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REVIEW

Novel Microbiome-Driven Approaches to Counteract Chemotherapy-Induced Mucositis in Breast Cancer Patients

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Abstract: Chemotherapy-induced mucositis (CIM) is a clinically important toxicity in breast cancer care that adversely affects oral and gastrointestinal mucosa, quality of life, nutritional status, and treatment tolerability. While CIM is less frequently dose-limiting in contemporary standard regimens (eg, AC–T, TC) compared with hematologic and neurotoxicities, it remains a significant supportive care challenge, particularly in dose-dense schedules, older cytotoxic protocols, and with selected targeted agents and antibody–drug conjugates. Emerging evidence indicates that chemotherapy-associated dysbiosis can amplify mucosal inflammation and barrier dysfunction, acting as a modifier of injury rather than the primary driver, which is direct epithelial cytotoxicity. A narrative review was conducted using structured searches of PubMed/Medline, Scopus, and Web of Science up to 2025 to identify preclinical and clinical studies addressing the pathobiology of CIM, chemotherapy-associated microbiome perturbations in breast cancer, and microbiome-targeted preventive or therapeutic strategies. Evidence was synthesized qualitatively, with explicit distinction between mechanistic preclinical data and emerging clinical findings. Chemotherapy induces reproducible alterations in oral and gut microbial communities, characterized by reduced microbial diversity, depletion of commensal taxa involved in epithelial homeostasis, and relative expansion of pathobionts. Preclinical models demonstrate that dysbiosis can exacerbate inflammatory signaling, impair epithelial repair, and increase susceptibility to ulceration and infection. Early-phase clinical studies and small randomized trials in heterogeneous oncology populations suggest that selected probiotics, prebiotics, and dietary interventions may modestly attenuate the incidence or severity of mucositis, although robust breast cancer–specific evidence remains limited. More advanced approaches, including postbiotics, fecal microbiota–based strategies, and engineered live biotherapeutics, are largely investigational. CIM in breast cancer is a multifactorial toxicity primarily driven by direct chemotherapy-induced epithelial injury, with the microbiome functioning as an important biological modifier of inflammation, barrier integrity, and mucosal repair. Microbiome-targeted interventions represent a promising adjunct to conventional supportive care rather than a stand-alone solution. Well-designed, breast cancer–specific clinical trials incorporating longitudinal microbiome and metabolomic profiling are required to define clinical efficacy, safety, and patient subgroups most likely to benefit from precision microbiome modulation.

Keywords: microbiome modulation, mucosal injury, breast cancer, chemotherapy-induced mucositis, microbiota-targeted therapeutics

Introduction

Breast cancer remains the most commonly diagnosed malignancy among women globally, and systemic chemotherapy continues to play a central role in curative and palliative treatment paradigms across molecular subtypes and disease stages. Contemporary combination regimens such as anthracycline–taxane–based protocols (eg, AC–T) and docetaxel–cyclophosphamide (TC) have substantially improved survival outcomes.[1,2] In current clinical practice, however, dose-limiting toxicities are more frequently driven by hematologic complications (notably neutropenia), peripheral neuropathy, and cardiotoxicity, rather than severe chemotherapy-induced mucositis (CIM). Nevertheless, mucositis remains

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a clinically meaningful supportive care challenge in breast cancer, particularly with dose-dense schedules, older cytotoxic regimens, and selected targeted therapies and antibody–drug conjugates, where the incidence and severity of mucosal injury may be higher. Even when not dose-limiting, CIM substantially impairs oral intake, nutritional status, symptom burden, treatment adherence, and health-related quality of life, thereby contributing to indirect treatment modifications and increased healthcare utilization.[3,4]

CIM encompasses inflammatory and ulcerative injury of the oral and gastrointestinal mucosa that arises as an off-target consequence of cytotoxic therapy. Clinically, patients experience pain, dysphagia, diarrhea, and heightened susceptibility to local and systemic infections, particularly in the context of treatment-related neutropenia. Current preventive and therapeutic approaches—including oral care protocols, cryotherapy, topical anesthetics, anti-inflammatory agents, and growth factor–based interventions in selected settings—provide partial and inconsistent benefit. Their limited efficacy reflects the complex, multifactorial pathobiology of CIM, which is primarily driven by direct epithelial DNA damage and oxidative stress, with secondary amplification through inflammatory cascades and barrier dysfunction. Consequently, there remains a clear unmet need for biologically informed adjunctive strategies that can complement existing supportive care measures and improve patient-centered outcomes.[5–7]

