International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
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ARTICLE TITLE	THE IMPACT OF ANTIBIOTIC THERAPY ON THE EFFECTIVENESS OF IMMUNOTHERAPY: A REVIEW OF CURRENT EVIDENCE
DOI	https://doi.org/10.31435/ijitss.1(49).2026.4882
RECEIVED	29 December 2025
ACCEPTED	14 March 2026
PUBLISHED	20 March 2026
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THE IMPACT OF ANTIBIOTIC THERAPY ON THE EFFECTIVENESS OF IMMUNOTHERAPY: A REVIEW OF CURRENT EVIDENCE

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ABSTRACT

Background: Immune checkpoint inhibitors have transformed cancer treatment, yet only a subset of patients achieve durable clinical benefit. Increasing evidence indicates that the intestinal microbiota plays a key role in regulating antitumor immune responses. Antibiotic therapy, by disrupting microbial homeostasis, may negatively influence the effectiveness of immunotherapy.
Objectives: This narrative review aims to synthesize current preclinical and clinical evidence regarding the impact of antibiotic exposure on the efficacy of immune checkpoint inhibitor therapy, with particular attention to timing of exposure, tumor type, and underlying biological mechanisms.
Methods: A focused literature search was conducted using major biomedical databases to identify relevant preclinical studies, retrospective and prospective clinical cohorts, and systematic reviews examining the relationship between antibiotic use and immunotherapy outcomes. Due to heterogeneity in study design and exposure definitions, findings were analyzed narratively.
Results: Across multiple tumor types, antibiotic exposure was consistently associated with inferior clinical outcomes, including reduced progression-free survival, overall survival, and treatment response. The negative association was most pronounced when antibiotics were administered shortly before initiation of immunotherapy. Meta-analyses confirmed the robustness of this signal despite substantial heterogeneity and methodological limitations. Emerging translational and early interventional studies suggest that modulation of the gut microbiome may partially restore immunotherapy responsiveness.
Conclusions: Current evidence supports a clinically relevant association between antibiotic exposure and reduced immunotherapy efficacy. While causality cannot be definitively established, these findings highlight the importance of judicious antibiotic use in patients receiving immunotherapy and underscore the need for prospective, microbiome-integrated studies to guide future clinical practice.

KEYWORDS

Antibiotics, Immune Checkpoint Inhibitors, PD-1/PD-L1, CTLA-4, Gut Microbiome, Cancer

CITATION

Dominika Zdobylak, Monika Kowalska, Anita Zięba, Michał Domin, Justyna Całka, Katarzyna Ścibisz, Karolina Ollik, Kamil Harenza, Mateusz Taranowicz, Olga Kowalczyk. (2026) The Impact of Antibiotic Therapy on the Effectiveness of Immunotherapy: A Review of Current Evidence. *International Journal of Innovative Technologies in Social Science*. 1(49). doi: 10.31435/ijitss.1(49).2026.4882

Introduction

Immune checkpoint inhibitors (ICIs) targeting cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and the programmed cell death 1 (PD-1)/programmed death ligand 1 (PD-L1) axis have fundamentally transformed the treatment landscape of multiple malignancies (Li, Deng, Chu & Zhang, 2019; Reed, Devkota & Figlin, 2019; Shaikh, Gills & Sears, 2019). Durable clinical responses and prolonged survival have been achieved in subsets of patients with melanoma, non–small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and other solid tumors (Reed et al, 2019; Shaikh et al, 2019; Wekking et al, 2025). However, despite these advances, durable clinical benefit is limited to a subset of patients, while a substantial proportion fails to respond to ICIs (Reed et al, 2019; Shaikh et al, 2019). This marked interpatient heterogeneity has prompted intense investigation into host- and tumor-related factors that shape antitumor immune responses beyond tumor genomics alone (Gopalakrishnan et al, 2018; Matson et al, 2018; Routy et al, 2018).

In recent years, the gut microbiome has emerged as a critical modulator of systemic immunity and cancer immunotherapy efficacy. Preclinical studies provided the first compelling evidence that commensal microorganisms are not merely passive bystanders but active participants in shaping antitumor immune responses (Routy et al, 2018; Sivan et al, 2015; Vétizou et al, 2015). Seminal work demonstrated that the antitumor efficacy of CTLA-4 blockade is abrogated in germ-free or antibiotic-treated mice and can be restored through recolonization with specific bacterial species, establishing a causal relationship between gut microbiota composition and immune checkpoint activity (Vétizou et al, 2015). Similarly, distinct commensal

taxa were shown to promote spontaneous antitumor immunity and synergize with PD-1/PD-L1 blockade by enhancing dendritic cell maturation, $CD8^+$ T-cell priming, and intratumoral lymphocyte infiltration (Routy et al, 2018; Sivan et al, 2015).

