesting to note that, as reported by Chaput *et al.*[36], some bacterial species might be associated both with better clinical benefit from ICIs and with the occurrence of immune-related colitis—an observation that could reflect an epiphenomenon: the well-known positive correlation between ICI efficacy and immune-mediated enterocolitis, as reported by Beck *et al.*[40] in patients with RCC or melanoma treated with ipilimumab. However, that hypothesis also requires further prospective clinical trials.

Fecal microbiota transplantation is effective for the treatment of recurrent *Clostridium difficile* infection[41] or ulcerative colitis[42]. It is a safe technique with a low rate of adverse events[41–43]. In preclinical models, FMT enriched in *Bacteroides*[24] or *Bifidobacterium* species[25] from responder mice into germ-free or ABt mice increased the efficacy of ICIs; FMT from non-responder mice did not improve the response to ICIs[27,28]. Enrichment in *Bifidobacterium* was also shown to reduce colitis in mice treated with CTLA-4 inhibitors[44]. No data are available about FMT to improve ICI efficacy in human patients. However, Wang *et al.*[39] reported two cases of the use of FMT in ICI-treated human patients to alleviate ICI-mediated colitis. One patient had developed glucocorticoid-refractory colitis and experienced complete recuperation of symptoms 2 weeks after a single FMT. The second patient, a 78-year-old man, had been enrolled on an immunotherapy trial for prostate cancer. He also developed an immune-related refractory colitis. Complete resolution of symptoms occurred after 2 colonoscopic FMTs. Even if that strategy appears promising, further trials are needed to explore the clinical implications of FMT.

The recommended treatments for high-grade irAEs are, first, corticosteroids; if corticosteroids fail, biologic agents targeting tumour necrosis factor α are then administered. However, the latter agents can generate many metabolic and immunologic adverse events. In future, FMT might be used as the first-line therapy for high-grade immune-related colitis if that treatment's efficacy and toxicity profile are proved to be more beneficial than current first-line therapies. Notably, Wang *et al.* did not specifically prepare or enrich the bacterial content used for their FMT. A major challenge should be to enhance control of immune-related colitis or even the efficacy of ICI by the addition of beneficial bacteria species to the material used for FMT or probiotic administration.

Our review of the literature confirmed the negative effect of antibiotics on the anticancer efficacy of ICIs and highlighted potential correlations between the GM composition and ICI efficacy and irAEs. However, our work has multiple limitations. First, we searched for publications only in the MEDLINE system. However, we hypothesize that most relevant clinical trials were included in our investigation because of our complete scan of the references in the publications (n = 111) found by our initial research algorithm. Second, only papers written in English or French were included, although the number of articles in other languages was low. Third, the included trials focused on various cancers being treated with a variety of therapies (anti–CTLA-4, anti–PD-1, and anti–PD-L1), regardless of the patient's PD-L1 status, prior therapies, and baseline characteristics. Most of the trials were not prospective and included a small number of patients. Given the large number of variables, it is difficult to certify that the ABn and ABt groups were well balanced with respect to baseline characteristics. Furthermore, the types of antibiotics used were often unknown, as were the reasons for their initiation.

CONCLUSIONS

If possible, use of antibiotics must be avoided before or during ICI treatment because of their negative effect on the anticancer efficacy of ICIs and on patient outcomes. However, we cannot precisely define the optimal timing of antibiotic exposure when necessary or prioritize the classes of antibiotics that should be avoided in patients being treated with ICIs. No specific commensal bacterium was found to be associated with high ICI efficacy; however, an intact GM, with high bacterial diversity and a good ratio of "responder-associated" bacteria to "non-responder-associated" bacteria, seems to be associated with beneficial clinical outcomes. Fecal microbiota transplantation is a promising concept to reduce ICI-associated colitis, but further investigation into current clinical practice is needed because of the heterogeneity of the relevant studies and the difficulty in obtaining accurate quantitative data.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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