In parallel with advances in oncology, high-resolution profiling of the human microbiome has revealed its integral role in maintaining mucosal homeostasis, epithelial barrier integrity, and immune regulation.[8,9] Chemotherapy is increasingly recognized to perturb oral and gut microbial ecosystems, resulting in reduced microbial diversity, depletion of commensal taxa associated with epithelial repair and immune tolerance, and relative expansion of pathobionts.[6,10] Accumulating preclinical and translational evidence suggests that such dysbiosis does not initiate mucosal injury per se, but can act as a biological modifier that amplifies inflammatory signaling, delays mucosal healing, and increases susceptibility to ulceration and secondary infection. These insights have prompted growing interest in microbiome-targeted interventions—ranging from dietary modulation and probiotics to postbiotics and next-generation live biotherapeutics—as potential adjuncts to mitigate the severity and duration of CIM.[11,12]

Despite this promise, the clinical evidence base for microbiome-directed strategies in breast cancer–specific CIM remains limited, heterogeneous, and largely exploratory. Moreover, the safety, timing, and patient selection criteria for such interventions in immunocompromised oncology populations require careful consideration. A critical synthesis of current knowledge is therefore needed to delineate the biological rationale, summarize emerging translational and clinical evidence, and identify gaps that must be addressed before microbiome modulation can be integrated into routine supportive care in breast cancer.[13] Accordingly, this narrative review aims to (i) summarize the contemporary clinical context and unmet needs of chemotherapy-induced mucositis in breast cancer, (ii) outline the emerging evidence linking chemotherapy-associated dysbiosis to mucosal injury and impaired repair, and (iii) critically appraise novel microbiome-driven preventive and therapeutic strategies, with emphasis on their translational readiness, limitations, and future research priorities.

Methods

This narrative review was conducted to comprehensively evaluate current evidence on the role of the gut microbiome in chemotherapy-induced mucositis among breast cancer patients, with an emphasis on mechanistic insights, microbiome-driven interventions, and translational applications. A systematic search of electronic databases including PubMed, Scopus, Web of Science, and Google Scholar was performed to identify relevant studies published up to December 2025. Search terms included combinations of “breast cancer”, “chemotherapy”, “mucositis”, “gut microbiome”, “dysbiosis”, “probiotics”, “prebiotics”, “fecal microbiota transplantation” and “microbiome-targeted therapy”.

Inclusion criteria encompassed original research, clinical trials, preclinical studies, and review articles focusing on chemotherapy-induced mucosal toxicity and microbiome interactions in breast cancer patients. Studies addressing microbiome modulation strategies, including probiotics, prebiotics, synbiotics, postbiotics, and engineered microbial therapeutics, were also included. Articles not published in English, case reports, conference abstracts without full text, and studies lacking direct relevance to breast cancer chemotherapy or mucositis were excluded.

Data were extracted regarding chemotherapy regimens, microbiome alterations, mechanisms of mucosal injury, therapeutic interventions, clinical outcomes, and translational implications. Emphasis was placed on studies elucidating

mechanistic pathways linking microbial dysbiosis to mucosal injury, as well as emerging therapeutic strategies with preclinical or clinical evidence. Findings were synthesized narratively, integrating mechanistic, clinical, and translational perspectives to provide a comprehensive overview of the current state of knowledge and identify areas for future research.

Pathophysiological Basis of Chemotherapy-Induced Mucositis

Chemotherapy-induced mucositis (CIM) represents one of the most clinically significant toxicities encountered during breast cancer treatment. Beyond causing localized pain and discomfort, CIM disrupts oral intake, compromises immune defenses, increases infection risk, and often necessitates chemotherapy dose reductions or delays. Contemporary understanding positions CIM not merely as an epithelial injury but as a complex, multi-phase pathological process integrating cellular, immunological, microbial, and vascular pathways. Insights into its pathophysiology reveal mechanisms that can be targeted for microbiome-driven therapeutic interventions.[14,15] The onset of mucositis begins with direct cytotoxic effects of chemotherapy on rapidly dividing mucosal epithelial cells. Agents commonly used in breast cancer—such as anthracyclines, taxanes, cyclophosphamide, and antimetabolites—induce DNA strand breaks, chromosomal instability, and apoptosis in the basal epithelial layer of the gastrointestinal tract. This direct damage compromises epithelial integrity, reducing barrier function and exposing the underlying submucosa to inflammatory mediators and microbial products.[16]