These foundational observations were rapidly translated into the clinical setting. Independent studies in patients with metastatic melanoma revealed that baseline gut microbiome composition and diversity are strongly associated with response to anti–PD-1 therapy. Responders consistently exhibited higher microbial diversity and enrichment of specific bacterial taxa, whereas non-responders displayed features of dysbiosis (Gopalakrishnan et al, 2018; Matson et al, 2018; Routy et al, 2018). Importantly, fecal microbiota transplantation from responding patients into germ-free mice conferred improved tumor control and restored sensitivity to PD-1 blockade, providing functional evidence that human microbiome signatures are not merely correlative but mechanistically linked to therapeutic efficacy (Gopalakrishnan et al, 2018; Matson et al, 2018). Collectively, these studies established the gut microbiome as a determinant of immune checkpoint responsiveness in humans and highlighted its capacity to influence both systemic and tumor-localized immunity.

Within this biological framework, antibiotic therapy has emerged as a clinically relevant modifier of immunotherapy outcomes. By disrupting commensal ecosystems, antibiotics can precipitate dysbiosis characterized by loss of beneficial taxa, altered microbial metabolism, and impaired immune homeostasis (Li et al, 2019; Reed et al, 2019; Shaikh et al, 2019; Wekking et al, 2025). Preclinical models have demonstrated that antibiotic-induced microbiome depletion compromises antitumor immune responses and attenuates the efficacy of immune checkpoint blockade, reinforcing concerns regarding their potential impact in the clinical setting (Routy et al, 2018; Sivan et al, 2015; Vétizou et al, 2015).

Consistent with these insights, early retrospective clinical studies reported an association between antibiotic exposure and inferior outcomes in patients receiving ICIs, including reduced progression-free survival (PFS) and overall survival (OS). Although these observations do not establish causality and are subject to confounding factors such as infection severity and baseline patient fitness, they have raised important questions regarding the interaction between antibiotic therapy and immunotherapy efficacy (Derosa et al, 2018; Pinato et al, 2019). As a result, antibiotic use has become a focus of growing interest within the broader context of host–microbiome–immune interactions in cancer treatment (Reed et al, 2019; Shaikh et al, 2019; Wekking et al, 2025).

Against this background, a comprehensive synthesis of current evidence is warranted. Understanding how antibiotic therapy influences immunotherapy outcomes is essential for interpreting clinical data, refining patient management strategies, and informing future interventional approaches aimed at modulating the microbiome. This review therefore examines the biological rationale and clinical evidence linking antibiotic exposure to the effectiveness of immune checkpoint inhibitors, highlighting mechanisms of action, key clinical observations, and remaining knowledge gaps in this rapidly evolving field.

The aim of this narrative review is to synthesize current preclinical and clinical evidence regarding the impact of antibiotic exposure on the efficacy of immune checkpoint inhibitor therapy, with particular emphasis on timing of exposure, tumor type, and underlying biological mechanisms.

Methods of the Review

This narrative review was informed by a focused search of the biomedical literature conducted in PubMed/MEDLINE and Embase, supplemented by citation tracking in Web of Science to identify influential and recently published studies. The search strategy aimed to capture both mechanistic and clinical evidence examining the relationship between antibiotic exposure and the effectiveness of immune checkpoint inhibitor therapy.

The literature search was performed using the following keywords: “antibiotics”, “immune checkpoint inhibitors”, “PD-1/PD-L1”, “CTLA-4”, “gut microbiome”, and “cancer”. Relevant preclinical studies, retrospective and prospective clinical studies, and high-quality reviews published in English were considered. Given the substantial heterogeneity in study designs, tumor types, and definitions of antibiotic exposure, the available evidence was synthesized narratively rather than through a formal systematic review framework.

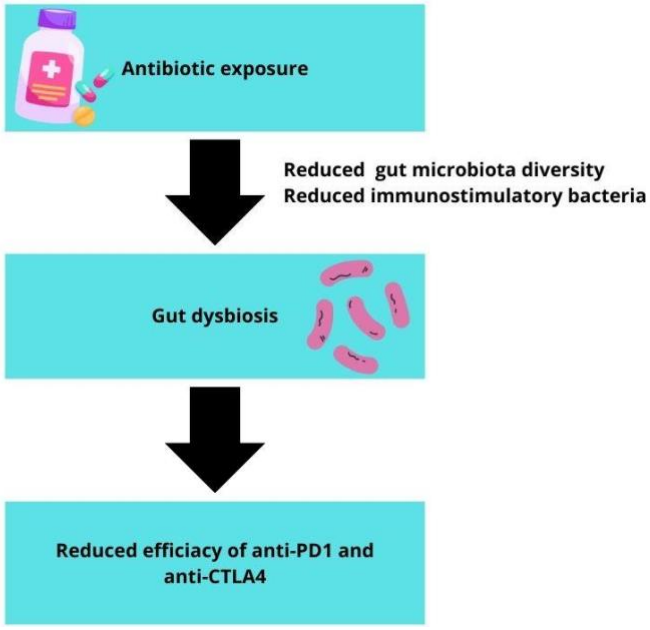

Fig. 1. *Mechanism of action - antibiotic-induced dysbiosis.*

Clinical Evidence

The first clinical evidence linking antibiotic exposure with impaired outcomes of ICIs therapy emerged from retrospective cohort studies conducted across multiple tumor types. These early investigations were motivated by strong preclinical data implicating antibiotic-induced dysbiosis as a potential modifier of antitumor immune responses.

One of the earliest and most influential studies was reported by Derosa et al. (2018), who evaluated the impact of antibiotic exposure in patients with advanced renal cell carcinoma (RCC) and non–small cell lung cancer (NSCLC) treated with anti-PD-(L)1–based immunotherapy. In this multicenter analysis, antibiotic use within 30 days prior to ICI initiation was observed in approximately 13% of RCC patients and 20% of NSCLC patients. In RCC, antibiotic exposure was associated with shorter PFS and a higher rate of primary progressive disease (PD), whereas in NSCLC it remained independently associated with shorter OS but not with PFS after multivariate adjustment.

These findings were extended by Pinato et al. (2019) in a prospective, multicenter cohort study including 196 unselected patients with various solid tumors treated with ICIs in routine clinical practice. This study distinguished between antibiotic exposure prior to ICI initiation (pATB) and concurrent antibiotic use (cATB), demonstrating that only prior exposure, defined as antibiotics administered within 30 days before ICI initiation, was associated with significantly worse outcomes. Patients receiving pATB experienced markedly reduced OS and poorer response to ICIs therapy across multiple tumor types, including NSCLC and melanoma. Notably, these associations remained significant after adjustment for antibiotic class, performance status, and corticosteroid use, and were confirmed in multivariate and propensity score–adjusted analyses. In contrast, cATB use was not associated with impaired survival, highlighting the potential importance of timing in the interaction between antibiotic therapy and immunotherapy efficacy.

Complementary evidence was provided by Elkrief et al. (2019), who focused specifically on patients with advanced melanoma treated with anti-PD-1 or anti-CTLA-4–based immunotherapy. In this retrospective study, antibiotic exposure within 30 days prior to ICI initiation was observed in 13.5% of patients and was associated with significantly shorter PFS and a higher likelihood of primary resistance to treatment. Although OS rate was smaller in antibiotic-exposed patients, this difference was not statistically significant in the overall cohort, underscoring limitations related to sample size and event number. Importantly, multivariate analysis confirmed antibiotic exposure as an independent predictor of shorter PFS, whereas the association with OS did not reach statistical significance.

Table 1. Summary of clinical studies and meta-analyses evaluating the impact of antibiotic exposure on immune checkpoint inhibitor efficacy