Concurrent with genotoxic stress, chemotherapy generates significant oxidative stress through the production of reactive oxygen species (ROS). These molecules damage cellular membranes, mitochondrial DNA, and intracellular proteins, further amplifying epithelial injury. The combination of DNA damage and ROS acts as the molecular trigger for downstream inflammatory signaling cascades, setting the stage for mucosal breakdown.[17] Following initial injury, the mucosa engages in a transcriptionally active response characterized by the up-regulation of pro-inflammatory pathways. Nuclear factor kappa B (NF-κB) is central to this phase, orchestrating the expression of tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and other cytokines. These mediators recruit immune cells, activate matrix metalloproteinases (MMPs), and induce cyclooxygenase-2 (COX-2), all of which contribute to submucosal inflammation, extracellular matrix degradation, and further epithelial fragility.[18] At this stage, signaling molecules amplify epithelial apoptosis and enhance vascular permeability. The local microenvironment becomes pro-oxidative and pro-inflammatory, favoring recruitment of neutrophils and monocytes that propagate tissue damage and potentiate nociceptor sensitization, leading to pain and hypersensitivity.[19]

During the amplification phase, localized epithelial injury evolves into a self-perpetuating cycle of mucosal inflammation. ROS, cytokines, and microbial products intensify each other's effects. Immune cell infiltration releases additional proteolytic enzymes and ROS, which degrade connective tissue and damage submucosal vasculature. Microvascular injury leads to localized ischemia, compounding epithelial vulnerability.[20] This phase is marked by the synergistic interplay of cellular and microbial signals. The damaged epithelium allows microbial translocation and pathogen-associated molecular patterns (PAMPs) to engage toll-like receptors (TLRs) on epithelial and immune cells, sustaining NF-κB activation and cytokine production. In essence, the mucosa becomes a battlefield where oxidative stress, inflammation, and microbial signaling converge to magnify tissue damage.[21] Ulceration represents the most clinically visible and debilitating stage of CIM. Loss of epithelial continuity exposes the submucosal tissue, creating a portal for microbial colonization and infection. Dysbiosis—a hallmark of chemotherapy—exacerbates this vulnerability. Commensals such as Lactobacillus, Bifidobacterium, and Faecalibacterium are depleted, reducing production of short-chain fatty acids (SCFAs) essential for epithelial energy, proliferation, and anti-inflammatory signaling. In parallel, opportunistic pathobionts—including Enterococcus, Enterobacteriaceae, and certain Clostridium species—expand and release endotoxins that further amplify inflammation.[22,23]

The interaction between microbial imbalance and epithelial injury creates a vicious cycle: microbial translocation triggers immune activation, which worsens barrier disruption, which in turn allows deeper microbial invasion. Clinically, this manifests as ulceration, pain, bleeding, dysphagia, and risk of systemic infection—particularly in neutropenic patients receiving breast cancer chemotherapy.[24] Once chemotherapy exposure diminishes and inflammation subsides, epithelial regeneration begins. Stem cell proliferation, angiogenesis, and extracellular matrix restoration gradually re-

establish mucosal integrity. Commensal microbiota repopulate the mucosa, and SCFA production gradually recovers, supporting barrier restoration. However, the healing process is often incomplete or delayed, especially in patients undergoing sequential or dose-dense chemotherapy. Persistent microbial dysbiosis and subclinical epithelial fragility contribute to recurrent mucositis in subsequent cycles, creating a cumulative burden.[25]

Modern models recognize that chemotherapy-induced dysbiosis is not merely a consequence of mucositis but a causal amplifier of disease severity. Microbial imbalance reduces SCFA production, compromises mucosal immunity, and increases permeability, feeding back into epithelial injury and inflammatory cascades. Dysbiosis-driven metabolite depletion and pathobiont expansion make the mucosa increasingly susceptible to ulceration and prolong recovery. This integration of epithelial, immune, and microbial factors provides a mechanistic basis for microbiome-targeted preventive and therapeutic strategies.[26,27] Breast cancer patients receiving anthracycline–taxane–based regimens are particularly vulnerable to CIM due to high cumulative cytotoxicity, frequent dose-dense scheduling, and systemic effects on immunity. Baseline factors such as pre-existing dysbiosis, metabolic syndrome, and estrogen–microbiome interactions (estrobolome activity) further modulate mucosal vulnerability. Recognizing the pathophysiological complexity of CIM supports the rationale for interventions that go beyond symptom management to target the epithelial–microbial–immune interface (Table 1).[28]

Microbiome Alterations Associated with Breast Cancer Chemotherapy

Chemotherapy profoundly disrupts the gut microbiome in breast cancer patients, producing changes that extend far beyond simple epithelial injury. The gastrointestinal microbiota plays a crucial role in maintaining mucosal barrier integrity, regulating local and systemic immunity, and supporting metabolic homeostasis. Cytotoxic regimens, particularly anthracyclines, taxanes, cyclophosphamide, and fluoropyrimidines, induce rapid and sustained alterations in this ecosystem, which in turn exacerbate chemotherapy-induced mucositis (CIM) and influence overall treatment tolerance.[29] One of the most consistent observations is a marked reduction in microbial diversity. High microbial diversity is typically associated with ecological resilience and functional redundancy, enabling the mucosa to withstand stressors such as oxidative injury and inflammation. Chemotherapy reduces this diversity dramatically, often within days of treatment initiation, particularly in patients undergoing dose-dense regimens. This loss diminishes the gut ecosystem's buffering capacity, rendering the mucosa more susceptible to epithelial damage, inflammatory escalation, and delayed healing (Figure 1).[30]

Table 1 Pathophysiological Basis of Chemotherapy-Induced Mucositis

Phase/Mechanism	Key Features	Molecular/Cellular Events	Clinical Implications
Initiation	Direct epithelial injury and oxidative stress	DNA damage, apoptosis of basal epithelial cells, ROS generation, mitochondrial dysfunction	Early mucosal thinning, initial pain, increased susceptibility to injury
Up-Regulation/Message Generation	Activation of inflammatory pathways	NF-κB activation, cytokine release (TNF-α, IL-1β, IL-6), MMP upregulation, COX-2 induction	Amplified local inflammation, epithelial fragility, early immune cell recruitment
Signal Amplification	Escalation of tissue injury	Neutrophil and macrophage infiltration, proteolytic enzyme release, further ROS production, microvascular damage	Worsening mucosal injury, enhanced pain, increased epithelial permeability
Ulceration	Barrier breakdown and microbial translocation	Epithelial sloughing, dysbiosis, overgrowth of pathobionts (Enterococcus, Enterobacteriaceae, Proteobacteria), TLR activation, endotoxin-mediated inflammation	Severe mucosal ulceration, pain, bleeding, dysphagia, risk of systemic infection
Healing/Recovery	Tissue regeneration and microbial recolonization	Stem cell proliferation, angiogenesis, extracellular matrix restoration, partial recovery of commensals (Lactobacillus, Bifidobacterium, Faecalibacterium)	Gradual symptom resolution, persistent subclinical vulnerability, potential for recurrent mucositis in subsequent cycles
Microbial Dysbiosis Contribution	Amplifies mucosal injury and delays recovery	Loss of SCFA-producing commensals, reduced mucin production, impaired epithelial proliferation, expansion of inflammatory pathobionts	Exacerbates severity and duration of mucositis, impairs epithelial repair, contributes to systemic inflammation