First author (year)	Tumor type	Study design	N (patients)	Therapy	Definition of antibiotic exposure	Key outcomes
Derosa (2018)	RCC, NSCLC	Multicenter retrospective	121 RCC; 239 NSCLC	Anti–PD-(L)1	ATB ≤60 days before ICI	↓ PFS in RCC; ↓ OS in NSCLC
Elkrief (2019)	Melanoma	Retrospective	74	Anti–PD-1 / Anti–CTLA-4	ATB ≤30 days before ICI	↓ PFS, ↑ PD
Hakozaki (2019)	NSCLC	Retrospective	90	Nivolumab	ATB for ≥3 days before 30 days ICI	↓ PFS and OS (univariate); not independent (multivariate)
Ruiz-Patiño (2020)	NSCLC	Multicenter retrospective	140	Anti–PD-(L)1	ATB ≤30 days before or during ICI	↓ OS
Hamada (2021)	NSCLC	Retrospective	69	Anti–PD-1	ATB ±21 days of ICI	↓ ORR, ↓ PFS and OS; PFS independent
Hu (2025)	NSCLC	Retrospective	199	ICIs	ATB ±30 days of ICI	↓ PFS and OS
Chorti (2024)	Melanoma	Multicenter retrospective	578	Anti–PD-1	ATB ≤60 days before or during ICI	↓ PFS and OS pATB; no effect if ATB during ICI
Gambichler (2025)	Melanoma	Systematic review & meta-analysis	5213	ICIs	ATB ≤6 weeks before ICI	↑ mortality risk
Pinato (2023)	HCC	Retrospective (trial database)	4,098	ICIs / TKI	ATB ±30 days	↓ PFS and OS across all therapies
Alshammari (2024)	HCC	Muliticenter retrospective	59	Nivolumab	ATB concurrently with Nivolumab	↓ OS (Child–Pugh A)
Zhang (2023)	Esophagogastric	Retrospective + meta-analysis	85	Anti–PD-(L)1	ATB ±1 month of ICI	↓ OS, ↓ PFS, ↓ DCR
Bonnefin (2025)	cSCC	Retrospective	104	Anti–PD-1	ATB ±1 or ±3 months	↓ OS, ↓ DSS, ↓ PFS, ↓ DCR (ATB ±1 month); ↓ DCR (ATB ±3 months)
Russi (2025)	Multiple	Observational	239	ICIs	ATB ±30 days of ICI	↓ OS and ↓ PFS
Kaderbhai (2017)	NSCLC	Retrospective	74	Nivolumab	ATB ≤3 months before or during ICI	No effect on ORR or PFS

First author (year)	Tumor type	Study design	N (patients)	Therapy	Definition of antibiotic exposure	Key outcomes
Tsikala-Vafea (2021)	Multiple	Systematic review & meta-analysis	12794	ICIs	<1 month during or after ICI initiation, >1 month prior to ICI initiation	↓ OS ↓ PFS ↓RR ↑ PD
Wu (2021)	Multiple	Meta-analysis	12492	ICIs	Various	↓ OS, ↓ PFS, ↓ ORR
Crespin (2023)	Multiple	Systematic review & meta-analysis	41663	ICIs	Various	↓ OS, ↓ PFS, ↓ ORR, ↑ PD
Alotaibi (2024)	GI tumors	Systematic review & meta-analysis	2214	ICIs	Various	↓ OS and ↓ PFS
Huo (2021)	NSCLC	Meta-analysis	787	Nivolumab	Various	↓ OS, and ↓ PFS
Jiang (2022)	Multiple	Meta-analysis	6010	ICIs	Various	↓ OS and ↓ PFS
Luo (2022)	RCC	Systematic review & meta-analysis	1104	ICIs	Various	↓ OS, ↓ PFS, ↓ ORR

Interpretation and consistency of early findings

In conclusion, these early retrospective studies consistently reported an association between antibiotic exposure preceding ICI therapy and inferior clinical outcomes, including reduced PFS, increased rates of primary resistance, and, in several cohorts, shorter OS. While causality cannot be inferred from these observational data, the reproducibility of the signal across independent cohorts, tumor types, and treatment settings strengthened the biological plausibility suggested by preclinical models.

At the same time, all three studies acknowledged important limitations inherent to retrospective analyses, including potential confounding by indication, variability in antibiotic class and duration, and limited availability of microbiome profiling. Differences in study design, patient populations, and definitions of antibiotic exposure further contributed to heterogeneity across reports. Nevertheless, these early clinical observations played a pivotal role in establishing antibiotic exposure as a clinically relevant variable in immunotherapy outcomes and laid the groundwork for subsequent tumor-specific analyses, meta-analyses, and ongoing prospective investigations.

Tumor-specific validation studies

Non–small cell lung cancer (NSCLC)

Following the initial pan-tumor observations, several tumor-specific retrospective studies further evaluated the association between antibiotic exposure and immunotherapy outcomes in NSCLC. Collectively, these studies support the reproducibility of the signal in this disease setting, while also highlighting substantial methodological heterogeneity.

In a study by Hakozaki, Okuma, Omori & Hosomi (2019), outcomes of nivolumab-treated NSCLC patients with prior antibiotic exposure were evaluated. The authors reported that prior antibiotic exposure was associated with significantly shorter PFS and OS in univariate analyses. However, this association did not remain statistically significant in multivariate analysis, although a trend toward worse outcomes with pATB use was observed.