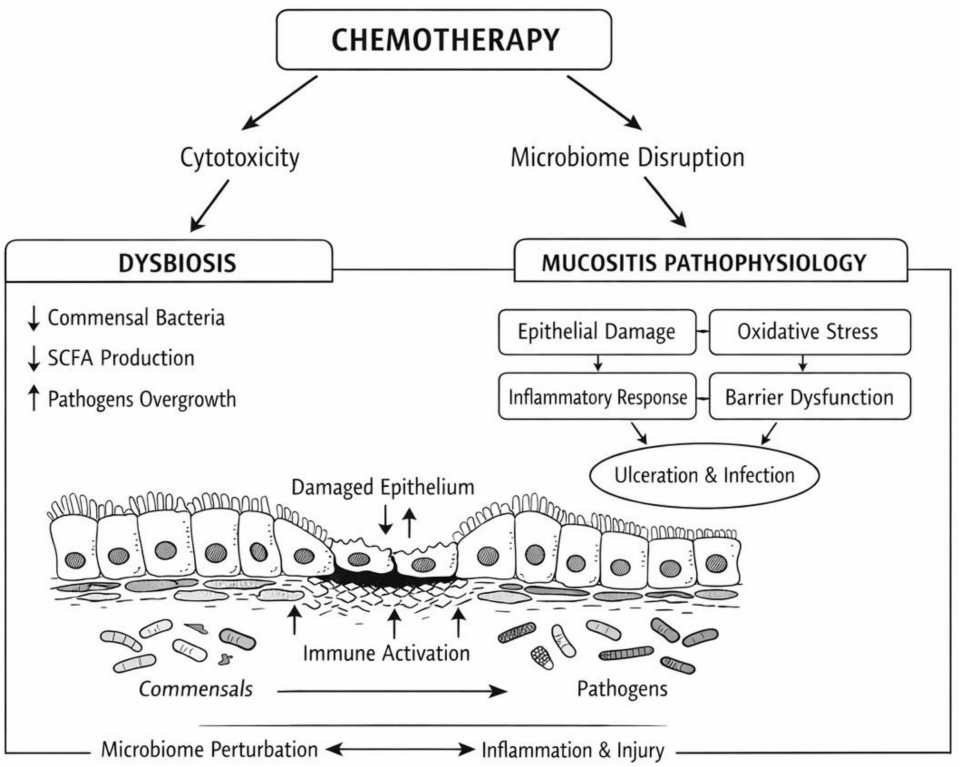

Figure 1 Chemotherapy and Microbiome Interaction.

In addition to global diversity loss, chemotherapy selectively depletes beneficial commensal bacteria. Lactobacillus species, which help maintain epithelial tight junctions and suppress pathogenic growth, are frequently diminished. Bifidobacterium, critical for the production of short-chain fatty acids (SCFAs) that nourish colonocytes and modulate immune responses, is also significantly reduced. Faecalibacterium prausnitzii, a major butyrate producer with anti-inflammatory properties, and Akkermansia muciniphila, which regulates mucin turnover and the protective mucus barrier, are similarly affected. The reduction of these taxa undermines epithelial energy supply, weakens anti-inflammatory signaling, and diminishes barrier resilience, creating a mucosa more vulnerable to ulceration and infection.[31] Chemotherapy simultaneously favors the expansion of opportunistic pathobionts, including Enterococcus species, Enterobacteriaceae such as Escherichia coli and Klebsiella, and certain Clostridium and Proteobacteria species. These bacteria thrive in inflamed, oxygen-rich environments and release endotoxins that further activate toll-like receptors and pro-inflammatory pathways. The overgrowth of pathobionts amplifies epithelial injury, sustains inflammation, and increases the likelihood of microbial translocation, creating a self-reinforcing cycle that exacerbates mucositis severity.[32]

Functional and metabolic disruptions accompany these compositional shifts. Genes responsible for SCFA production, particularly butyrate and propionate, are downregulated, limiting critical energy substrates for epithelial repair. Bile acid metabolism is altered, which impairs local immune regulation and epithelial signaling. Amino acid metabolism is disrupted, reducing the availability of substrates necessary for mucin and epithelial protein synthesis. Surviving microbial populations often upregulate oxidative stress response genes, reflecting an environment hostile to both microbes and host tissue rather than adaptive homeostasis. These functional impairments compound epithelial vulnerability and prolong mucosal recovery.[33,34]

Different chemotherapy regimens produce distinct microbial signatures. Anthracyclines are associated with depletion of Firmicutes and butyrate-producing taxa alongside expansion of Proteobacteria. Taxanes reduce Faecalibacterium and Akkermansia, favoring mucin-degrading species, while cyclophosphamide alters gut permeability and promotes translocation of gram-positive spore-forming bacteria. Fluoropyrimidines induce crypt epithelial apoptosis and expand

inflammatory Enterobacteriaceae populations. These regimen-specific alterations underscore the need for tailored interventions that consider both chemotherapy type and patient-specific microbiome profiles.[35–37] The impact of chemotherapy-induced dysbiosis extends beyond the gut, influencing systemic physiology through the gut–breast axis. Dysbiotic changes modulate estrogen metabolism via the estrobolome, affect immune cell priming, and alter systemic inflammatory tone, all of which may influence treatment response, toxicity, and overall patient outcomes. Recovery of the microbiome after chemotherapy is often incomplete. While partial recolonization occurs over weeks, residual dysbiosis, functional deficits, and reduced SCFA availability persist, particularly in patients undergoing multiple cycles, leaving them at cumulative risk for recurrent mucositis and delayed tissue repair (Table 2).[38,39]