Subsequently, Ruiz-Patiño et al. (2020) analyzed a Hispanic NSCLC population (AB-CLICaP cohort) and demonstrated shorter OS in patients exposed to antibiotics before or during ICIs therapy, while no significant differences were observed in PFS and outcomes were not influenced by antibiotic class.

Antibiotic exposure within a narrow peri-treatment window was associated with reduced objective response rates (ORR) and shorter PFS and OS in univariate analyses. In multivariate analysis, Hamada et al. (2015) reported that antibiotic use remained an independent negative predictor of PFS, whereas the association with OS did not retain statistical significance.

Most recently, Hu et al. (2025) reported that antibiotic exposure, particularly within 30 days before or after immunotherapy initiation, was associated with shorter PFS and OS. However, the authors emphasized that due to the retrospective design and limited sample size, a direct causal effect of antibiotics on immunotherapy efficacy could not be established and the findings require further validation.

Taken together, NSCLC-focused studies consistently suggest a negative association between antibiotic exposure and ICI efficacy, although differences in exposure definitions, timing windows, and covariate adjustment complicate direct comparison across cohorts.

Melanoma

Melanoma is widely regarded as one of the most immunotherapy-responsive tumor types and has frequently been used as a clinical model to investigate host-related factors influencing immune checkpoint blockade (Vétizou et al, 2015).

In a large multicenter retrospective cohort of treatment-naïve patients with advanced melanoma receiving first-line anti-PD-1–based immune checkpoint blockade, Chorti et al. (2024) demonstrated that antibiotic exposure within 60 days prior to treatment initiation was independently associated with worse PFS and OS. Notably, antibiotic use after the start of immunotherapy was not associated with impaired outcomes, highlighting the importance of timing, while residual confounding inherent to retrospective analyses could not be fully excluded.

Complementing these findings, Gambichler et al. (2025) reported that pre-ICI antibiotic exposure in cutaneous melanoma was associated with increased mortality risk, as reflected by pooled hazard ratios for OS exceeding 1 in both fixed- and random-effects models.

Together, melanoma-specific studies reinforce the consistency of the association between antibiotic exposure and inferior immunotherapy outcomes in a tumor type that is highly sensitive to immune modulation, while also underscoring persistent methodological constraints (Chorti et al, 2024; Gambichler et al, 2025).

Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma presents a particularly complex clinical context in which to study antibiotic–immunotherapy interactions, given the frequent coexistence of cirrhosis, hepatic dysfunction, and infection risk (Pinato, 2023).

In a study by Pinato et al. (2023) outcomes of patients with unresectable or metastatic hepatocellular carcinoma treated with ICIs, targeted therapies, or placebo were analyzed. Authors found that antibiotic exposure in these groups was associated with shorter PFS and OS across treatment modalities. The authors noted that this non–treatment-specific effect highlights the unique clinical context of HCC, characterized by cirrhosis, infection risk, and gut–liver axis dysfunction, and cautioned against causal interpretation.

Similarly, Alshammari et al. (2024) demonstrated that concurrent antibiotic exposure was associated with reduced OS in patients with Child–Pugh class A advanced HCC treated with anti–PD-1 therapy. The study population was restricted to patients with Child–Pugh class A or early class B cirrhosis, thereby limiting the influence of advanced hepatic decompensation on survival analyses; however, the retrospective design precludes complete control of confounding.

These HCC-specific studies highlight both the reproducibility of the negative association and the heightened vulnerability of this disease setting to confounding, reinforcing the need for cautious interpretation (Alshammari et al, 2024; Pinato et al, 2023).

Gastrointestinal malignancies

Beyond traditionally immunotherapy-responsive tumors, emerging data suggest that the association between antibiotic exposure and ICI outcomes may extend to gastrointestinal malignancies.

Zhang et al. (2023) reported that antibiotic use during ICIs treatment was associated with reduced survival in patients with advanced esophagogastric cancer. Although limited by retrospective design and relatively small cohort size, this study expands the clinical scope of antibiotic–immunotherapy interactions and suggests that microbiome-mediated effects may be relevant across a broader spectrum of malignancies.

Cutaneous malignancies and real-world evidence

Additional evidence has emerged from less extensively studied tumor types and real-world clinical settings. In a retrospective cohort of patients with advanced cutaneous squamous cell carcinoma treated with ICIs, Bonnefin et al. (2025) reported that antibiotic exposure around ICIs initiation was associated with reduced disease control and inferior survival outcomes. This study extends the antibiotic–immunotherapy signal beyond melanoma to other cutaneous malignancies.