Microbiome-Driven Therapeutic Strategies: Clinical Evidence and Translational Implications

Mounting preclinical and translational evidence implicates chemotherapy-associated dysbiosis as a biological modifier of mucosal injury, inflammatory amplification, and epithelial repair. Accordingly, multiple microbiome-targeted strategies have been proposed as adjunctive approaches to mitigate chemotherapy-induced mucositis (CIM). However, the maturity of evidence varies substantially across modalities, and breast cancer–specific clinical data remain limited. Below, we synthesize current strategies, explicitly distinguishing mechanistic insights from preclinical models and emerging clinical findings, and discuss translational readiness, limitations, and safety considerations.[40]

Probiotics

In murine models of chemotherapy-induced intestinal injury, selected probiotic strains (eg, *Lactobacillus rhamnosus* GG, *Bifidobacterium longum*) have been shown to attenuate epithelial apoptosis, preserve tight junction integrity, and reduce

Table 2 Microbiome Alterations Associated with Breast Cancer Chemotherapy

Microbiome Feature	Alteration Observed	Mechanistic Consequence	Clinical Implication
Microbial Diversity	Global reduction in alpha diversity and richness	Loss of ecological redundancy and resilience	Increased susceptibility to mucosal injury, delayed recovery, higher mucositis severity
Beneficial Commensals	Depletion of Lactobacillus, Bifidobacterium, Faecalibacterium prausnitzii, Akkermansia muciniphila	Reduced SCFA production, impaired mucin turnover, weakened epithelial barrier, diminished anti-inflammatory signaling	Enhanced epithelial vulnerability, increased inflammation, delayed mucosal healing
Opportunistic Pathobionts	Expansion of Enterococcus spp., Enterobacteriaceae, Clostridium spp., Proteobacteria	Release of endotoxins, activation of TLRs, amplification of NF-κB signaling	Exacerbation of mucosal inflammation, increased risk of ulceration and systemic infection
Metabolic and Functional Shifts	Downregulation of SCFA biosynthesis, impaired bile acid and amino acid metabolism, upregulation of microbial oxidative stress response genes	Reduced epithelial energy supply, impaired mucosal regeneration, enhanced oxidative damage	Prolonged mucositis, delayed recovery, increased treatment-related toxicity
Regimen-Specific Signatures	Anthracyclines: reduced Firmicutes, increased Proteobacteria; Taxanes: reduced Faecalibacterium and Akkermansia; Cyclophosphamide: gram-positive spore-formers; Fluoropyrimidines: expansion of Enterobacteriaceae	Chemotherapy-specific microbial disruption impacting metabolite production and immune modulation	Risk stratification and tailored microbiome interventions based on chemotherapy type
Systemic Interactions	Dysbiosis affects the estrobolome and systemic immune modulation	Altered estrogen metabolism, immune priming, and inflammatory tone	Potential influence on treatment toxicity, adherence, and systemic side effects
Recovery Dynamics	Incomplete recolonization and persistent functional deficits	SCFA and metabolite deficiency, suboptimal mucin and epithelial repair	Cumulative vulnerability to recurrent mucositis and prolonged gastrointestinal toxicity

pro-inflammatory cytokine expression through modulation of NF-κB signaling and enhancement of mucosal immune tolerance. These effects are strain-specific and context-dependent, underscoring the need for mechanistic precision in probiotic selection.[41] Small randomized controlled trials and observational studies in heterogeneous oncology populations (predominantly gastrointestinal and head-and-neck cancers) suggest that probiotic supplementation may modestly reduce the incidence, severity, or duration of oral and gastrointestinal mucositis. However, breast cancer–specific data are sparse, and results across studies are heterogeneous with respect to strains, dosing, timing, and outcome measures. Importantly, existing trials are underpowered to draw definitive conclusions regarding efficacy in contemporary breast cancer regimens.[42] Safety remains a critical consideration in immunocompromised patients, particularly during periods of neutropenia, with rare but documented cases of probiotic-associated bacteremia and fungemia. Consequently, probiotics should be considered investigational adjuncts in this population, and future trials must incorporate rigorous safety monitoring and standardized formulations.