Complementary real-world evidence was provided by Russi et al. (2025), who analyzed antibiotic exposure in a heterogeneous cohort of patients with solid tumors receiving ICIs in routine clinical practice. In this observational study, higher cumulative antibiotic exposure was associated with survival outcomes and reduced immunotherapy effectiveness. Notably, outcomes appeared to correlate with the timing and cumulative extent of antibiotic use, as well as tumor type and disease stage.

Together, these studies reinforce the external validity of earlier tumor-specific observations while underscoring the challenges of disentangling microbiome-mediated effects from confounding clinical factors inherent to retrospective and real-world analyses.

Negative and neutral findings

Not all studies have demonstrated a detrimental association between antibiotic exposure and immunotherapy efficacy. Kaderbhai et al. (2017) reported no significant impact of antibiotic exposure on response rates or PFS in nivolumab-treated patients with NSCLC. This neutral finding is important for contextual balance, as it underscores the heterogeneity of reported outcomes and highlights the potential influence of methodological factors, including limited sample size, timing of antibiotic exposure, and patient selection.

Such discrepant results emphasize the inherent limitations of retrospective analyses and suggest that the effect of antibiotics on immunotherapy outcomes may be context-dependent rather than universal.

Meta-analyses and systematic reviews

Several systematic reviews and meta-analyses have synthesized the growing body of predominantly retrospective evidence examining the association between antibiotic exposure and outcomes of immune checkpoint inhibitor therapy. Across these analyses, antibiotic use has been consistently associated with inferior clinical outcomes, albeit with substantial heterogeneity and important methodological limitations.

In one of the earliest comprehensive meta-analyses, Tsikala-Vafea, Belani, Vieira, Khan & Farmakiotis (2021) reported that antibiotic exposure was associated with significantly worse OS and PFS across multiple tumor types treated with ICIs, despite variability in study design and exposure definitions. Similarly, Wu Q, Liu, Wu S, Xie (2021) pooling data from 44 independent cohorts, demonstrated that antibiotic exposure was significantly associated with worse OS and PFS across multiple cancer types treated with ICIs, supporting the consistency of this association across malignancies.

More recent analyses have further strengthened and refined these observations. Crespin et al. (2023) performed the largest systematic review and meta-analysis to date, encompassing over 41,000 cancer patients treated with ICIs. Antibiotic exposure around ICI initiation was consistently associated with worse OS and PFS, reduced ORR, and an increased risk of PD, with the strongest negative effects observed when antibiotics were administered shortly before or after treatment initiation. Although limited by observational data, this analysis provides the strongest quantitative support to date for an association between antibiotic use and impaired immunotherapy outcomes.

Tumor-specific meta-analyses have provided additional context. In gastrointestinal malignancies, Alotaibi et al. (2024) reported that antibiotic use was associated with inferior survival outcomes in patients treated with ICIs, extending the relevance of these findings beyond traditionally immunotherapy-responsive cancers. In advanced or metastatic NSCLC, Huo et al. (2021) demonstrated that antibiotic exposure in nivolumab-treated patients was associated with significantly worse PFS and OS, with pooled hazard ratios indicating a clinically meaningful reduction in benefit. Similarly, Jiang et al. (2022) confirmed that antibiotic use was associated with shorter PFS and OS across major tumor types, including NSCLC, RCC, and melanoma, while noting the presence of publication bias and the limitations inherent to retrospective data.

Finally, a dedicated meta-analysis in renal cell carcinoma by Luo et al. (2022) showed that antibiotic exposure was associated with significantly shorter PFS and OS, as well as lower ORR, with low to moderate heterogeneity across included studies, supporting the robustness of this association within the RCC setting.

Collectively, these meta-analyses provide quantitative support for a consistent association between antibiotic exposure and reduced immunotherapy efficacy. However, they uniformly emphasize the predominance of retrospective data, heterogeneity in exposure definitions, and the potential for confounding by indication, thereby precluding definitive causal inference. These limitations highlight the need for prospective, microbiome-integrated studies with standardized assessment of antibiotic exposure.

Discussion

This narrative review describes evidence that antibiotic exposure is associated with impaired clinical outcomes in patients treated with ICIs across multiple tumor types. Although the available data are largely retrospective and heterogeneous, a consistent signal emerges linking antibiotic use, particularly when administered shortly before immune checkpoint inhibitor initiation, with reduced PFS, OS, and treatment response. These findings align with preclinical observations and underscore the clinical relevance of host-related modifiers of immunotherapy efficacy.

A central biological explanation for this association lies in the role of the gut microbiome as a regulator of systemic and antitumor immunity (Lei W, Zhou, Lei Y, Li, Zhu, 2025). Preclinical studies have demonstrated that commensal bacteria influence antigen presentation, dendritic cell maturation, cytotoxic T-cell priming, and cytokine signaling pathways essential for immune checkpoint blockade efficacy (Routy et al, 2018; Sivan et al, 2015). Antibiotic-induced dysbiosis disrupts these processes, leading to impaired immune surveillance and diminished antitumor responses (Vétizou et al, 2015). The convergence of preclinical data and clinical observations strengthens the biological plausibility of the antibiotic–immunotherapy interaction.

Importantly, clinical evidence suggests that the impact of antibiotics is not uniform but context-dependent. Timing of exposure appears to be a critical determinant, with antibiotics administered prior to immune checkpoint inhibitor initiation consistently associated with worse outcomes, whereas concurrent or post-treatment exposure shows more variable effects (Chorti et al, 2024; Hakozaki et al, 2019). This temporal relationship is biologically plausible, as early microbiome disruption may impair immune priming at the initiation of immunotherapy, while later perturbations may have less pronounced effects. Tumor type also appears to modulate the magnitude of the association, with more consistent signals observed in melanoma, non–small cell lung cancer, and renal cell carcinoma, while hepatocellular carcinoma presents a particularly complex scenario due to cirrhosis, infection risk, and gut–liver axis dysfunction (Pinato et al, 2023).

Beyond observational associations, emerging interventional studies provide proof-of-concept evidence that targeted modulation of the gut microbiome may enhance responsiveness to immune checkpoint blockade. Early-phase clinical trials demonstrated that fecal microbiota transplantation (FMT) from immunotherapy responders could restore sensitivity to anti–PD-1 therapy in a subset of patients with PD-1–refractory melanoma. These interventions were associated with durable microbiome remodeling, increased intratumoral cytotoxic T-cell infiltration, and favorable immune reprogramming within the tumor microenvironment (Davar et al, 2021). More recent studies extended these findings to patients with advanced solid tumors, including gastrointestinal malignancies, showing increased immune activation and clinical benefit following microbiota-based interventions (Kim et al, 2024). Although limited by small sample sizes and exploratory designs, these studies support a causal role of the gut microbiome in modulating immunotherapy response and highlight microbiome-directed strategies as a potential approach to mitigate antibiotic-associated dysbiosis.

From a clinical perspective, these findings raise important considerations regarding antibiotic stewardship in patients receiving immune checkpoint inhibitors. While antibiotics remain essential and often lifesaving, unnecessary or prolonged exposure, particularly in the peri-immunotherapy period, may compromise treatment efficacy. At present, however, the evidence does not support withholding antibiotics when clinically indicated. Instead, these data underscore the need for judicious antibiotic use and increased awareness of potential downstream effects on immunotherapy outcomes.

Clinical implications and antibiotic stewardship

The accumulated evidence reviewed herein carries important clinical implications for the management of patients receiving immune checkpoint inhibitors. Across multiple tumor types, antibiotic exposure—particularly when administered shortly before ICI initiation—has been repeatedly associated with inferior survival outcomes and reduced treatment efficacy (Ruiz-Patiño et al, 2020; Tsikala-Vafea, 2021). Although causality cannot be definitively established, the consistency of these findings suggests that antibiotic use represents a potentially modifiable factor influencing immunotherapy outcomes.

From a clinical perspective, these data underscore the importance of judicious antibiotic stewardship in patients undergoing immunotherapy. Antibiotics remain indispensable in oncologic care and should not be withheld when clinically indicated, particularly in the setting of severe or life-threatening infections or neutropenia. However, when alternative management strategies are available, the timing, duration, and necessity of antibiotic therapy—especially broad-spectrum or prophylactic regimens—may warrant careful consideration in patients scheduled to receive ICIs (Reed et al, 2019; Shaikh et al, 2019; Vétizou et al, 2015, Wekking et al, 2025). Increased awareness of the potential downstream immunological consequences of antibiotic exposure may support more individualized decision-making, including optimization of treatment duration, early de-escalation strategies, and interdisciplinary collaboration with infectious disease specialists.

At present, no evidence-based guidelines exist to inform antibiotic prescribing specifically in the context of immunotherapy. Prospective studies integrating clinical outcomes with microbiome profiling are therefore essential to determine whether antibiotic stewardship interventions can meaningfully improve immunotherapy efficacy without compromising patient safety.