Prebiotics and Dietary Modulation

Prebiotics, including fermentable dietary fibers, selectively promote the growth of commensal taxa associated with epithelial homeostasis and anti-inflammatory metabolite production. In preclinical models, high-fiber diets enhance short-chain fatty acid (SCFA) production, improve barrier function, and attenuate inflammatory responses following chemotherapy-induced mucosal injury.[43] Clinical data directly linking prebiotic supplementation to reduced CIM in breast cancer are limited. Observational studies suggest that baseline dietary patterns and nutritional status may influence microbiome resilience and treatment-related gastrointestinal symptoms, but interventional evidence remains preliminary.[44] Dietary modulation represents a low-risk, scalable adjunct to supportive care. However, individual variability in microbiome responsiveness, tolerability during chemotherapy-related gastrointestinal symptoms, and the absence of standardized prebiotic formulations complicate clinical implementation. Controlled trials incorporating dietary interventions with microbiome and metabolomic endpoints are needed.[45]

Postbiotics and Microbiota-Derived Metabolites

Postbiotics—defined as non-viable microbial products or metabolites such as SCFAs and indole derivatives—exert barrier-protective and immunomodulatory effects in experimental models of mucosal injury. These metabolites enhance epithelial energy metabolism, promote tight junction integrity, and support regulatory immune pathways implicated in mucosal healing.[46] To date, clinical evaluation of postbiotics in CIM is minimal, and evidence is largely extrapolated from inflammatory bowel disease and radiation-induced mucosal injury models. No robust breast cancer–specific trials have been completed. Postbiotics offer theoretical safety advantages over live microorganisms in immunocompromised hosts. However, optimal dosing, formulation, and delivery strategies remain undefined, and clinical validation in chemotherapy-associated mucositis is required.[47]

Fecal Microbiota Transplantation and Next-Generation Live Biotherapeutics

Restoration of microbial diversity and functional capacity via fecal microbiota transplantation (FMT) or defined microbial consortia has demonstrated efficacy in refractory dysbiosis and selected inflammatory conditions. Preclinical oncology models suggest that microbiome restoration may mitigate mucosal injury and modulate inflammatory responses following cytotoxic therapy.[48] Clinical data supporting FMT for CIM are extremely limited, and no controlled trials in breast cancer populations have been completed. Current use of FMT in oncology is largely restricted to refractory *Clostridioides difficile* infection, with emerging exploratory studies in immunotherapy-related toxicities.[49] Safety, donor screening, regulatory oversight, and the potential for unintended immunologic consequences pose substantial barriers to routine application in chemotherapy recipients. Next-generation live biotherapeutic products and engineered commensals capable of delivering defined anti-inflammatory or epithelial reparative functions represent promising but early-stage translational avenues.[50]

Precision Microbiome Modulation and Biomarker-Guided Interventions

Baseline microbiome composition and functional capacity may influence susceptibility to mucosal injury and recovery trajectories in preclinical models. Systems biology approaches integrating metagenomics and metabolomics have identified candidate microbial signatures associated with epithelial resilience and inflammatory tone.[51] In the specific context of CIM, clinical validation of microbiome-based risk stratification remains preliminary. While early translational studies suggest associations between microbial diversity and treatment-related gastrointestinal toxicity, prospective evidence demonstrating that baseline profiling can guide targeted microbiome interventions in breast cancer patients is lacking.[52] Future precision supportive oncology frameworks may incorporate microbiome-informed risk models to tailor preventive strategies. However, such approaches require prospective validation, standardized analytical pipelines, and demonstration of incremental clinical benefit over existing supportive care measures.[53]

Clinical Context and Unmet Needs

Chemotherapy-induced mucositis (CIM) remains an important supportive care issue in the management of breast cancer, although its clinical impact has evolved alongside advances in systemic therapy and supportive oncology. In contemporary practice, commonly used regimens such as anthracycline–taxane combinations (eg, AC–T) and docetaxel–cyclophosphamide (TC) are more frequently limited by hematologic toxicities, peripheral neuropathy, and, in selected populations, cardiotoxicity, rather than by severe mucositis.[54,55] High-grade oral or gastrointestinal mucositis is now relatively uncommon with standard dosing schedules; however, lower-grade mucosal injury remains prevalent and clinically meaningful, contributing to pain, impaired oral intake, gastrointestinal symptoms, and diminished quality of life. These toxicities can indirectly compromise treatment adherence through dose delays, supportive medication use, unplanned clinic visits, and hospitalizations, particularly in vulnerable patient populations, including older adults and those with comorbidities or baseline nutritional compromise.[56,57]

The burden of mucositis may be accentuated in specific clinical contexts, including dose-dense chemotherapy schedules, older cytotoxic protocols, and combination regimens administered with curative intent in patients with limited physiologic reserve. Beyond conventional cytotoxic chemotherapy, the therapeutic landscape of breast cancer has expanded to include targeted agents and antibody–drug conjugates (ADCs), some of which are associated with distinct mucocutaneous toxicities. For example, inhibitors of the PI3K/AKT/mTOR pathway have been linked to oral stomatitis with characteristic aphthous-like lesions, and certain ADCs may induce gastrointestinal mucosal injury through off-target cytotoxic effects. In these settings, mucosal toxicity can represent a more prominent and clinically challenging adverse event, underscoring a persistent unmet need for effective, mechanism-informed supportive interventions across the evolving spectrum of breast cancer therapies.[58,59]

Current strategies for the prevention and management of CIM in breast cancer are largely supportive and symptom-directed. Standardized oral care protocols, cryotherapy, topical anesthetics, antimicrobial mouth rinses, nutritional support, and dose or schedule modifications constitute the mainstay of management.[60,61] While these measures can reduce symptom burden in some patients, their efficacy is variable, and they do not consistently prevent mucosal injury or accelerate epithelial repair. Moreover, existing interventions primarily address downstream manifestations of mucositis rather than upstream biological drivers of mucosal vulnerability, such as epithelial regenerative capacity, inflammatory amplification, and host–microbe interactions. As a result, CIM remains a source of residual morbidity even in the context of modern supportive care.[62,63] Importantly, the clinical impact of CIM extends beyond patient-reported symptoms to encompass broader health system and economic considerations, including increased utilization of supportive medications, outpatient visits, and occasional inpatient care for complications such as dehydration or infection. These burdens highlight the need for more effective, durable, and biologically grounded preventive strategies that can be integrated into routine oncology practice without compromising safety in immunocompromised patients.[64–71]

Conclusion

Chemotherapy-induced mucositis in breast cancer is a multifactorial toxicity in which direct cytotoxic injury to rapidly renewing mucosal epithelium represents the principal pathogenic driver, with secondary amplification through inflammatory cascades, barrier dysfunction, and host–microbe interactions. While perturbations of the oral and gut microbiome

do not initiate mucosal injury, accumulating preclinical and translational evidence suggests that dysbiosis can meaningfully modify the severity, duration, and clinical expression of mucositis by shaping local immune tone, epithelial repair capacity, and susceptibility to secondary infection. Microbiome-targeted interventions—including probiotics, prebiotics, dietary modulation, postbiotics, and emerging live biotherapeutic products—therefore represent biologically plausible adjuncts to conventional supportive care rather than stand-alone solutions. At present, however, the clinical evidence base supporting these strategies in breast cancer populations remains limited, heterogeneous, and largely exploratory, with most data derived from preclinical models or mixed oncology cohorts. Safety considerations in immunocompromised patients, variability in microbial responses, and the absence of standardized formulations further constrain immediate clinical translation.

Future progress will depend on well-designed, breast cancer–specific prospective trials incorporating longitudinal microbiome and metabolomic profiling, standardized mucositis endpoints, and rigorous safety monitoring. Such studies are needed to clarify which patients are most likely to benefit from microbiome modulation, to define optimal timing and modality of intervention relative to chemotherapy, and to establish whether microbiome-informed supportive care can meaningfully reduce residual mucosal morbidity without compromising oncologic efficacy. Until such evidence is available, microbiome-driven strategies should be viewed as promising investigational adjuncts within an evolving precision supportive oncology framework rather than established components of routine clinical practice.

Disclosure

The authors report no conflicts of interest in this work.

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