Role of antibiotic classes and spectrum of activity

An unresolved question concerns whether the detrimental association between antibiotic exposure and ICI efficacy is driven by specific antibiotic classes or reflects a broader effect of microbiome disruption. Most retrospective studies and meta-analyses included in this review were not designed to detect class-specific effects and generally reported no statistically significant differences between antibiotic categories (Derosa et al, 2018; Ruiz-Patiño, 2020). This likely reflects limited statistical power, heterogeneity in exposure definitions, and incomplete reporting of cumulative dose and duration.

In a subset of retrospective studies, information on antibiotic classes was reported, with beta-lactams and fluoroquinolones being the most frequently prescribed agents. However, most studies did not provide detailed data on antibiotic class, duration, or indication, precluding reliable assessment of class-specific effects (Derosa et al, 2018; Hu et al, 2025; Ruiz-Patiño et al, 2020). These antibiotics are known to exert profound and sustained effects on gut microbial diversity, raising the possibility that spectrum of activity, rather than antibiotic class per se, may be a critical determinant of immunotherapy interference. Narrow-spectrum agents or shorter treatment courses may theoretically exert less detrimental immunomodulatory effects, although this hypothesis remains largely untested in clinical settings.

Importantly, few studies accounted for the indication or severity of infection, limiting the ability to disentangle microbiome-mediated effects from confounding by disease burden. Future prospective trials should systematically evaluate antibiotic class, spectrum, duration, and timing in relation to ICI initiation, ideally combined with longitudinal microbiome analyses, to clarify whether certain antibiotic strategies are more compatible with effective immunotherapy.

Limitations

Several limitations must be considered when interpreting the evidence summarized in this review. First, the majority of available clinical data derive from retrospective observational studies, which are inherently susceptible to confounding by indication, selection bias, and incomplete adjustment for prognostic factors. Patients receiving antibiotics often have more advanced disease, infections, or comorbidities that may independently influence survival outcomes.

Second, there is substantial heterogeneity in how antibiotic exposure is defined across studies, including differences in timing windows, duration, cumulative exposure, and antibiotic class. This variability limits comparability between cohorts and precludes precise determination of dose–response or temporal thresholds. Information on infection severity and antibiotic indication is frequently unavailable, contributing to residual confounding.

Third, microbiome profiling was not routinely incorporated into most clinical studies, preventing direct correlation between antibiotic-induced microbial changes and immunotherapy outcomes in humans. Mechanistic interpretations therefore rely largely on extrapolation from preclinical models and small translational studies.

Finally, publication bias cannot be excluded, as studies reporting neutral or negative findings may be underrepresented. Although meta-analyses provide quantitative support for observed associations, the predominance of retrospective data precludes definitive causal inference.

Conclusions

Accumulating clinical and meta-analytic evidence indicates that antibiotic exposure, particularly when administered in close temporal proximity to immune checkpoint inhibitor initiation, is consistently associated with inferior clinical outcomes across multiple solid tumor types. Although causality cannot be definitively established due to the predominance of retrospective data and potential confounding by indication, the reproducibility of this association across tumor types and treatment settings supports a biologically plausible link between antibiotic-induced microbiome disruption and impaired immunotherapy efficacy.

In addition to immune checkpoint blockade, these observations highlight broader implications for immune-based cancer therapies. There is a pressing need to investigate the impact of antibiotic prophylaxis in hematologic malignancies, particularly acute leukemias, where prolonged and pre-emptive antibiotic use is routine due to sustained neutropenia and high infectious risk. In this context, antibiotics may induce profound and long-lasting alterations of the gut microbiome, with potential consequences for immune reconstitution, treatment responsiveness, and long-term outcomes as immunotherapeutic approaches are increasingly explored in these diseases.

Similarly, the role of antibiotic exposure in the setting of chimeric antigen receptor (CAR) T-cell therapy remains insufficiently characterized. Given the reliance of CAR-T efficacy on T-cell expansion, persistence, and functional fitness—processes increasingly linked to microbiome composition—antibiotic-induced dysbiosis may represent an underappreciated modifier of both therapeutic response and toxicity. Prospective, microbiome-integrated studies are therefore urgently needed to clarify how prophylactic and therapeutic antibiotic strategies influence outcomes of CAR-T therapy.

Taken together, these findings underscore antibiotic stewardship as a potentially modifiable factor in optimizing immune-based cancer therapies. While antibiotics remain indispensable in oncologic care, particularly in immunocompromised populations, a more nuanced understanding of their immunological and microbiome-related consequences will be essential to balance infectious risk against long-term therapeutic benefit.

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